

# Sensors and Automation in Single- Use Systems

Sartorius, Göttingen, June 15<sup>th</sup>, 2022

# Introduction

## *Digital & Analytics Trends in the Pharma Industry*

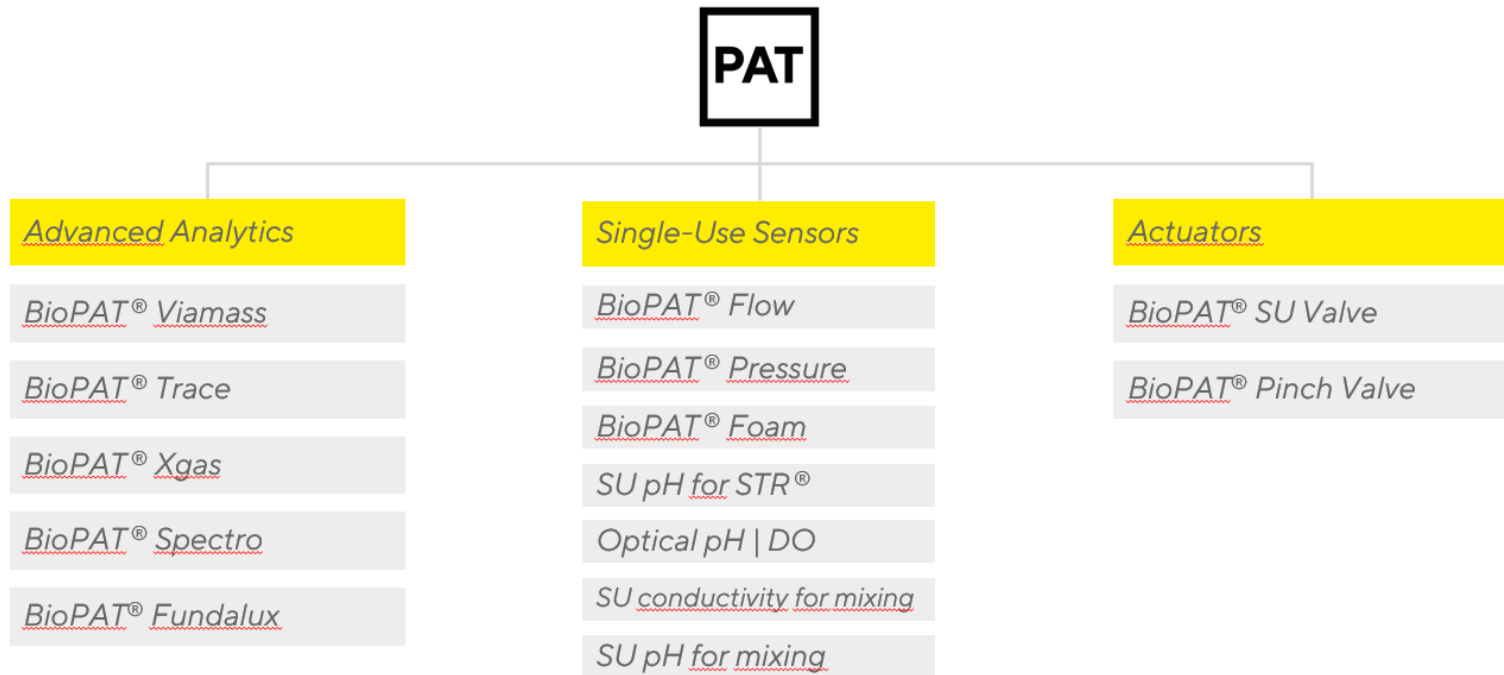
### *Pharma 4.0 will:*

- *Leverage Multi-Variate Data Analytics (MVDA) and process forecasting based on covariant CPP data*
- *Drive the adoption of advanced Model Predictive Control (MPC) as processing becomes more flexible, autonomous, and scalable*
- *Provide a holistic representation of the entire manufacturing process across unit operations*
- *Provide soft sensors: Real-time estimation of Critical Process Parameters (CPPs) & Critical Quality Attributes (CQAs) based on measurements paired with online parameter estimations*
- *Enhance chemometric models: Extract data from multidimensional spectra*
- *Within Biopharma require to improve the mechanistic understanding of the underlying kinetics of advanced biotransformations as well as protein separation & purification*





*→ Closed-loop adaptive model predictive control*

# Sensors in Single-Use Applications



# Overview





# SU sensors in GMP \_ upstream

	<i>Pre-use Calibration   Certificate</i>	<i>Certificate Traceability</i>	<i>Adjustment   Calibration Before Usage</i>	<i>Readjustment During Process</i>	<i>Functional Check of Reusable Transmitters</i>	<i>Functional Check of SU Component</i>	<i>Post-use Calibration</i>
 <p><b>Optical pH</b></p>	<i>lot-wise pre-calibration, 13 sensors of each lot (size:1000) are tested --&gt; calibration parameters for the lot are determined</i>	<i>calibration pH buffers of reference electrode at supplier are NIST certified</i>	<i>1-point adjustment (at current pH) VS external reference</i>	<i>1-point adjustment (at current pH) VS external reference</i>	<i>Signal simulators</i>	<i>plausibility check if amplitude and phase value (raw values of sensor) are within expected range</i>	<i>before/during harvest: take sample and compare to offline reference</i>
 <p><b>Optical DO</b></p>	<i>lot-wise pre-calibration, 13 sensors of each lot (size:1000) are tested --&gt; calibration parameters for the lot are determined</i>	<i>certified gas mixes are used for calibration at supplier</i>	<i>1-point adjustment at 100% air oxygen saturation</i>	<i>theoretically 1-point adjustment possible VS external reference, but procedure prone to high errors</i>	<i>Signal simulators</i>	<i>plausibility check if amplitude and phase value (raw values of sensor) are within expected range</i>	<i>before/during harvest: take sample and compare to offline reference but procedure prone to high errors</i>
 <p><b>SU pH STR</b></p>	<i>each electrode is precalibrated, values printed on label and certificate available via <a href="http://mt.com/pro-certificates">http://mt.com/pro-certificates</a></i>	<i>calibration pH buffers at supplier are NIST certified</i>	<i>1-point adjustment (at current pH) VS external reference</i>	<i>1-point adjustment (at current pH) VS external reference</i>	<i>With pH probe and certified calibration buffers or via pH simulator (no Sartorius product)</i>	<i>check internal temperature probe, pH value can be checked after initialization time in process</i>	<i>before/during harvest: take sample and compare to offline reference</i>
 <p><b>BioPAT@Viamass (SU application)</b></p>	<i>Transmitter: factory calibration of electronics incl. adaption of electronics to SU application based on stastical evaluation of SU components (cell constant)</i>	<i>factory calibration traceable to national or international standards - calibration certificate provided</i>	<i>Zeroing function</i>		<i>Two signal simulators (0 pF/cm, 0 mS/cm, and 100 pF/cm, 40 mS/cm) for calibration check only</i>	<i>plausibility check if capacity and conductivity values are within expected range</i>	<i>take sample at end of process and check at certified offline analyzer /// electronic can be tested again via signal simulators</i>

# SU sensors in GMP \_ downstream

	<i>Pre-use Calibration   Certificate</i>	<i>Certificate Traceability</i>	<i>Adjustment   Calibration Before Usage</i>	<i>Readjustment During Process</i>	<i>Functional Check of Reusable Transmitters</i>	<i>Functional Check of SU Component</i>	<i>Post-use Calibration</i>
 <p><b>BioPAT@Flow</b></p>	<p>Transmitter: precalibrated (calibration tables stored on Flow Clamp-On), calibration report from supplier provided with Clamp-On</p>	<p>measurement equipment from supplier is traceable</p>	<p>Zeroing function (offset correction)</p>	<p>readjustment possible at 0 flow</p>	<p>At connection of Clamp-On transmitter to amplifier unit calibration tables are transferred. If they are displayed the connection is successfully established. /// additionally: Clamp-on sensor can be checked on SU Flow Pipe in an external calibration loop</p>	<p>Coupling can be checked after filling with media. (must be &gt;= 50%)</p>	<p>Clamp-on sensor can be checked on SU Flow Pipe in an external calibration loop</p>
 <p><b>BioPAT@Pressure</b></p>	<p>Transmitter: is calibrated at supplier (test report provided) SU component: statistically qualified</p>	<p>test report according to supplier procedure, test equipment at supplier is regular monitored inspection equipment</p>	<p>Zeroing function (offset correction)</p>	<p>readjustment possible at 0 barg</p>	<p>Transmitter can be checked on SU Pressure Pipe via connected pressure controller at process line or in external test setup (also using a SU Pressure Pipe)</p>	<p>Offset after attachment of SU component onto transmitter can be checked (must be within 100 mbar - 1150 mbar) /// additionally: SU Pressure Pipe can be tested via connected pressure controller at process line (system must be closed, e.g. via valves)</p>	<p>Transmitter can be checked on SU Pressure Pipe via connected pressure controller at process line</p>

# SU sensors in GMP \_ mixing

	<i>Pre-use Calibration   Certificate</i>	<i>Certificate Traceability</i>	<i>Adjustment   Calibration Before Usage</i>	<i>Readjustment During Process</i>	<i>Functional Check of Reusable Transmitters</i>	<i>Functional Check of SU Component</i>	<i>Post-use Calibration</i>
<p><b>pH Mixing</b></p> 	<p>electrode specification is checked at supplier and SU electrode can be identified via serial number</p>		<p>2-point calibration can be performed directly before usage</p>	<p>1-point adjustment (at current pH) VS external reference /// The electrode can be retracted during process and a 2-point calibration can be performed. Then the electrode can be pushed back into the bag. This readjustment can only be performed once.</p>	<p>pH simulator (no Sartorius product)</p>	<p>check mV value in storage buffer: typical value for KCl storage buffer (pH 6.5 @20°C) /// check temperature value</p>	<p>2-point calibration possible (retraction of electrode)</p>
<p><b>Conductivity</b></p> 	<p>precalibrated (cell constant determined at sensor supplier, provided on label on SU component)</p>	<p>usage of certified buffers at supplier</p>	<p>insert cell constant into automation software</p>	<p>not necessary (cell constant does not change as sensor dimensions do not change)</p>	<p>Conductivity simulator (no Sartorius product)</p>	<p>check temperature probe /// plausibility check of conductivity value in process possible</p>	<p>take sample at end of process and check at certified offline analyzer /// transmitter can be tested again via signal simulator</p>

# Usage of sensors in intensified production \_ as an example



# What are intensified processes?

*Process intensification summarizes all processes that are designed to optimize the productivity of unit operations. They all involve perfusion.*

## *Continuous Bioprocess*

- *bleed control*
- *cells are kept in the exponential growth phase at a constant viable cell density (VCD)*
- *the product is constantly removed and further processed from the harvest container*
- *feed and harvest control*
- *process can run for long times*

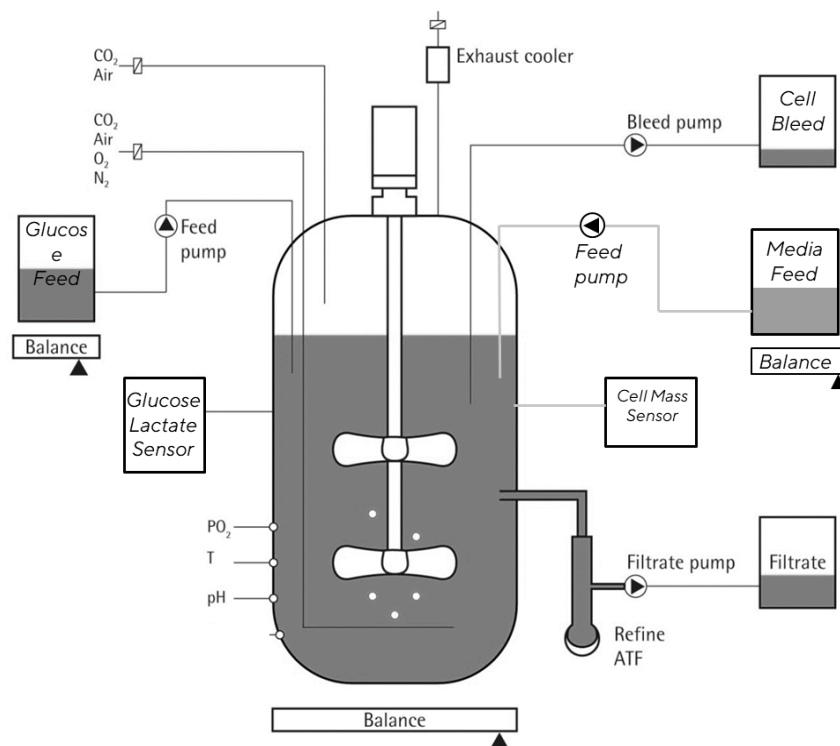
## *Concentrated Fed-Batch*

- *the product is retained in the bioreactor*
- *no bleed control*
- *feed and permeate (filtrate) control*
- *media is constantly exchanged*
- *process runs for a normal time*
- *the VCD and the product titer is higher than in conventional Fed-Batch*

## *N-1 Perfusion*

- *N-1 refers to last seed train bioreactor before the production bioreactor*
- *the product of the N-1 are the cells*
- *goal: Minimize the steps of the seed train and to reach very high viable cell densities*
- *allows seeding the production bioreactor at a higher starting cell density, which shortens the production bioreactor run time*

# Intensified processes can be automated by analytical technologies



## Requirements

- cell retention device
- realtime, robust sensor technologies in-situ
- automated control loops for feed and bleed

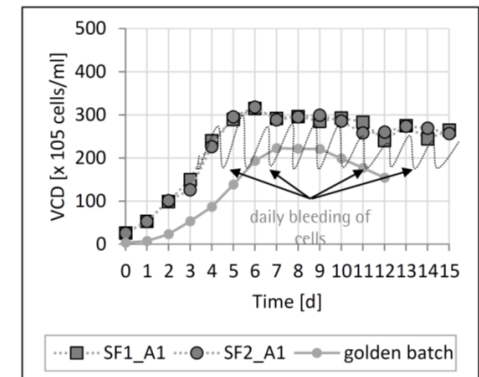
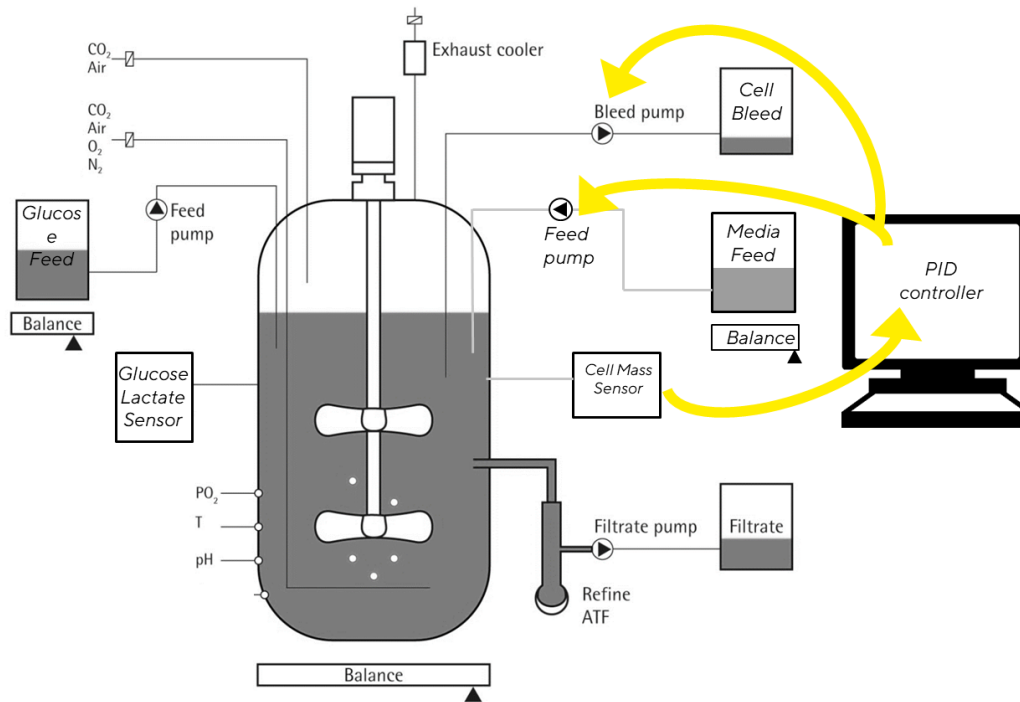
## Advantages of perfusion

- extended process time
- up to 5-fold enhanced productivity per bioreactor
- maximizes product/cell yield
- reduced CoG

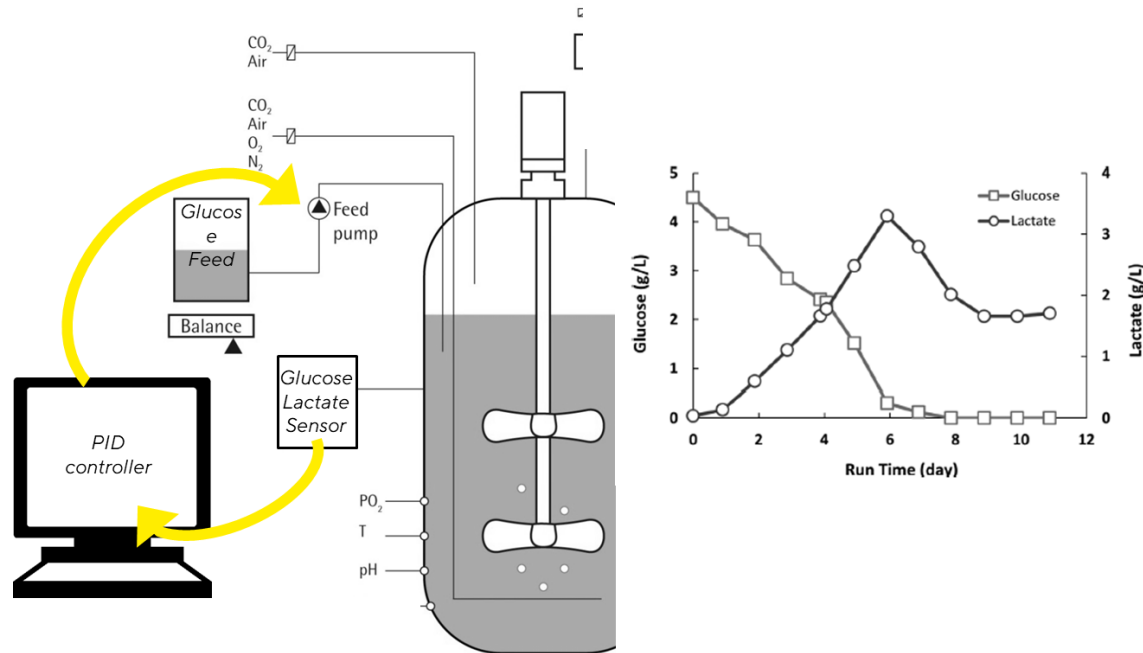
## Advantages of automation

- 100% batch monitoring
- reduced risk of contamination
- free up operators
- increased quality and productivity

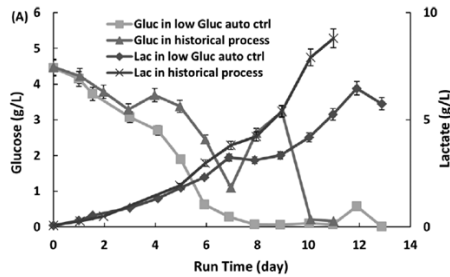
# An inline biomass sensor controls the cell bleed



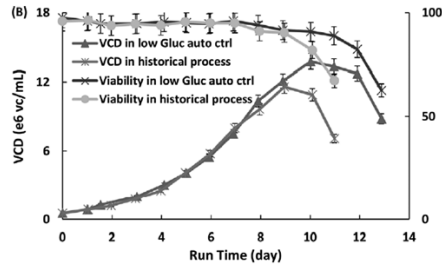
# A glucose/lactate sensor can control a low glucose concentration



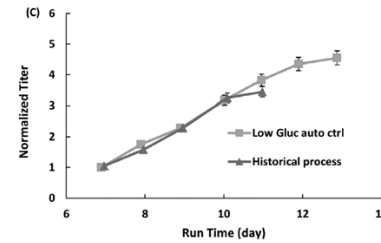
# Low glucose has significant positive impact on product titer and quality



- low glucose control (<0.5g/l) maintains low lactate levels



- low lactate levels lead to higher peak cell density and longer cell viability
- The culture time could be extended by 2 days



- low glucose control results in titer increase (32% overall titer increase)

## Benefits of glucose control below 1g/l:

- longer cultivations
- higher viable cell densities
- increased product titers
- homogenous glycation

## Requirements for low glucose control:

- measurement of both glucose and lactate
- high sampling frequency: min. 30min
- no sample removal required
- easy PID control implementation

Source: Advanced process monitoring and feedback control to enhance cell culture process production and robustness. Zhang et al., *Biogen, Biotech and BioEng*, 2015

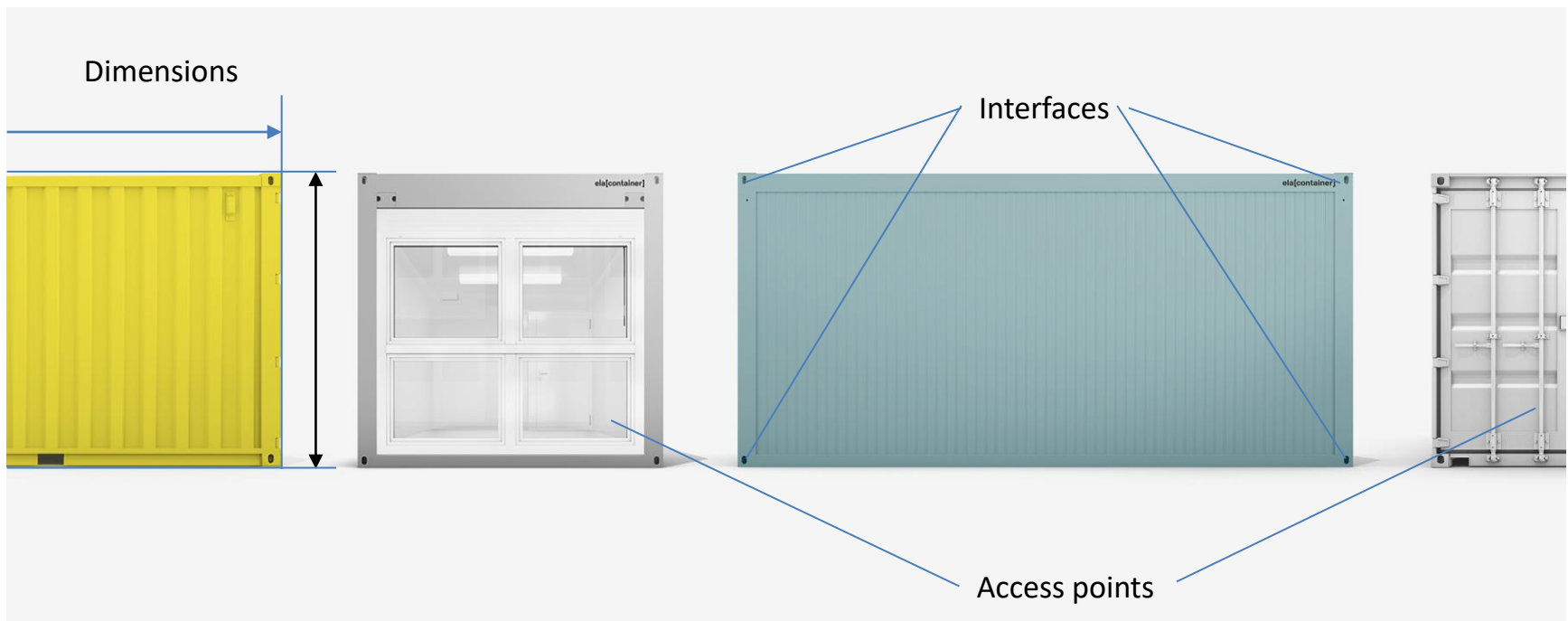
# Automation for Single-Use Applications

How modularization can help future manufacturing concepts

# Modularization needs Standardization



# Example Container



Copyright Sartorius Stedim Biotech



# Benefits of Modularization

## Increase in Efficiency

- container boosted worldwide logistic chains
- interoperability between:  
ships, trucks, airplanes



Copyright Sartorius Stedim Biotech



# Benefits of Modularization (cont.)

## Increase in Flexibility

- SmartHome modules
- fast and easy setup
- flexibility of networks (initial and in lifecycle)
- change functionality of module by parametrization
- easy integration of new appliances
- interoperability between vendors partly given



Bosch SmartHome program

# Modularization in single-use technologies

Past



- High initial cost
- Considerable cleaning effort
- Risk of cross-contamination
- **Mostly dedicated plants with dedicated, 'monolithic' automation**

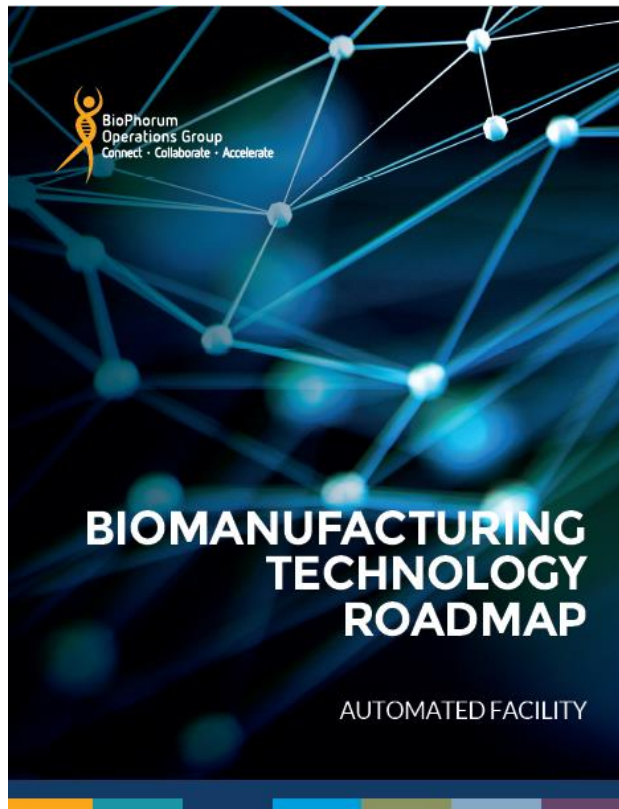
Present



- + CAPEX reduction over entire lifecycle
- + Lower water and energy consumption
- + **Higher flexibility**
- + **Base for flexible manufacturing (ballroom)**
- + **Modularization needed (Hardware & Automation)**

Copyright Sartorius Stedim Biotech

# Automated Facilities need standardized integration to reduce build times of facilities



“  
...  
full integration allows  
quicker and cheaper build times ...”

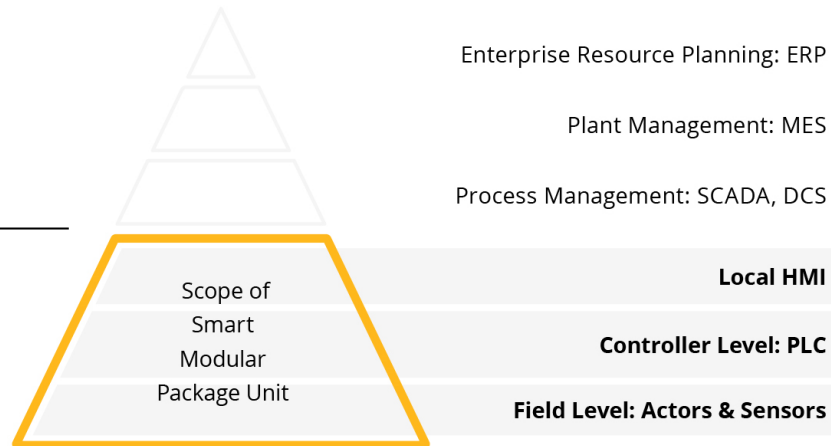
*BPOG Technology Roadmap  
Automated Facility*

# Smart Modular Package Units

- ... focus on local automation of a process step
- ... integrates well into upper SCADA or DCS world
- ... has a range of interfaces
- ... integrates sensors and actuators
- ... form basic controls
- ... offers executable sequences & recipes

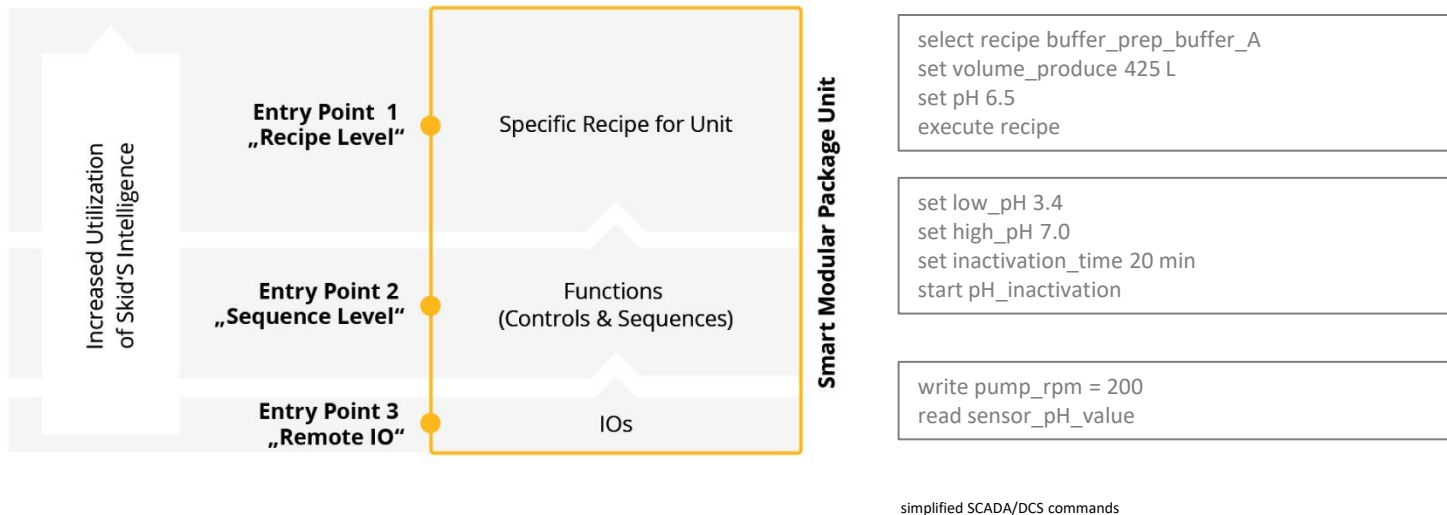


Copyright Sartorius Stedim Biotech



# Integration of package unit into SCADA / DCS - Options

Based on customer requirements different integration options can be used:



# Modular Integration lead to 50-75% time reduction

Activity	Remote IO	Modular Integration
Functional Specification	●	●
Software Design Specification	●	○
Hardware Design Specification	●	○
Module Design and Configuration Specifications (CM/EM/EPH)	●	○
Construction, Coding and Configuration	●	●
Module Design and Configuration Testing (CM/EM/EPH)	●	○
Software Integration Testing	●	●
Hardware Acceptance Testing	●	●
Factory Acceptance Testing	●	●
Site Acceptance Testing	●	●

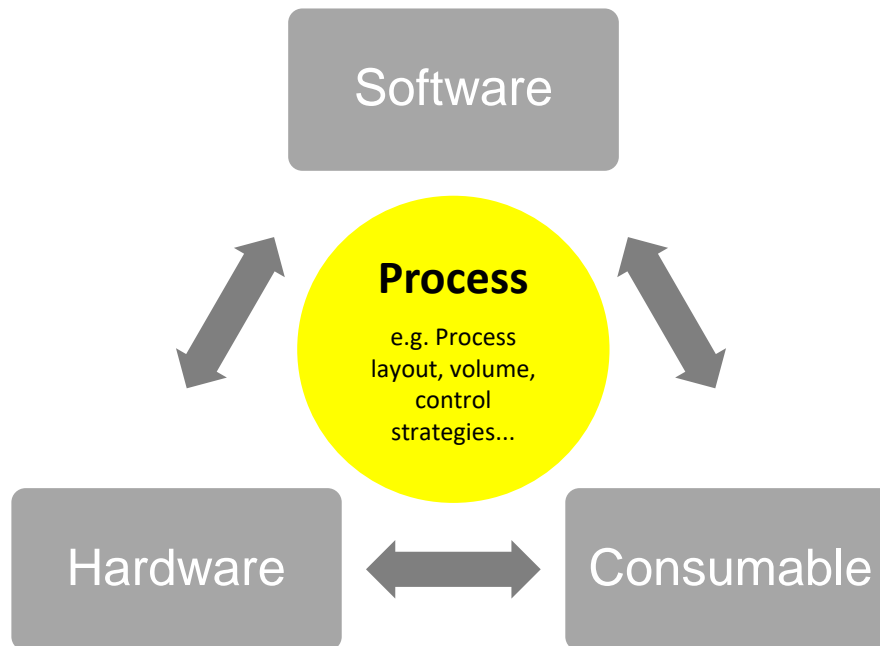
Copyright Sartorius Stedim Biotech

based on entry level 2 – Sequence Level

# Flexibility



# Software, Hardware & Consumables have to follow process requirements

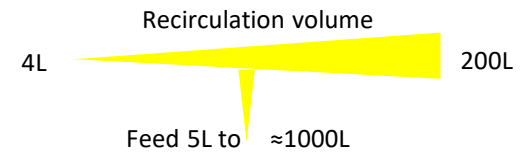


Copyright Sartorius Stedim Biotech



# Case FlexAct® | Crossflow filtration: example parametrization

**Design space flexibility (over 30k variations)**

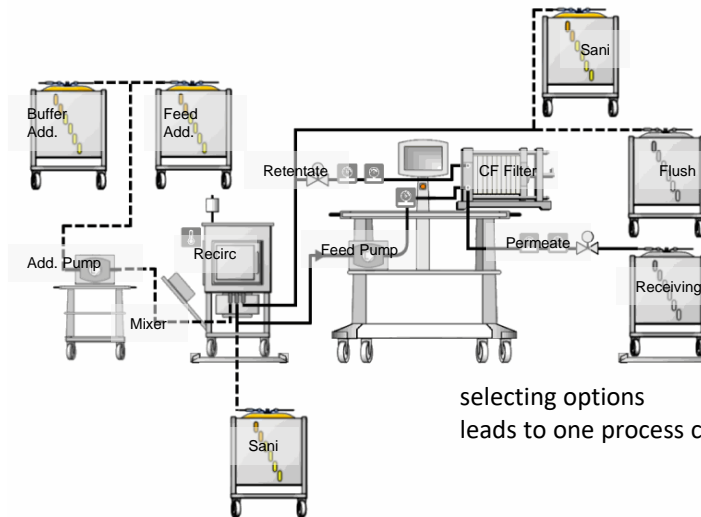


Example options:

Sartorius filter option:  
Membrane material,  
molecular weight cut off or  
3<sup>rd</sup> party filters

Process control  
Temperature control, pH  
and conductivity  
monitoring

Permeate tubing diameter  
½", 3/8" and ¼"

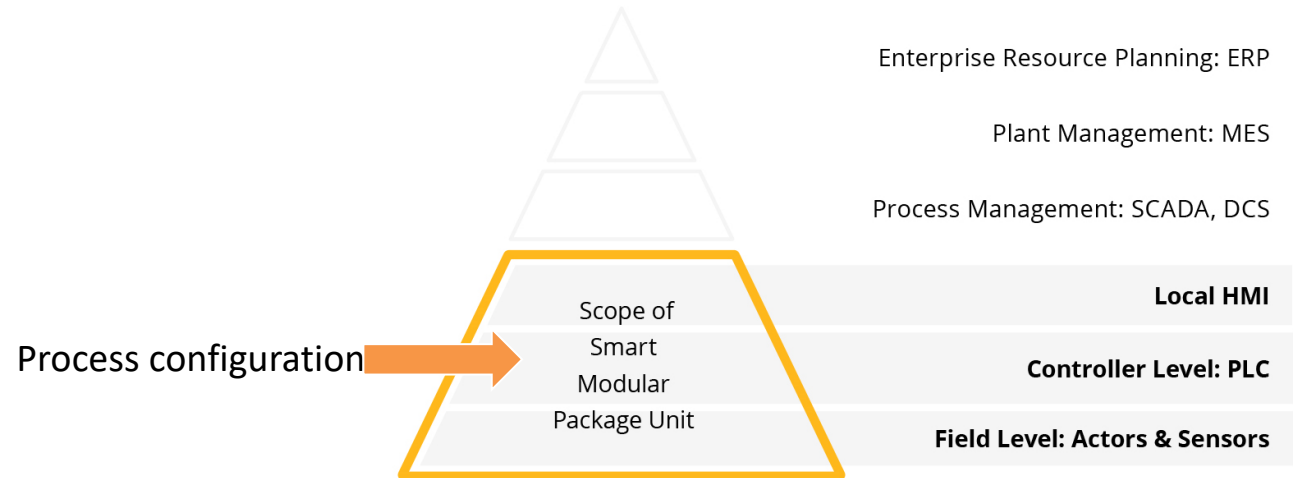


selecting options  
leads to one process configuration

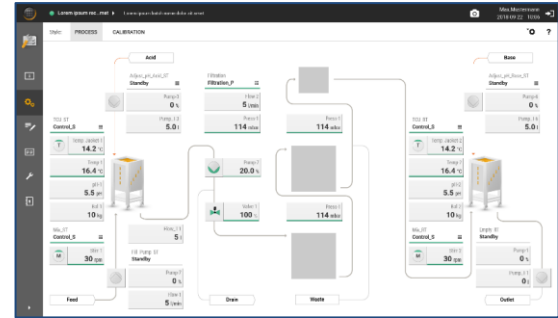
# Automation flexibility

Based on the process configuration, the system will:

- ... change the unit operation e.g. buffer-preparation, crossflow filtration ...
- ... activate the right sensors & actuators including controls
- ... pre-parametrize sequences & recipes
- ... adapt the HMI



# Automation and user interface follows selected hardware and consumables



Change your hardware and consumable set-up

Copyright Sartorius Stedim Biotech

# Local Automation

# Seed train products: Biostat<sup>®</sup> RM and STR<sup>®</sup> powered by Biobrain<sup>®</sup>

- Today a closer look at local automation
- Biopharma customer requirements



# Some definitions

- What's in ?

**Embedded**

Integral part of our bioprocess instrument

**Enable**

Functions needed for the instrument in USP, DSP & FMT

**Local**

Represent the local automation

- What's out ?

**Not a focus on the whole production line**

- Automation of a full production line
- Process Recipe & batch report
- Full process data historian





# Produce as early as possible

*"Time-to-facility is business critical for many commercial manufacturing scenarios"*

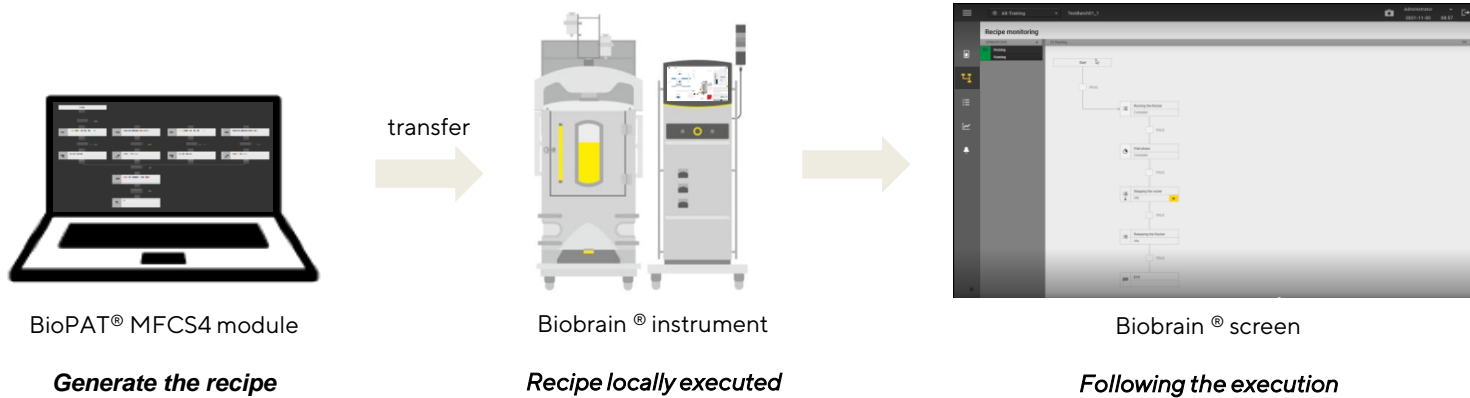
- Produce early with GMP compliance and integrate later
  - Biobrain® GMP stand-alone capability
  - No initial integration
  - Generate batch record, stored and archived
  
- Integrate faster with support
  - Up-to-date OPC UA interface standard in Biobrain®
    - Transfer all recorded process data, alarms & events and audit trails upwards
    - Execute ANSI-88 conform functions in Biobrain® by higher automation systems
  - Detailed documentations & interface consulting service are easing implementation



# Advanced process control reduces risk of batch loss

**“False operator actions are a major root cause for rejected batches”**

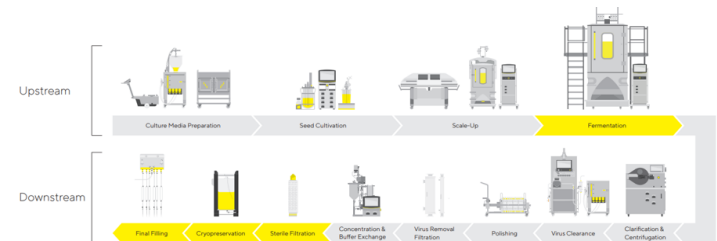
- Automate as much as possible to reduce operator interaction



- Customized recipe service available

## Key for flexible, modular manufacturing concepts

- Modularity does not stop with hardware
- Hardware, Consumable and Software to follow process requirements
- Flexibility is important to adapt for process changes
- Different integration scenarios support:
  - Produce as early as possible
  - Speed up in integration
  - Reduce errors



# Thank You !

Andreas Prediger

Manager Single-Use Sensors

[andreas.prediger@sartorius.com](mailto:andreas.prediger@sartorius.com)  
+49 160 9689 3337

Henry Weichert

Technology Consultant PAT

[henry.weichert@sartorius.com](mailto:henry.weichert@sartorius.com)  
+49 176 1894 1334

Burkhard Joksch

Technology Consultant Automation

[burkhard.joksch@sartorius.com](mailto:burkhard.joksch@sartorius.com)  
+49 176 1894 1356