

CONVERGENCE OF KEY TECHNOLOGIES - TOOLS TO SUCCESS

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Preparation, Separation,
Filtration & Monitoring Products

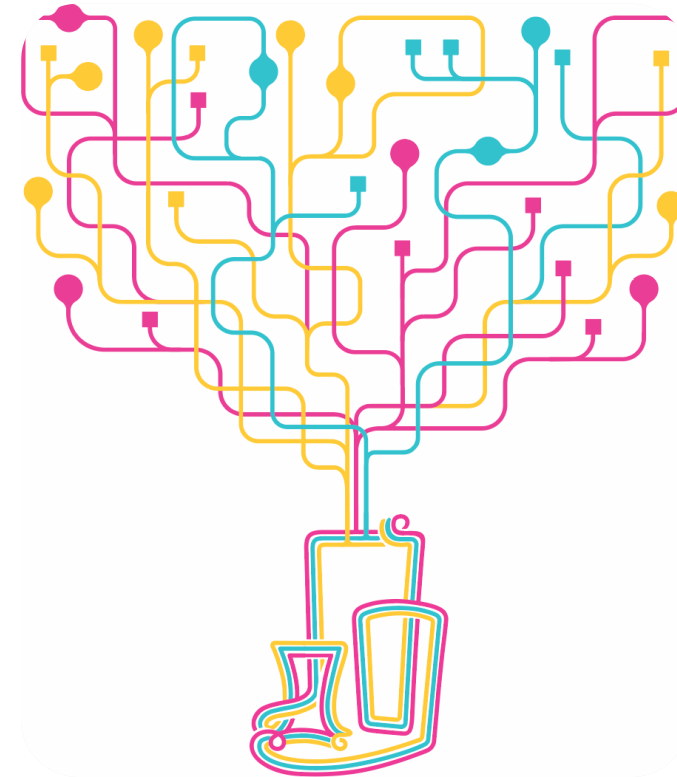


The Life Science business
of Merck KGaA, Darmstadt, Germany operates
as MilliporeSigma in the U.S. and Canada



Agenda

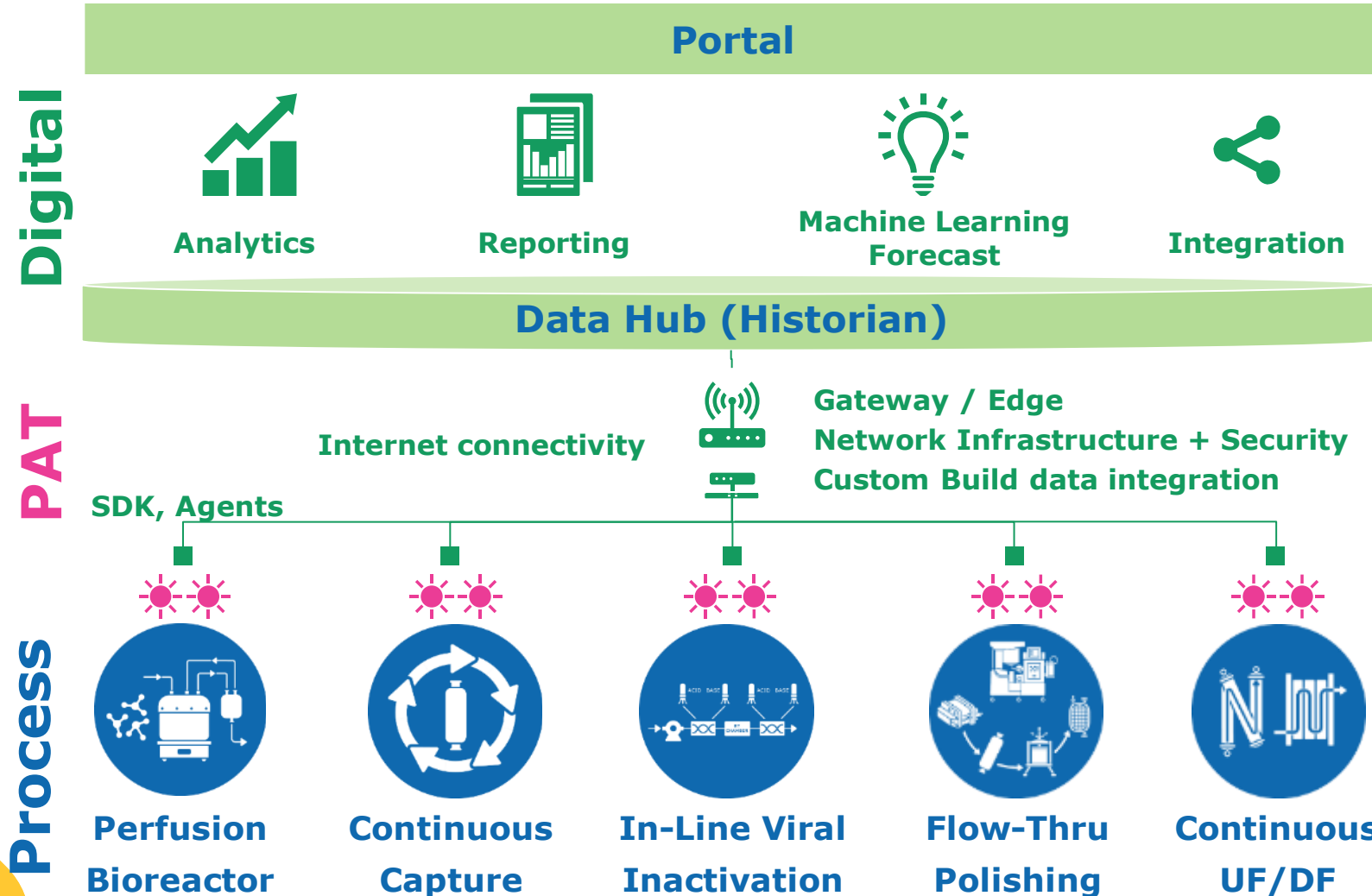
- 1 Convergence of technologies
- 2 PAT using ProCellics™ Raman
- 3 Data Analytics with ProcessPad™
- 4 Automation with Orchestrator
- 5 Q & A



BioContinuum™ Platform Approach

Millipore®

Facility-of-the-Future Requires Convergence across Disciplines



Bio4C™ Orchestrator Software

- Equipment connectivity

Bio4C™ ProcessPad Software

- Data collection and analytics

ProCellics™ Raman Analyzer & Bio4C™ PAT Raman Software

- In-Line/on-line Sensors
- Chemometric modeling software to analyze Raman spectra for realtime process analytics

Processing Technologies

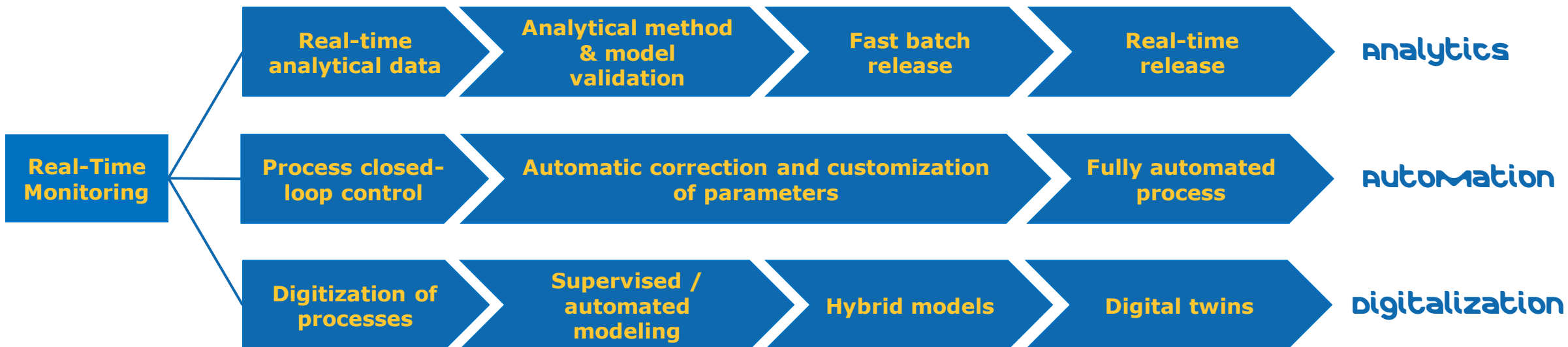
- HW Systems
- Consumables & Device formats
- Single use tech



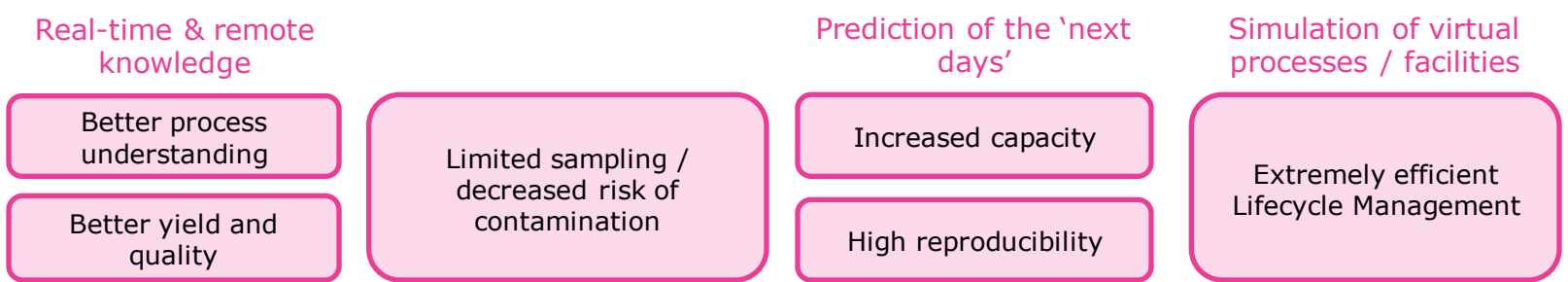
Raman for Bioprocess Monitoring Towards industry 4.0

TODAY

Fully Mature Next
Generation Facility



benefits

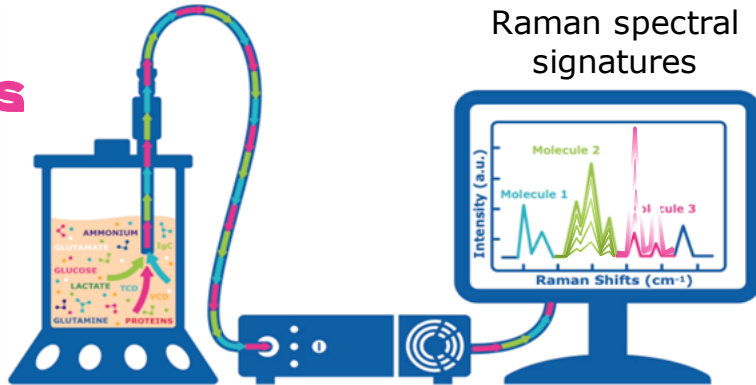


Procellics™ Raman Analyzer

A multi-attribute in-line sensor

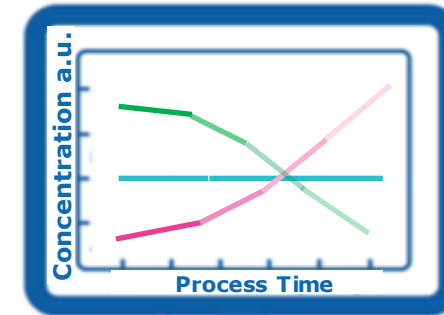
MOLECULE concentrations

Examples:
glucose, titer, VCD, aggregates, others...



Quantitative Monitoring

$$\text{Raman} \propto [C]$$



In-line and real-time monitoring



Process understanding & automated control



Several process parameters measured simultaneously



Excellent selectivity

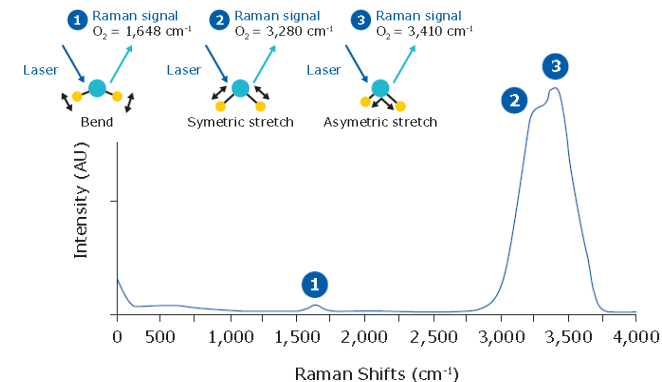


Non-destructive method



Time and resource savings & fast decision-making

Raman effect: incident photons on a substance excite the vibration modes of the molecular bonds and each vibration mode results into the emission of photons at a wavelength difference with the incident light characteristics of this vibration mode.



A global solution for real-time monitoring of bioprocesses

Raman PAT Platform from Process Development to Manufacturing

upstream processes

APPLICATIONS

Cell Culture Media preparation

- Dissolution
- Raw material addition
- Dilution

Bioreactor production (cell culture and microcarrier based cell culture)

- Batch, Fed batch
- Perfusion (N-1, N Steady-state, N dynamics)

Harvest

CPP/CQA

Nutrients like Glucose, Lactate, Glutamine, Ammonium, Amino Acids

Cells: VCD, TCD

Proteins: Protein titer, Glycosylation

Impurity: Aggregates (HMW, LMW), HCP

Three criteria to monitor a parameter or an attribute with a multivariate model

- 1) It is a molecule or related to a set of molecules
- 2) In a sufficient concentration (dependent on process and analyte of interest)
- 3) There is a reference measurement available

downstream processes

Potential APPLICATIONS

Chromatography

Viral inactivation

TFF, buffer exchange

Polishing: CEX and AEX

Mixer (static measurement)

CPP/CQA

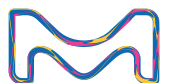
Proteins: Protein concentration (Monomer), Glycosylation

Impurity: Aggregates (HMW, LMW), HCP, DNA

Challenges

Low concentration and **variability in concentration**

High DOE is requested



ProCellics™ Raman Analyzer Benefits

High ingress protection:
The analyzer is IP65 enclosed preventing ingress of dust and water jets from any angle.

Adaptable:
Six meters of optical cable between the analyzer and the probe allows for flexibility in placement and ease of use.

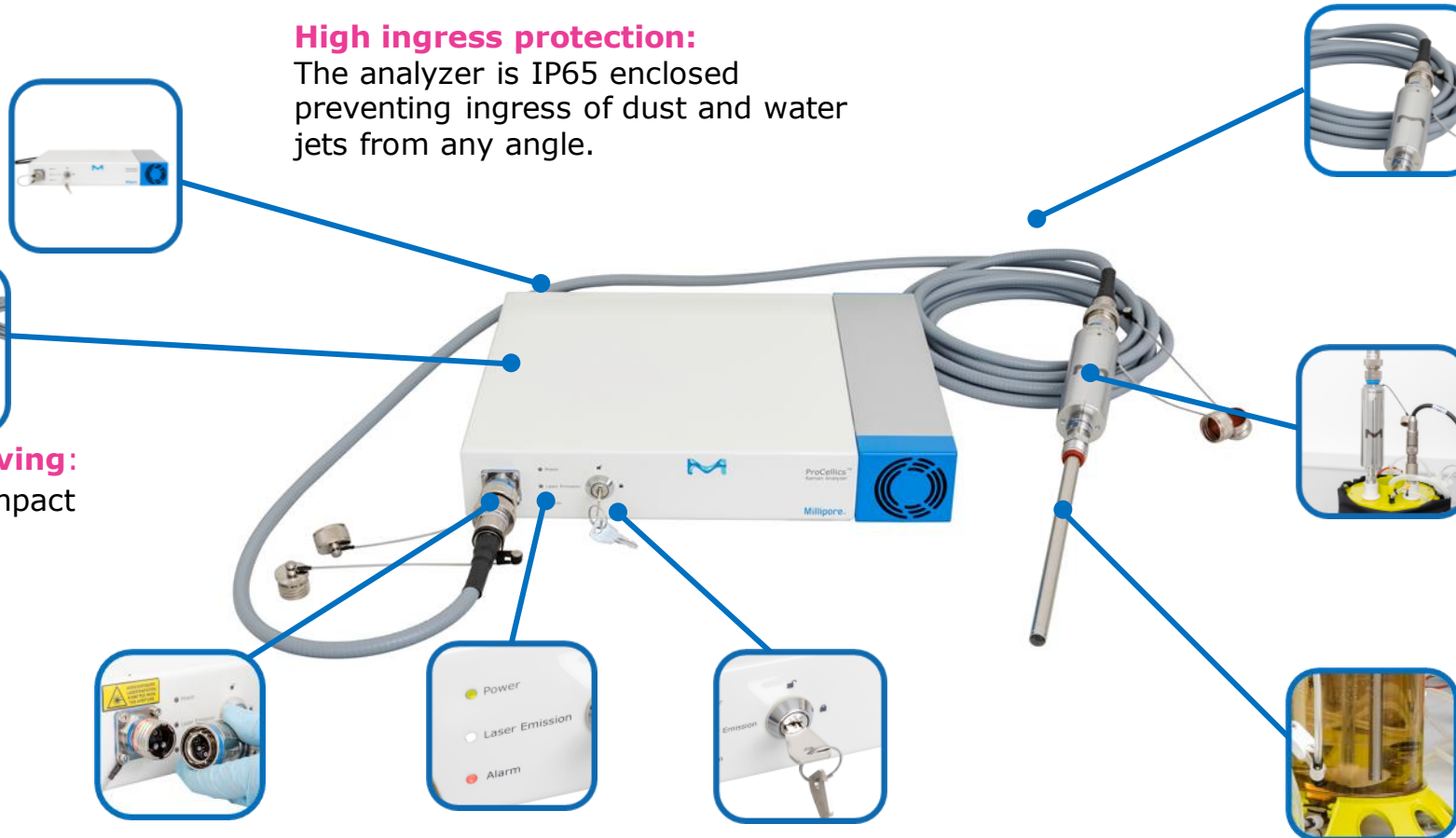
Space-saving:
Small, compact footprint

Easy implementation:
The probe head and tube can be easily assembled and disassembled. The probe tube (12 mm diameter) and its port adapter (PG13.5) are compatible with standards ports of single-use bags and bioreactors.

CIP/SIP compatibility:
The stainless-steel immersion tube is compatible with CIP/SIP and autoclave sterilization.

Interlock systems – Warning lights – Laser key control

User safety: The safety laser management system protects personnel from accidental exposure to possible laser hazards.



A global solution for real-time monitoring of bioprocesses

Hardware

ProCellics™ Raman Analyzer

Single Channel (1 probe)



Multi-Channel (4 probes)



Software

Bio4C® PAT Raman Software



Bio4C® PAT Chemometric Expert



OPC Compatible

Support

Facilitates user experience



Customer evaluation
1-2 months



Expert support package
10 days



On-site
Training



Chemometric
Model Building
Training

Services

A valuable service offering



IQQQ



Service
Plan

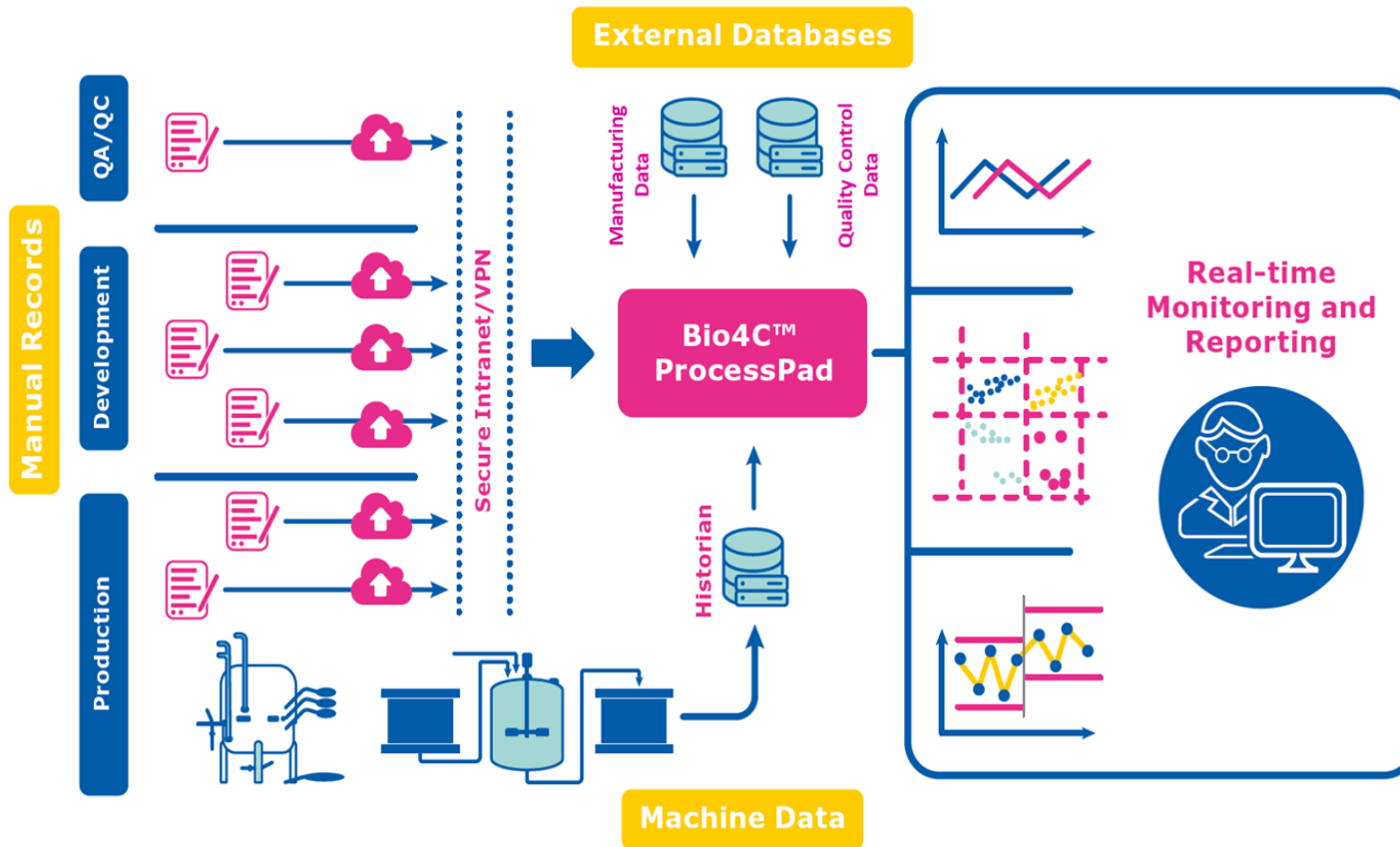


Spare
Parts



Effective Data Management Platform for Acquisition, Aggregation, and Analysis of Process Data

Bio4C® ProcessPad™



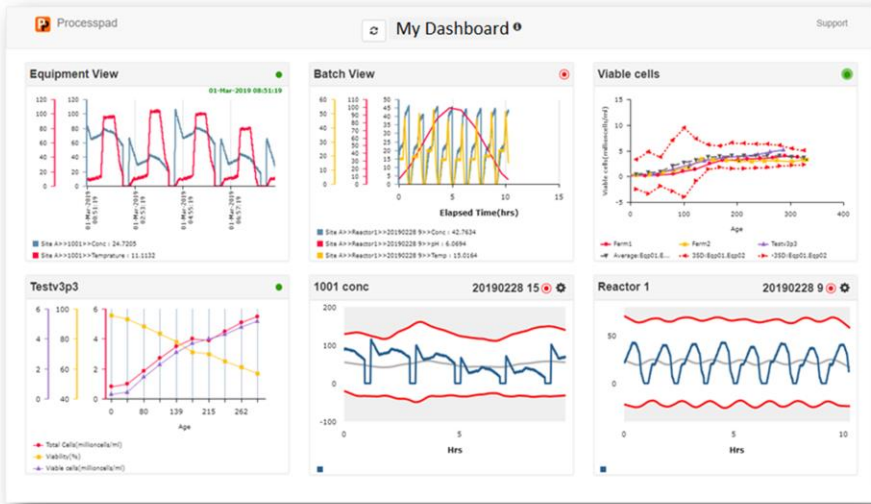
CORE CAPABILITIES

- Easy to use and quick to deploy
- Manual and automated machine data capture
- Facilitates regulatory compliance
- Visualizations and process monitoring
- Statistical Process Control & Charting
- Configurable Reporting
- MVDA-PCA/PLS
- Data sharing & collaboration
- Ready to use data format



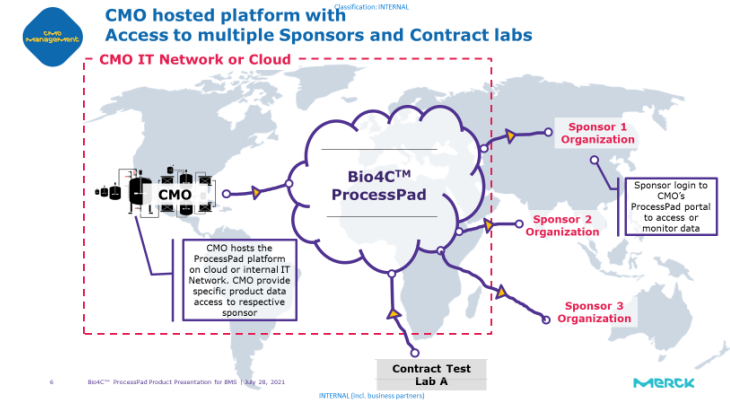
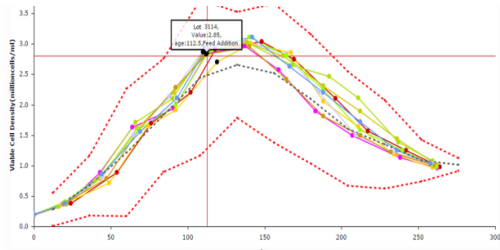
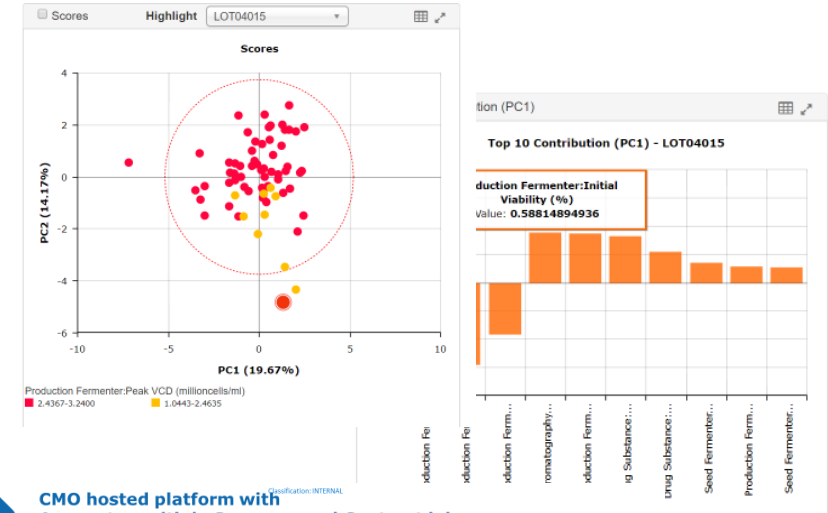
Applications for Bio4C[®] ProcessPad

Millipore[®]



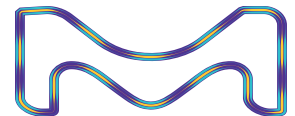
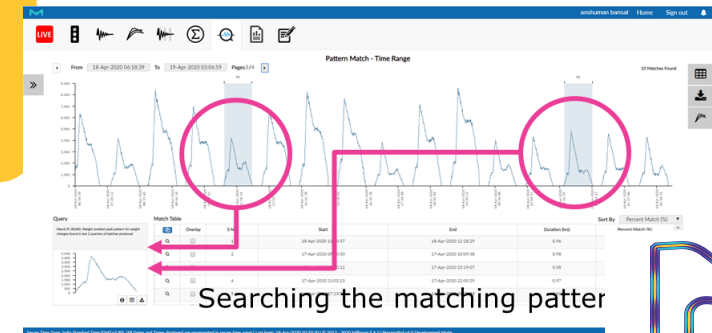
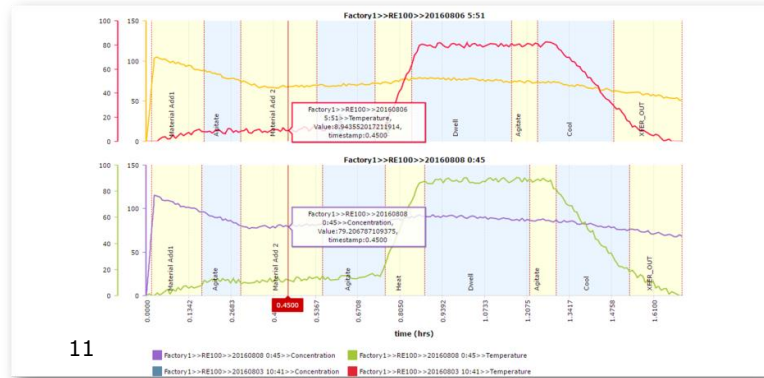
continued process verification

PROCESS MONITORING
Scale up/tech transfers/Multisite monitoring



Annual product quality reviews

Investigations



How Bio4C® ProcessPad™ Software Helps



process lifecycle Management

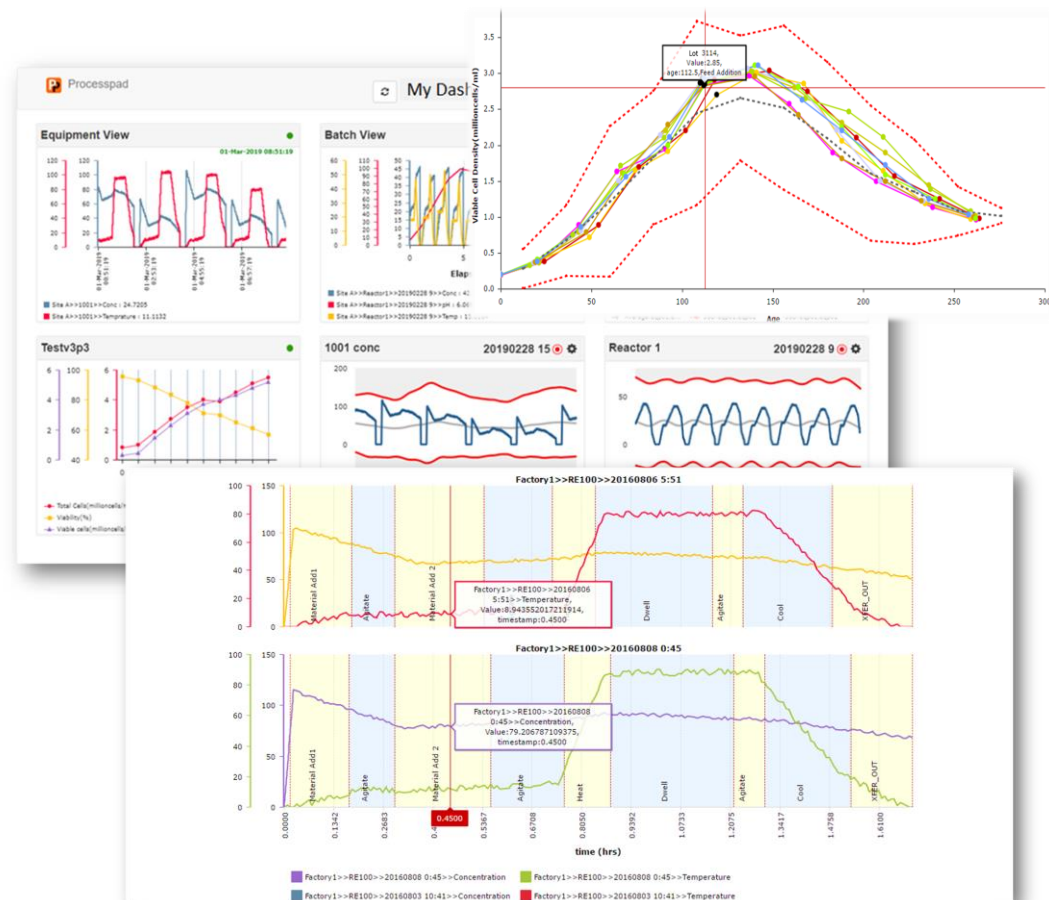
- Capture all development, scale-up, and commercial data on one platform
- Simplify tech transfer process
- Access to the latest version of process map

continued process verification and analytics

- Aggregate real-time and offline process data
- Statistical process control (SPC) and process capability
- Preconfigured trending rules to aid process monitoring
- Process analysis tools to aid investigations & process troubleshooting
- Control limits management

Reporting

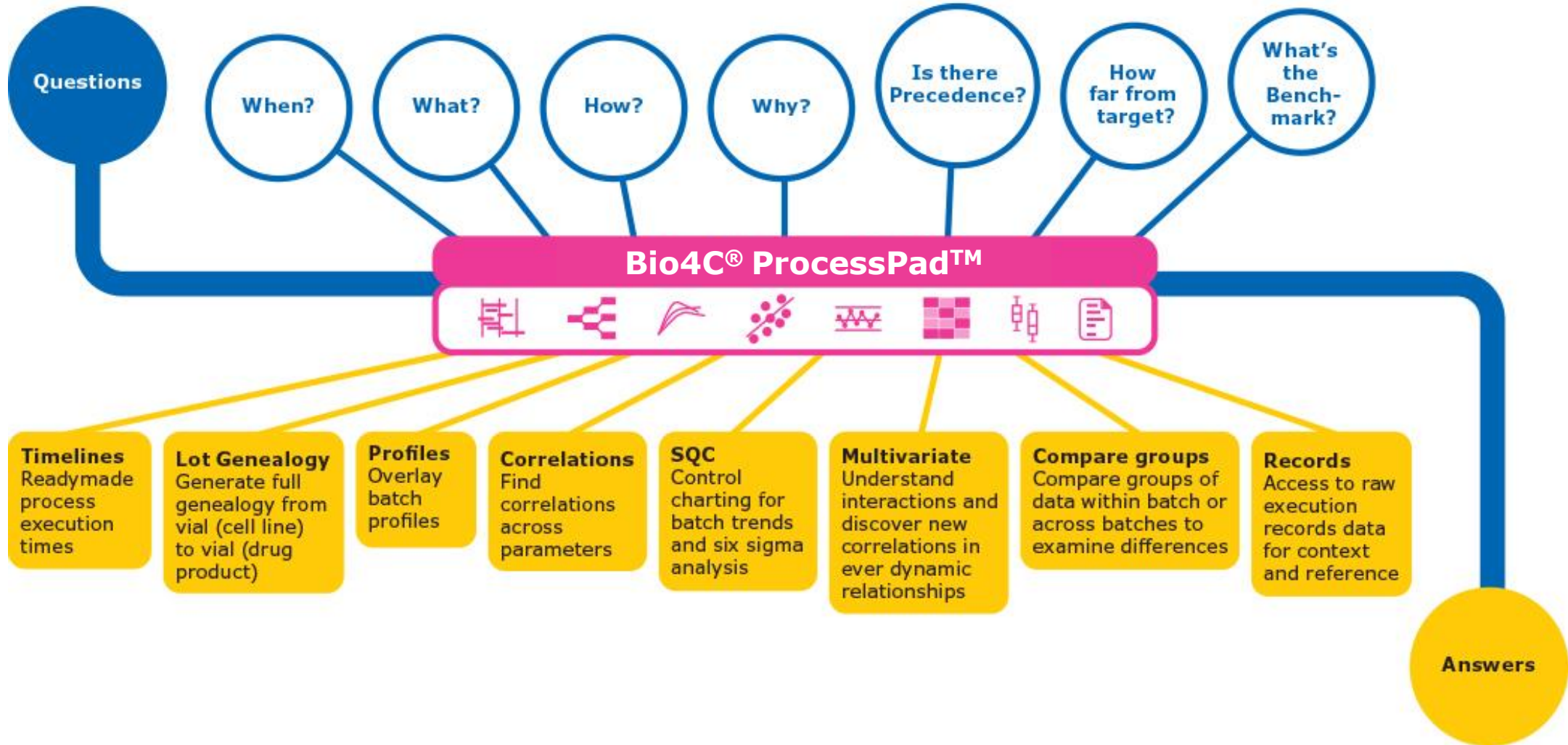
- Generate process summary reports
- Create ad-hoc reports required in root cause investigations
- Batch excursion reports, equipment utilization



Through data aggregation, management, visualizations, and analysis, Bio4C® ProcessPad™ makes all critical bioprocess data readily available.



Toolset for Efficient Process Troubleshooting

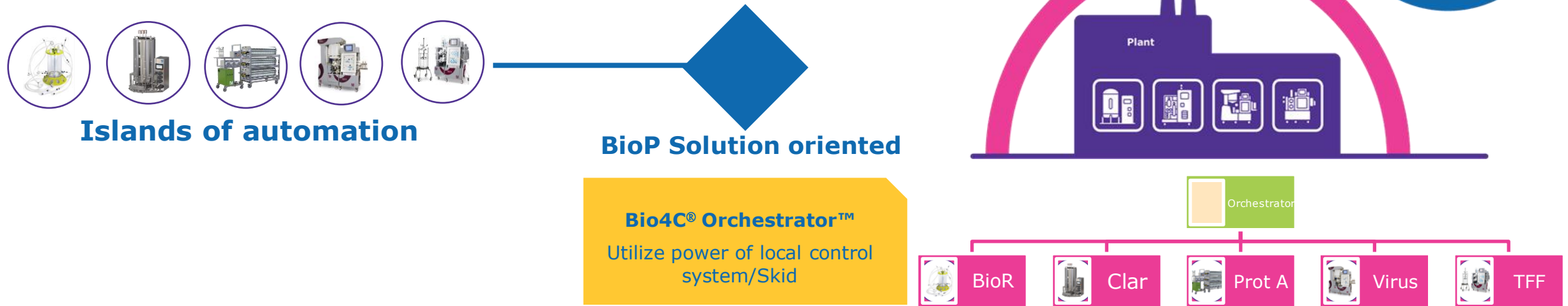


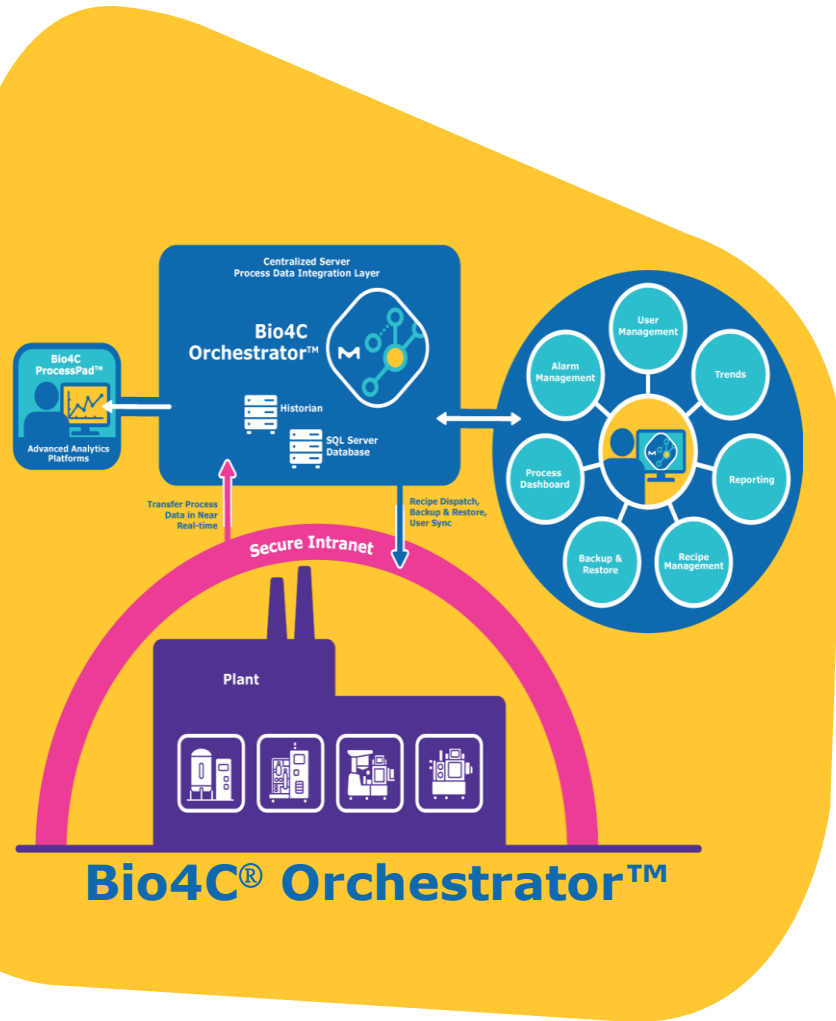
Bio4C® Orchestrator™ :



Transitioning from Islands of automation to digitally connected plant

Technology landscape and our approach





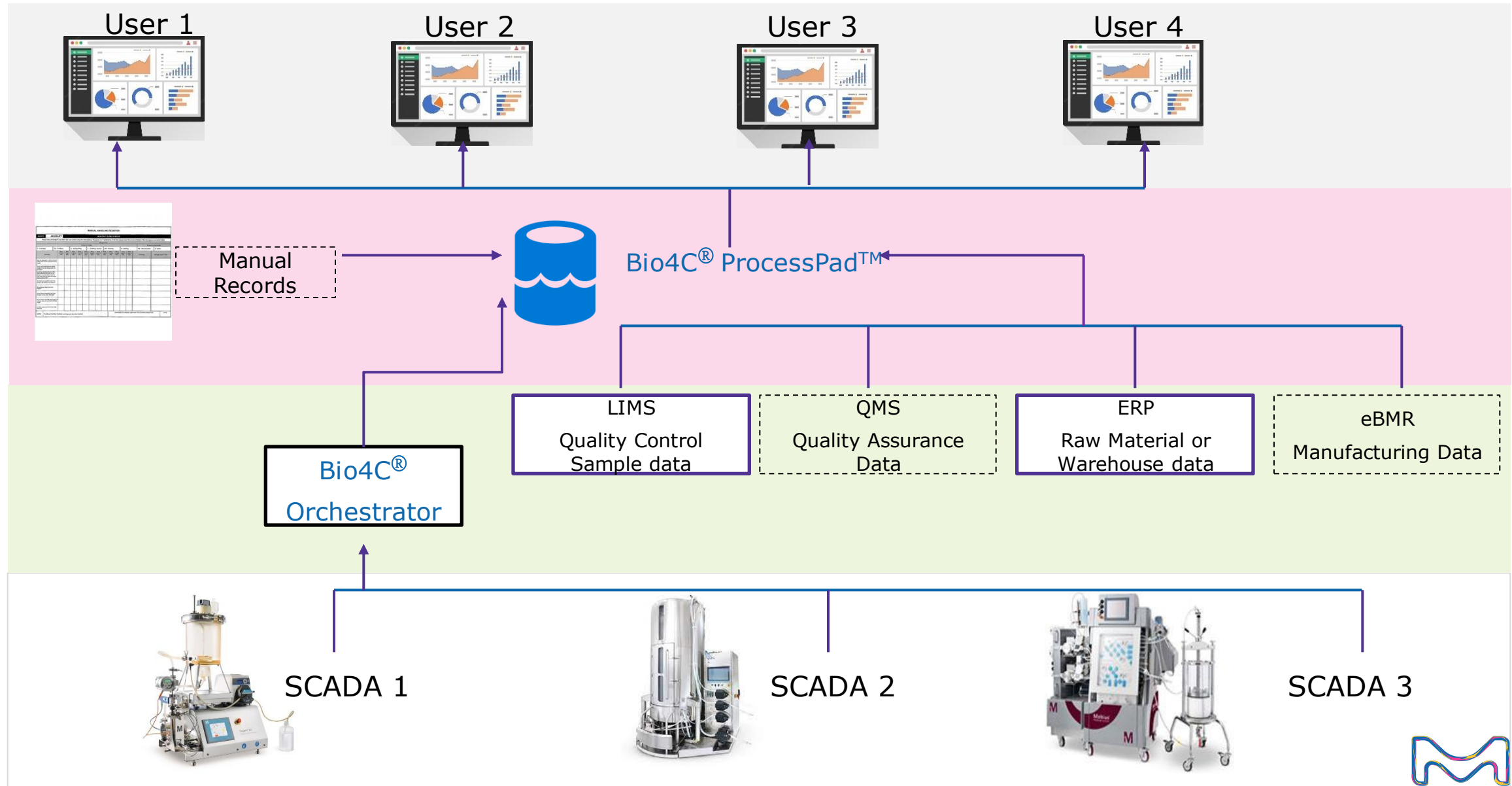
Overview of the capabilities

- Standard & configurable vendor agnostics connectivity with process equipment
- Open platform to integrate with other application such as historians, MES, BES etc.
- Enables IT/OT convergence through vertical integration between shop-floor to top floor.
- Centralized platform for effective data acquisition, efficient trend monitoring, unified visibility and monitoring of regulatory-compliant biomanufacturing systems and processes
- Provides remote access to systems, recipes, reports, user accounts, and alarms from a centralized process dashboard
- Browser-based to extend accessibility and data sharing across the entire organization
- Process data management and configurable reporting
- Access to contextualized data for further consumption (EBR, Analytics Software)

While out-of-the-box capabilities are differentiator, we are open for service driven customization to meet specific need of the customer



Connectivity with Bio4C® Orchestrator™ and ProcessPad™



Conclusion

1

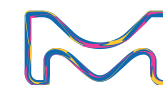
Facility of the Future and Industry 4.0 require convergence of process technologies, automation, PAT, and data analytics

2

Online PAT and real-time data analytics are key drivers for better process efficiency, robustness, and product quality

3

People, Process, and Data continues to be invaluable assets



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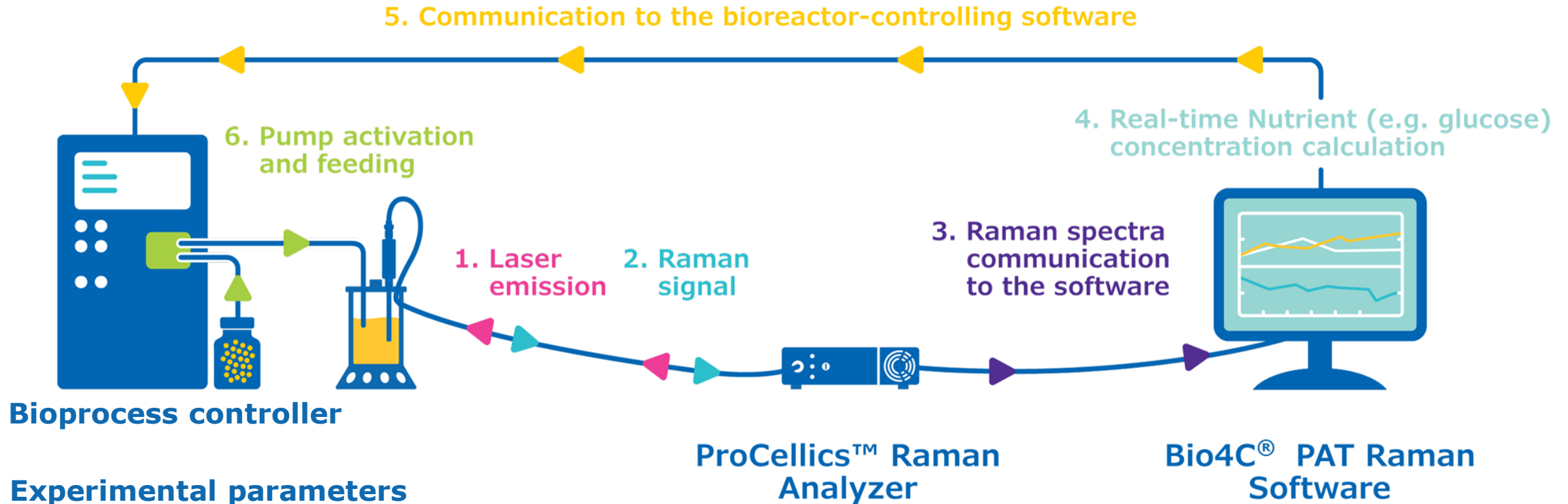
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**PROCELICS RAMAN
technology
– use cases**



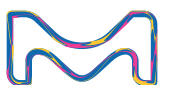
Use Case: Auto Feeding Strategy in CHO Cell Culture (1/3)

Towards automation of bioprocesses



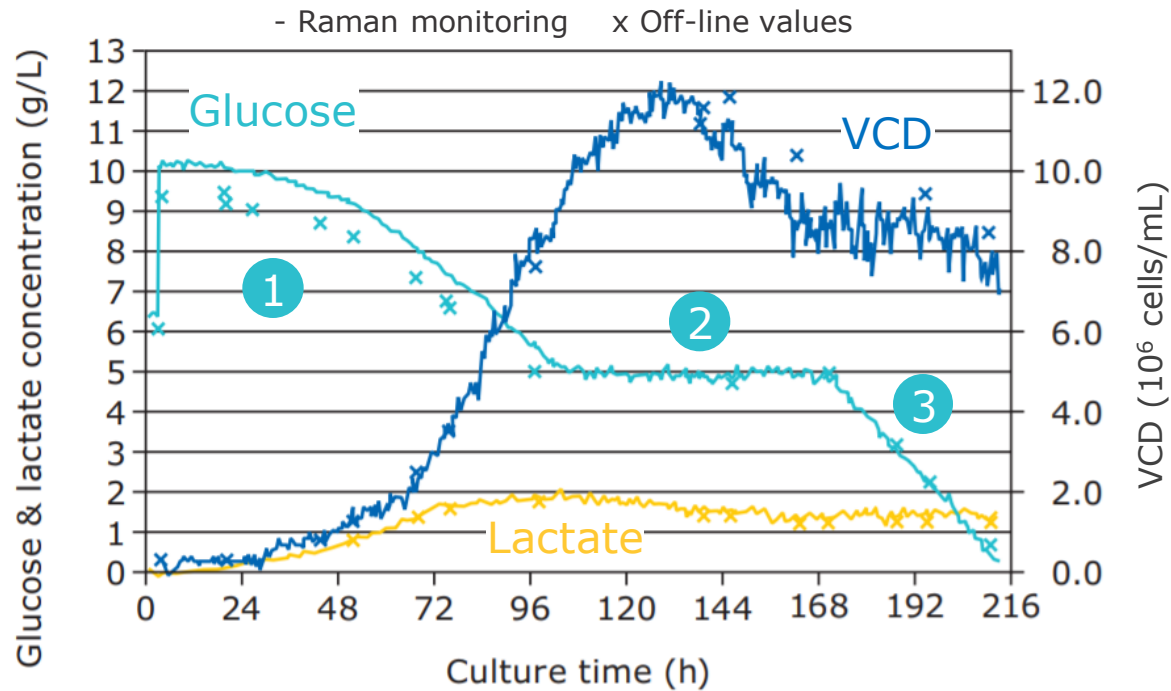
Experimental parameters

- CHO-S cells (up to 12 Mcells/mL)
- CD-CHO medium
- Fed-batch (5 L bioreactor)
- Model trained on four batches (103 points)



Use Case: Auto Feeding Strategy in CHO Cell Culture (2/3)

Towards automation of bioprocesses



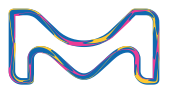
Parameter	Concentration range	RMSEP	Relative error
Glucose (g/L)	0.1 – 9.5	0.6	6%
VCD (MCells/mL)	0.3 – 11.9	0.6	5%
Lactate (g/L)	0.1 – 1.8	0.2	8%

Results

- 1 Glucose was consumed by the cells until the minimum until the minimum set-point of 5 g/L
- 2 Glucose concentration was precisely maintained at 5 g/L for 3 days by the programmed feedback loop
- 3 Feeding was stopped when maximum vessel volume was achieved and glucose down to 0 g/L

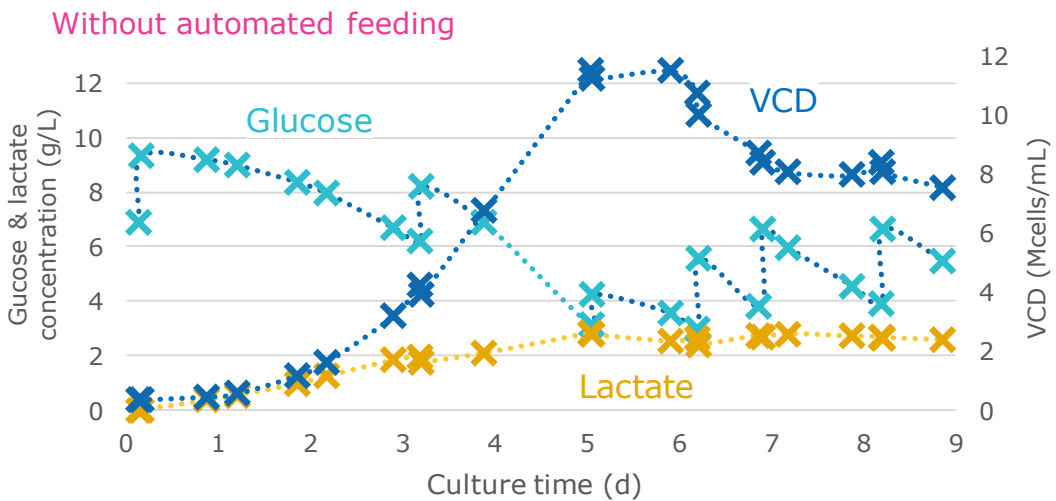
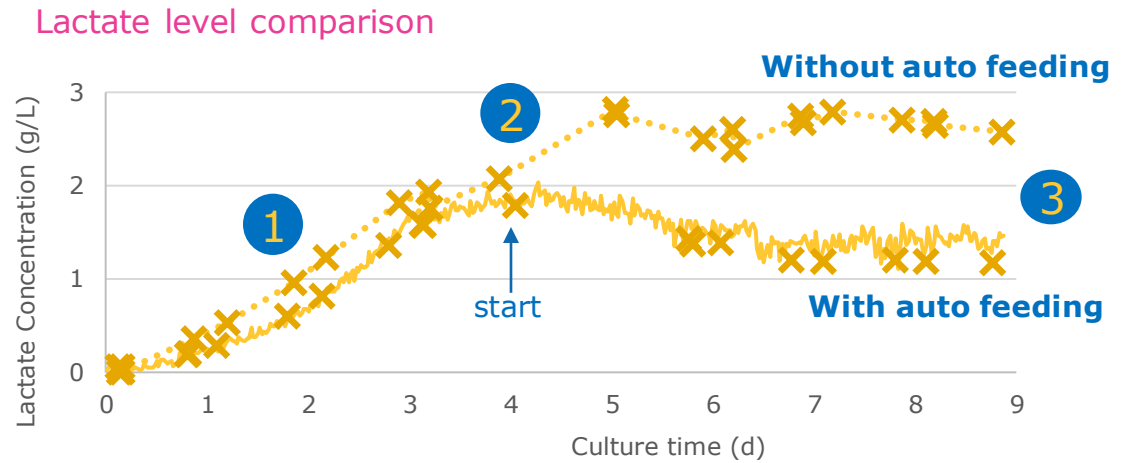
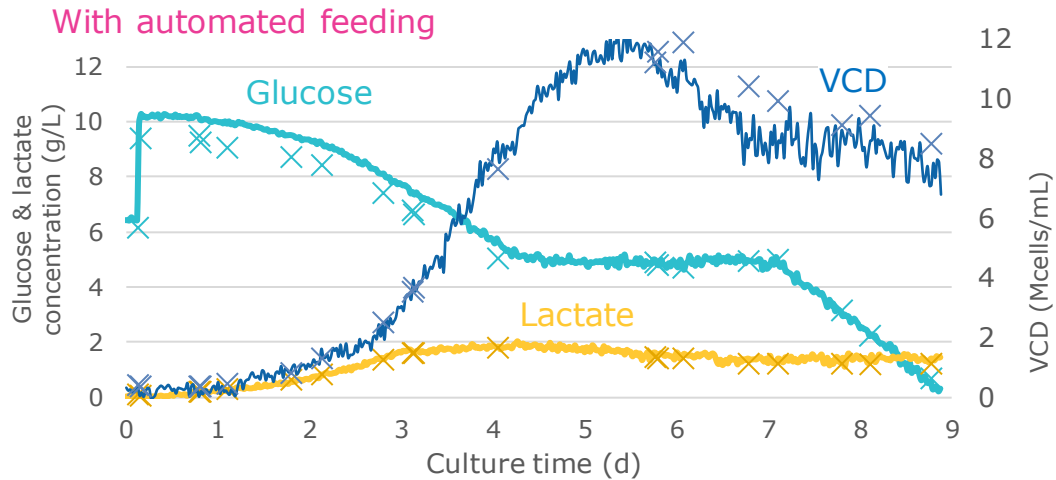
An extremely stable glucose concentration was achieved along with accurate measurements by the Raman analyzer.

For more details, please refer to [this application note](#).



Use Case: Auto Feeding Strategy in CHO Cell Culture (3/3)

Towards automation of bioprocesses



Results

- 1 Similar lactate kinetics before starting auto feeding
- 2 Change of lactate kinetics from the start of the automated feeding
- 3 35% decrease in lactate with automate feeding

An extremely stable glucose concentration seems to decrease the lactate concentration.
For more details, please refer to this [application note](#).



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BIO4C PROCESSPAD – USE CASES



Use Case 1:

Multi-Product, Multi-Site Commercial Manufacturing

Background:

- Multi-national pharmaceutical company with multiple manufacturing sites across geographies
- Adopted Bio4C™ ProcessPad Offline module to solve their business challenges with process data management & regulatory reporting requirements

Business Goals

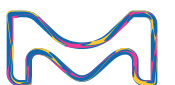
- Software platform for CPV, Annual reporting, process investigations and robustness

Scope of Implementation

- 20 manufacturing sites
- 16 Admins
- ~350 users
- ~1650 products

Business Outcomes

- Structured and robust CPV program meeting compliance needs
- Improvement in Quality Metrics
- Ready access to data for process investigations/root cause analysis leading to positive impact on operational metrics



Use Case 2:

Multi-Product Biologics Manufacturing Site

Background:

- Multi-national pharmaceutical company with commercial manufacturing of several biologics products
- Adopted Bio4C™ ProcessPad Offline and Realtime modules for centralized data gathering and statistical data analysis

Business Goals

- Software platform for regular process monitoring and troubleshooting, investigations and statistical data analysis

Scope of Implementation

- 6 Manufacturing Suites and 1 Process Development Suite
- ~50 Users
- ~15 Products

Business Outcomes

- Process Optimization driving yield improvements and batch to batch consistency
- Process Lifecycle Management capturing all development and commercial data on single platform
- Improved process understanding and knowledge leading to proactive response to issues
- Regular Process Robustness Review and reporting



THANK YOU

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