

**PAT**  
PROCESS  
ANALYTICAL  
TECHNOLOGY



numera

Unique  
Modular  
PAT System  
for Bioprocesses

# Innovation is our passion

Since our foundation as a spin-off from the ETH Zurich in 1992, we have been passionately combining analytics, data processing and process control. Through interdisciplinary thinking, we have been developing innovative solutions to simplify and optimize the development of biotechnological processes. Our vision is a bioprocess in which the substrate or product concentration will be as precisely and easily controlled as the temperature or the pH value today. With Numera we are opening up new possibilities in process control thanks to QbD.

Follow us as we enter a new era in bioprocessing technology.

## **Carlo Andretta**

CEO, Ph. D. sc. nat. ETH



Pre-designed, modular software and hardware concepts are the key to efficient implementation of customized total solutions. As an engineering company we network interdisciplinary know-how and develop innovative concepts for your tasks regarding all aspects of the bioprocess.

### **Process Analytics (PAT)**

We see the PAT initiative not merely as a measurement-related task, but rather as a comprehensive range of tasks, from sampling through to data processing. We focus on extracting information and the associated increase in yield and product quality.

### **Data Processing**

The data processing of bioprocesses implies far more than simple data recording. Lucullus PIMS unifies the core competences of the process development in one system: Planning – Preparation – Execution – Evaluation. We focus on the increase of efficiency executing bioprocesses and therefore on cost reduction.

### **Automation**

With our platform “Biocontrol System”, we cover a wide range of requirements of the automation of engineering development and pilot systems in the bioprocessing technology. Whether a project involves providing a new automation system or replacing old control systems – we offer customized controllers as bench-top or cabinet solutions.



# PAT system requirements in biotechnology

## Christoph Herwig

Univ.-Prof. Dipl.-Ing. Dr. techn., Professor for Bioprocess Engineering, Research Area Biochemical Engineering, Institute of Chemical Engineering, Vienna University of Technology

According to its original definition PAT (Process Analytical Technology) is “a system for designing, analyzing and controlling manufacturing through timely controlled measurements of critical quality and performance attributes with the goal of ensuring final product quality”<sup>[1]</sup>. The goal of PAT is to identify critical process parameters (CPP) and quality attributes (CQA), to control them these in order to ensure the product quality. Apart from Risk Analysis<sup>[2]</sup>, Design of Experiments<sup>[1]</sup> and Quality Management<sup>[3]</sup> it is an important tool of the overall concept of Quality by Design<sup>[4]</sup>.

The use of PAT permeates every stage of the product life cycle, from development through the transfer of technology and scale-up to production. In order to safeguard that life cycle, PAT must be applied as early as during process development and therefore a PAT system has to meet high demands.

Due to the complexity of growth media for biological systems (many components in low concentrations in a temporally varying background) it is important to measure the process variables such as substrates, metabolites, products, and biomass with high frequency as well as selectivity and resolution. In the development with ever changing process conditions, spectroscopic systems

are often limited by sparsely solid calibration models. Therefore, in many cases HPLC or enzymatic-photometric measuring principles are used. These measuring systems are attached on-line, i.e. by automatic sampling, to the bioreactor.

However, choosing the right on-line measurement principle by itself will not lead to good measurement results. A PAT system must also include sampling, the preparation of samples and transporting samples for measurement. These elements must be individually adapted to the process environment. In order to enable accelerated process development to be carried out even in small reactors being operated in parallel, the whole system must be able to work with small sample volumes. Furthermore, the system must provide inter-

faces to common analytical devices.

After analytics comes analysis. Data must be merged and checked for consistency<sup>[5]</sup>. For the purpose of comparing processes, data has to be converted into key figures which are neither dependent on scale nor initial conditions<sup>[6]</sup>. A PAT system must offer the findings on interdependencies between CPPs and CQAs regarding process models in form of a control strategy<sup>[7]</sup>. These integrated PAT systems enable accelerated process development and lead to a high level of reproducibility, increased yield from the production process and consistent product quality.

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- <sup>[1]</sup> ICH, Q8, Pharmaceutical Development (R2), [www.ich.org](http://www.ich.org), (2009).
- <sup>[2]</sup> ICH, Q9, Quality Risk Management, [www.ich.org](http://www.ich.org), (2005).
- <sup>[3]</sup> ICH, Q10, Pharmaceutical Quality System, [www.ich.org](http://www.ich.org), (2008).
- <sup>[4]</sup> A.S. Rathore, Roadmap for implementation of quality by design (QbD) for biotechnology products, *Trends Biotechnol.*, 27 (2009) 546-553.
- <sup>[5]</sup> P. Wechselberger, A. Seifert, C. Herwig, PAT method to gather bioprocess parameters in real-time using simple input variables and first principle relationships, *Chemical Engineering Science* 65 (2010) 5734-5746.
- <sup>[6]</sup> C. Herwig, Posch, A., Herausforderungen und Trends für zukünftige Bioprozesse, *pharmind*, 75 (2013) 1688-1694.
- <sup>[7]</sup> Garcia Thomas, Cook Graham, N. Roger, PQLI Key Topics - Criticality Design Space and Control Strategy, *Journal of Pharmaceutical Innovation*, 3 (2008) 60-68.
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# Individual. Modular. Precise.

Sampling, sample preparation and sample transport automated in a system, individually combinable and on demand with integrated analytics.

Thanks to small sample volumes, high frequency measurements in small reactors are possible. Even in parallel operations – which saves costs and work hours.

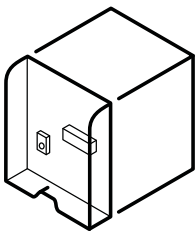
The combination with Lucullus PIMS allows the coordination of sampling, the collation of all process data and model-based process prediction, among other tasks.



# Module overview



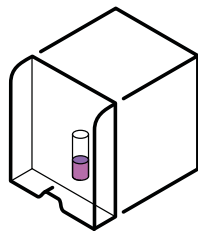
Our range of modules allows reproducing your individual task: Whether on-line, at-line or off-line analytics, cell culture technology or microorganisms, one or several bioreactors – here you will find the right solution.



## Transport Module

Module for periodical sampling optimized for cell-free sampling with filtration probes. Flow rate control and alarming in case of threatening clogging. Optionally with manual backwashing.

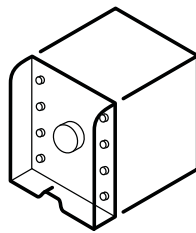
Transport: 2 ml/min



## Interface Module

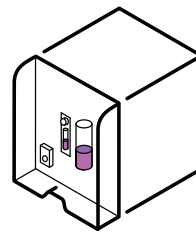
Module for sample collection, in particular in combination with the Transport Module. Sample transfer to other modules or analytical devices. Small sample loss and very low, reproducible dilution.

Volume: max. 7 ml



## Multiplexer Module

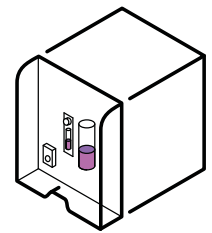
Module for connecting several bioreactors to a system. Can be configured either decentrally or centrally, also suitable for the combination of off-line and at-line analytics.



## Dilution Module

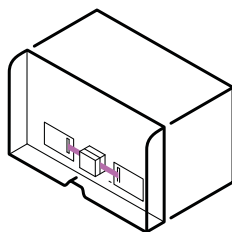
Module for sample dilution, e.g. for the expansion of smaller sample volumes before the transport, for the dilution of viscous samples from high-cell density cultivation or for the adaptation of the concentration to the measuring range of the analyzer.

Dilution: 1:5 to 1:100



## Precipitation Module

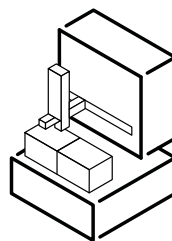
Module for the protein precipitation by adding a precipitating agent (saves the HPLC analytics). Can be used with cell-loaded samples. Simultaneous sample dilution possible. Ideal in combination with the Filtration Module.



## Filtration Module

Compact tape filtration module for the gentle filtration of cell-loaded samples. Allows a quick, reliable and almost loss-free filtration of the smallest sample volumes. The module detects filter clogging and is automatically cleaned.

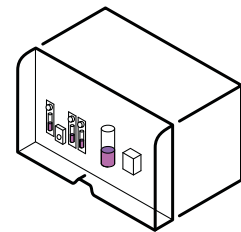
Volumes: ~2,5 ml with up to 80 g/L CDW,  
Filter: 0,45 µm, 1,2 µm



## Autosampler / Sample Collector

Samples processed can be collected or manually taken samples be processed: The ASX platform is available in different sizes and with a wide range of options (cooling system, injection valves, etc.)

Sample vessels: 2 – 50 ml



## Meta Master

Measuring system for glucose and other metabolites involved in metabolism: fast, precise, accurate! As a result, it is now possible for the first time to reliably measure and control the specific glucose absorption rate, for example.

Measurement cycle: ~6 minutes

Concentration range:  
0,01 – 40,0 g/l (glucose)

Precision and Accuracy: <1 %

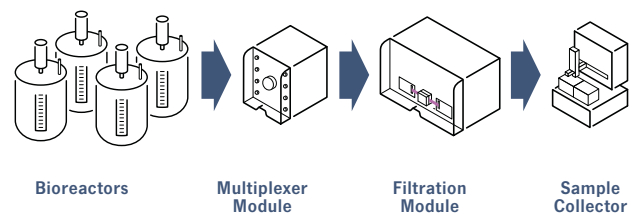
# Application scenarios

The implementation of automated process analytics involves a wide range of specific tasks – ranging from sampling to actual analysis or sample storage – each of which requires a specific solution. In order to meet the different requirements, our modules can be combined in customized solutions. This allows us to provide you with the perfect solution for every application.

Common application scenarios to collect and filter cell-loaded samples from bioprocesses are detailed below. Configure your individual solution with our web configurator: [www.numera-pat.com](http://www.numera-pat.com)

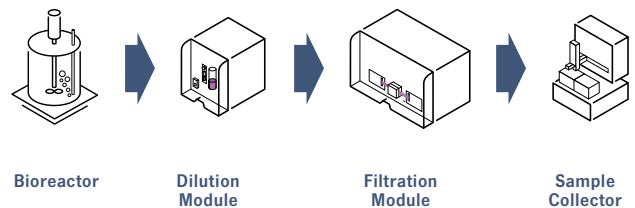
## Storage of cell-free samples

In order to collect a great amount of data a high measuring frequency with small sample volumes is required. Collect with Numera samples fully automatically and store the filtered, cell-free samples refrigerated in the sample collector in order to feed them later to your analytics.



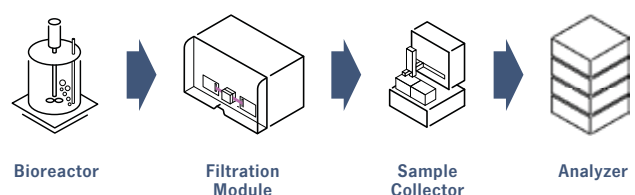
## Volume expansion / dilution

For the transportation of smaller sample volumes, it is useful to previously expand the sample volume. This can be achieved by means of a precise dilution. Dilution is also used if the concentration of the analyte must be reduced or if a sample is viscous due to high biomass concentration. The Dilution Module performs these tasks.



## On-line analytics

The Sample Collector cannot only collect samples but also feed them to directly connected analytical devices (e.g. a HPLC) without loss. Lucillus PIMS assumes the process coordination, merges the data of all systems and offers numerous data analysis functions.



## Reference installation Numera

The Department for Bioprocessing Technology at the ICBT conducts research on improved bioprocess design and control concepts. The use of Numera will promote the targeted implementation of new PAT and QbD strategies.

### High data density

With a sampling frequency of 1 h during a process duration of >72 h, data were obtained from repeated batch and fed-batch processes – with a 3 ml sample volume only (pre-sample included).

### Reproducible

Samples can be periodically taken from one or more reactors, processed and stored without additional extent.

### Reliable

The system took samples autonomously and reliably during cultivations of *Pichia pastoris* lasting several days and filtered them – even with up to 100 g/l of cell dry weight (CDW).

The Department for Bioprocessing Technology, headed by Prof. Dr. Karin Kovar, has developed into an interdisciplinary networked competence center for biosciences, natural sciences and engineering. At the ICBT, research is carried out into a wide range of bioprocesses, from classic microbial systems to innovative products from microalgae.

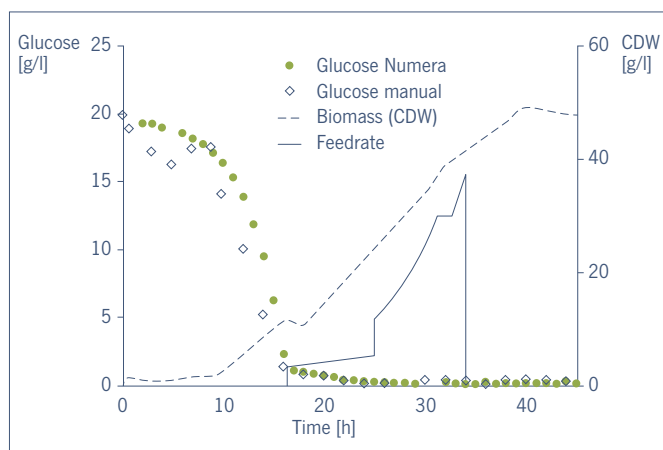
Process control during cultivation, the accompanying analytics as well as data evaluation and modelling require a modern, reliable and efficient infrastructure. Securecell has been supporting the ZHAW

through its products for many years. As a result, it has a number of “Advanced Biocontrol Systems” for bioreactors at its disposal for use in research and training. The bioreactors at the pilot plant of the ZHAW are connected to a central process gas analysis system (Extended Process Gas Analyzer EPGA) with mass spectrometer. All the data from the bioreactors and measurement devices are recorded and evaluated using the process information management system Lucullus PIMS. Lucullus is also used to implement complex process control strategies. With the PAT system

Numera, samples can be periodically taken from one or more reactors, be processed and stored in a reproducible manner. This enables a high density of data to be obtained without additional expense and process development and optimization to be progressed efficiently.

In a first phase, the ICBT tests automated sampling, filtration and storage. “We used the device during our practical work and compared the data obtained using it with the data obtained from manual sampling”, explains Lukas Neutsch, the deputy director of the Department for Bioprocessing Technology and lecturer at the ZHAW. “The system took samples autonomously and reliably during cultivations of *Pichia pastoris* lasting several days and filtered them – even with up to 100 g/l of cell dry weight (CDW). The data obtained impressively demonstrate the advantages of this PAT system.” (see graph)

frequency determination of glucose (and other metabolites). Neutsch: “Using the MetaMaster, in particular, we hope to make decisive methodological advances in process control. The precise determination of glucose to levels of less than 100 mg/l and with up to 10 measurement points per hour will enable new control concepts to be realized. That, in conjunction with model-based predictive control of Lucullus PIMS, will enable us to implement QbD strategies simply and practically and thus enter a new era of bioprocessing technology.”



Glucose fluctuation in fed-batch: Measurement comparison between samples processed manually and [◇] samples processed with Numera [●] Glucose analytics: off-line HPLC.

In the next phase, the MetaMaster by Securecell and a HPLC system by Agilent will be connected on-line. This will allow the continuous high-

## Contact

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 Grüental, 8820 Wädenswil

# Building Blocks for Customized Solutions

We are experts in process analytics, information processing and automation in bioprocess engineering. For more than 20 years, we have been designing solutions for international market leaders in the fields of chemistry and pharma as well as for universities and research institutes.

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