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Application note
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Bioprocess Information Management with Lucullus® PIMS for Biochemical Engineering at TU Wien

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Abstract

The TU Wien (Technische Universität Wien) maintains a laboratory in which a wide variety of bioprocesses are developed and optimized. This requires a variety of different reactors and equipment in use. Lucullus® PIMS facilitates the interaction between all devices as well as the management of the generated data. This enables the researchers at TU Wien to execute process development projects quickly, efficiently and flexibly. This application note gives an overview on how Lucullus® PIMS facilitates the integration of reactors and devices and enables Process Analytical Technology (PAT)-tools at TU Wien; it gives a short description of step chains and implemented control strategies. Finally we sum up the key benefits of a Lucullus® Lab in the academical environment.

Needs of a Bioprocess Development Lab

TU Wien maintains a laboratory in which a wide variety of bioprocesses are developed and optimized. Each process design depends on i) technical feasibility and ii) the process knowledge itself. The spectrum of investigated processes at TU Wien ranges from waste-to-value processes to biopharmaceutical processes. This requires the application of several organisms, including extremophilic organisms, microbials, yeasts, fungi and mammalian cell cultures. To enable the cultivation of this high variety of organisms, numerous reactor systems with different equipment are necessary. The final experimental set-up must allow supervision of process parameters, control and data acquisition of sensors and devices as well as high flexibility, to adapt to novel organisms and their requirements. This includes the implementation of new sensors and devices, the adaption of process chains and the implementation of novel control strategies. Conducted experiments during process development mainly aim to generate process knowledge. Therefore, the approach data to information to knowledge (Figure 2-6) is used. This means that all collected data represents an important "intermediate product" for subsequent analysis. To ensure this with reasonable effort, automation in data collection and data management are indispensable in a modern bioprocess lab.

In summary, a state of the art bioprocess development lab needs:

I. flexible setup of bioreactor systems
II. design and implementation of process chains
III. monitoring & control of bioprocesses
IV. centralized & secure data management

Lucullus® PIMS – Labs at TU Wien

TU Wien has three laboratories in two buildings where microbial and mammalian cultivations are performed. In sum, there are 20 reactor systems from different suppliers in use with 0.2 L up to 60 L scale. To reach maximal flexibility each reactor setup is equipped with multiple I/O modules and network enabled serial interfaces from different vendors (e.g. Siemens, Wago, Lantronix, etc.). This enables the fast integration and transfer of frequently used devices such as scales, pumps, valves and sensors. All our devices are integrated in Lucullus® PIMS.

Flexible Setups

One key requirement for a digital solution is flexibility. Regarding to bioprocesses, this means the applicability for different setups and the fast and easy rearrangement of devices and technology to get development projects done. Figure 2-1 gives an overview off different processes at TU Wien which are performed with Lucullus®: from waste-to-value processes to biopharmaceutical processes with the application of several organisms. Flexible setups at TU Wien for up-stream processing use reactor systems from various vandors. E.g.: for Mammalian cells (Infors AG), Microbial and Yeast (Eppendorf, Infors AG and Sartorius), Extremophiles (Sartorius, Infors AG, Baumgartner, etc.) and Fungi (Infors AG, Eppendorf). In addition, numerous peripheral devices such as scales, pumps, mass flow controllers, gas analyzers, biomass probes (OD880, dielectric spectroscopy), Numera® (liquid handling system), on-line enzymatic/ biochemical analyzers and online HPLCs are integrated.

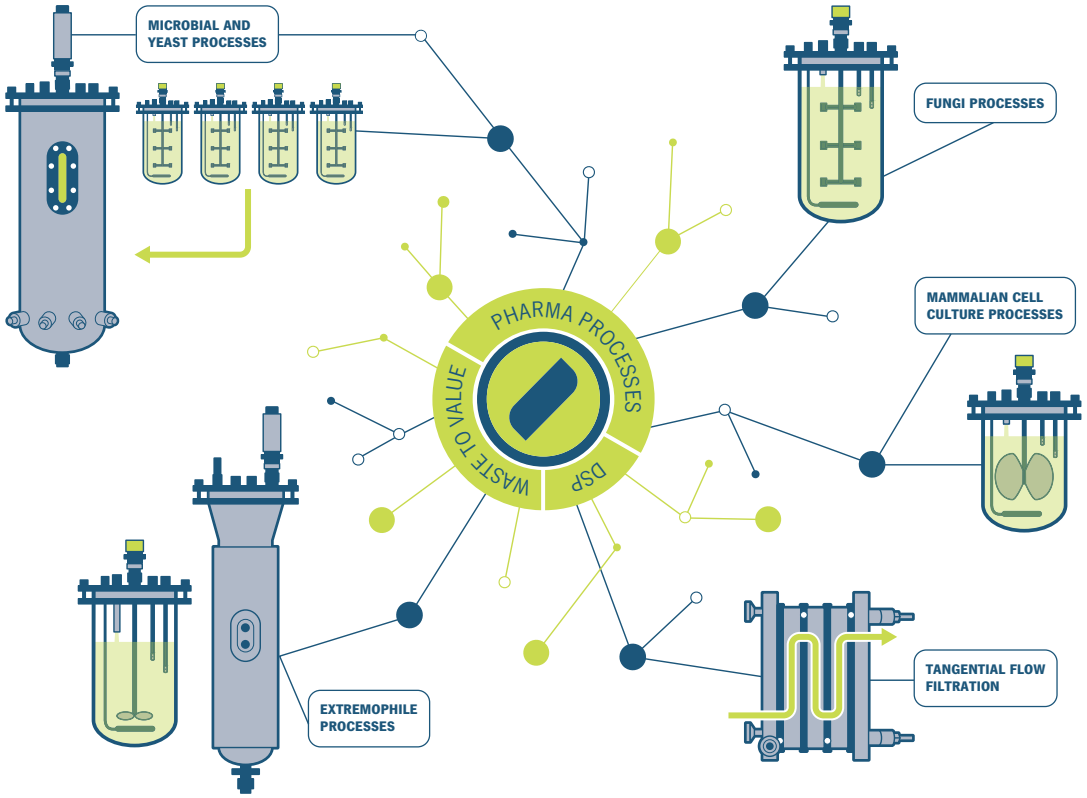

Figure 2 1: Sum-up of processes integrated into Lucullus PIMS at TU Wien: down-stream set-ups; up-stream processes for Fungi, Mammalian cells, Extremophiles, Microbial and Yeast processes; many different lab devices.

Figure 2-2: Set-up example for a PAT-bioreactor system with extensive on-line analytics, fully automated by Lucullus PIMS. The set-up includes a Numera system that is connected to an HPLC and a biochemical analyzer to facilitate automated sampling as well as on-line measurements of substrate, metabolites, products etc.

Figure 2-2 shows a fully automated twin reactor system for microbial processes with extensive on-line analytics. The set-up includes a Numera® system (Securecell AG, Switzerland) for automated sampling and sample processing, which is further connected to an HPLC (Ultimate 3000, Thermo Fischer) and a bioanalyzer (Bio HT, Roche). All shown devices are connected to Lucullus®. Via an OPC Server, a MATLAB connection was established. This enables the application of cutting edge technologies like model predictive control (MPC).

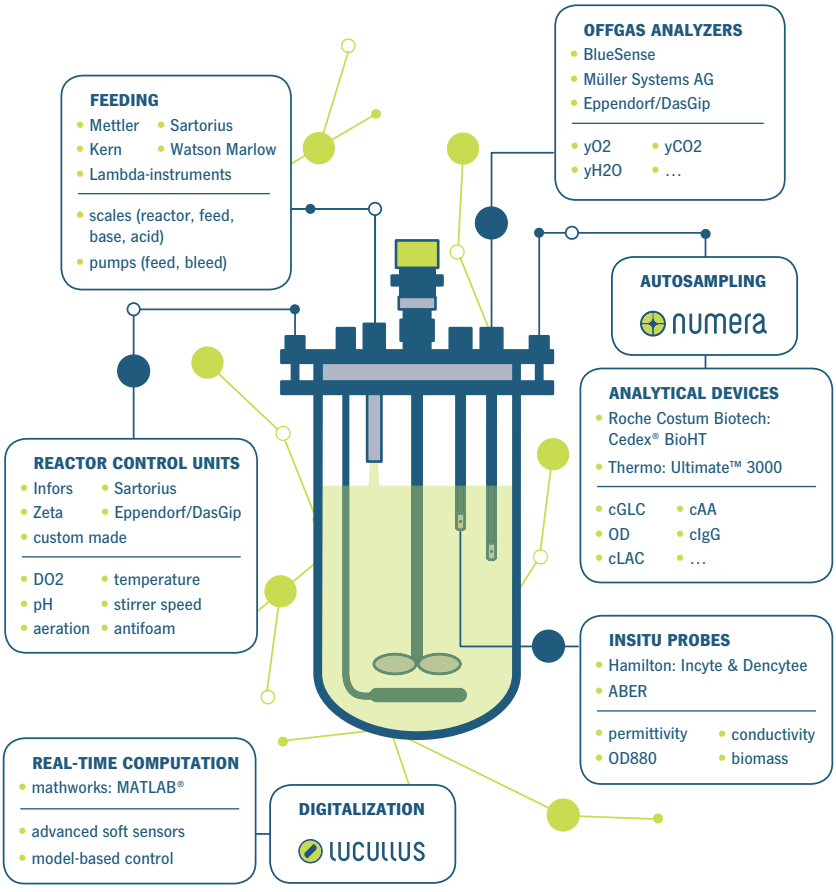

Figure 2-5: Summary of Devices and Interfaces of Lucullus® at TU Wien.

Design of Process Chains

High productivity and robustness are required for all bioprocesses. This can only be achieved by intelligent process design and process control. In Lucullus® PIMS, processes are designed by combining functional groups creating a step chain. Even the most complex processes can be realized using this approach. Based on individual building blocks, so-called “user devices”, e.g. user queries/ pop-ups, calculators and controllers, functional groups can be created. A good example for such a functional group is a cascaded dissolved oxygen (DO2) control (Figure 2-3).

The dissolved oxygen can be manipulated:

i) by the control of the stirrer speed
ii) by the control of the aeration rate
iii) by the supplement of pure oxygen (or the pressure in the vessel)

Based on single functional groups, whole process chains can be designed. An example of a process chain for a microbial process is illustrated in Figure 2-4. The process can be described by three phases: batch, fed-batch and induced fed-batch. The step chain based design enables a comprehensive setup and execution of a wide range of possible processes. Single functional groups can be easily interchanged and whole process chains can be adapted and used at different setups, building a solid and flexible enough basis for advanced bioprocesses in development and production environments.

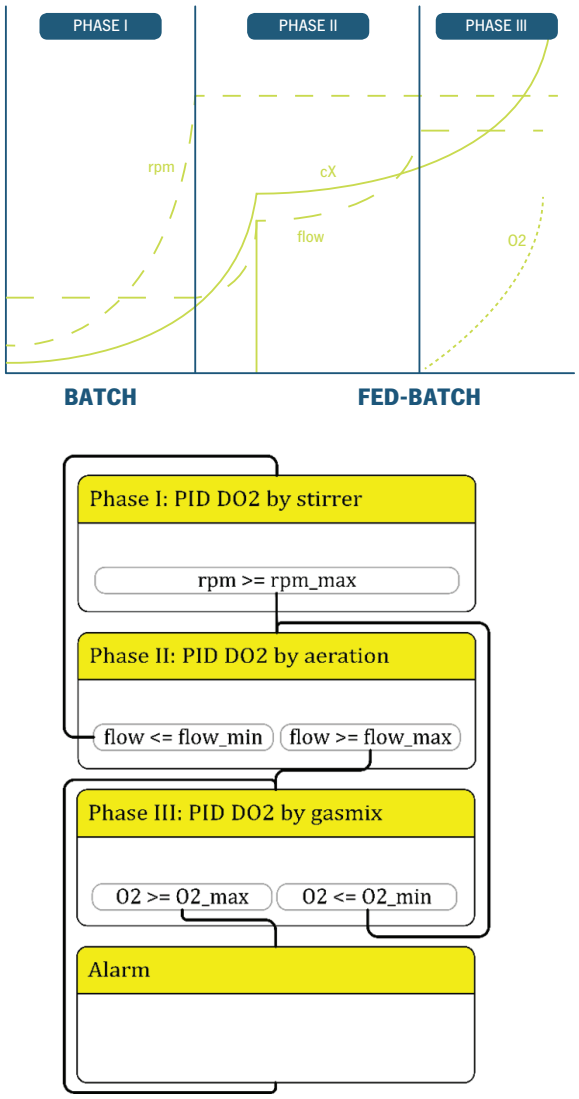

Figure 2-3: Example for a step chain-based process design. Cascaded dissolved oxygen (DO2) control function implemented in Lucullus® PIMS.

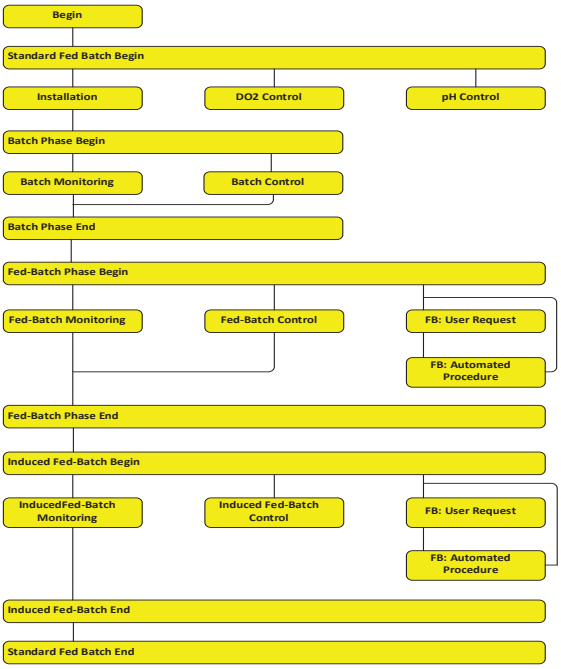

Figure 2-4: Step chain for a whole bioprocess including initialization, process overarching DO2 & pH control and the three process phases: batch, fed-batch and induced fed-batch. All monitoring, control and handmade actions are coordinated, controlled and documented by Lucullus® PIMS.

Monitoring & Control of Bioprocesses

To perform different processes, a multitude of different monitoring & control strategies have to be applied, which can be implemented in Lucullus® PIMS. Lucullus® PIMS centralizes all process data in one place to guarantee an optimal process overview from anywhere at any time. It enables fully automated control strategies like basic control algorithms, as they are provided by reactor manufacturers, as well as advanced and predictive control, used in academia and in innovationdriven industrial fields. In addition, interface-based control over third-party software such as MATLAB® is supported. Control tasks taken by Lucullus® PIMS are listed in Table 2-1. Figure 2-3 shows a time series of controlled variables (pH, DO2 and substrate concentration) for a cell culture process. Also, to control algorithms, Lucullus® PIMS provides smart agents, supporting users to detect process events. Such tools are helpful to detect and prevent process deviations and increase process robustness.

Controlled variable	Measured Variable	Manipulated Variable
Basic Control		
pH	pH	pump rates (Acid, Base), CO2 flow
DO2	DO2	stirrer speed, aeration rate, gasmix
temperature (T)	T	valves, heater
feed rates (F)	weights (W)	pump rates
volume (V)	W, V	pump rates
redox potential (Eh)	Eh	pumps
pressure (p)	p	valves, aeration rate, pump rates
Advanced Control		
DCO2	yCO2 offgas	gasmix
multiple feeds / mixed feed	weights (W)	Feeds
substrate concent-rations (cS)	biomass (X), cS	Feeds
specific rates (qs)	process specific	Feeds
Model-based control with 3rd party (MATLAB®)		
cS, qS, X	model-predictive control	process specific
max. product	optimal control	process specific
information	on-line re-design of experiments	process specific

Table 2 1: Summary of implemented control algorithms at TU Wien. Lucullus® PIMS is used as i) single software solution for standard and advanced control and ii) in combination with third-party software (MATLAB®) to perform model-based control.

Centralized Data Management

The Research Division of Biochemical Engineering employs about 30 people, who usually work there for shorter periods (students ~6 months, PhD students ~3 years). This high turnover makes centralized information management inevitable, to ensure that the data of whole projects or process lifecycles are secured and easily accessible in a comprehensive manner. Lucullus PIMS manages all data collected at the Institute in the last 10 years and ensures that nothing is lost. From this central database, the required data can be exported for more in-depth analysis. First data preprocessing, like data alignment by interpolation or smoothing, is done directly in Lucullus® PIMS. The standardized export allows easy transferability of evaluation procedures performed in third-party software (Excel, MATLAB, Origin, inCyght, Simca). This allows a fast and transferable execution of

calculations, extraction of features and the creation of key plots. For recurring procedures, these evaluation procedures can be integrated directly into Lucullus® PIMS to save even more time.The approach from data to information to knowledge to wisdom/application implies that more data with high information content will lead to more knowledge. Or to put it in another way, a certain amount of necessary knowledge can be obtained faster through extensive data collection and information management. Thanks to its extensive digitization, Lucullus® PIMS not only enables the use of automatic control and process supervision, it also catalyzes the generation of process knowledge and reduces development times resulting in a decreased time-to-market.

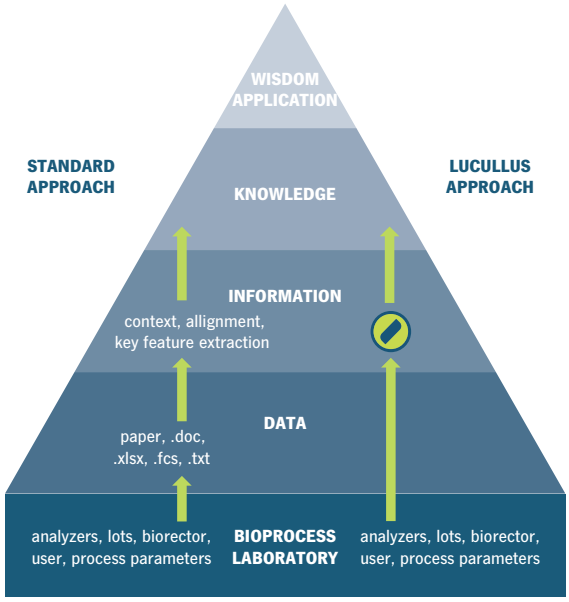

Figure 2-6: Practical appraoch from data to information to knowledge to wisdom or a final application. Illustration of the Lucullus® PIMS approach, which enables a significant speedup in process development based on extensive data and information management.

Summary

TU Wien maintains a bioprocess laboratory in which a wide variety of bioreactors and PAT-tools are used to perform state-of-the-art & future bioprocesses. To accomplish this, the bioprocess lab need to be digitized and specified workflows according to scientific principles must be performed. This means that all data must be available and step chains must be implementable. The solution for this is Lucullus® PIMS.

Lucullus® PIMS enables:

– flexible set-up of bioreactor systems

– intuitive design and implementation of basic and complex process chains

– monitoring & control for efficient & robust bioprocesses

– centralized and secure data management as basis for knowledge generation

– speed up of process development and reduction of time-to-market

CONTACT

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