10-9-2019

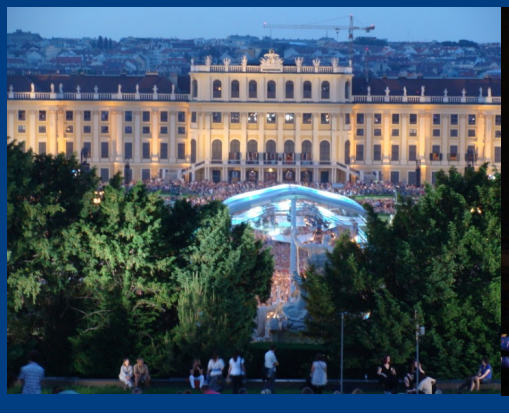
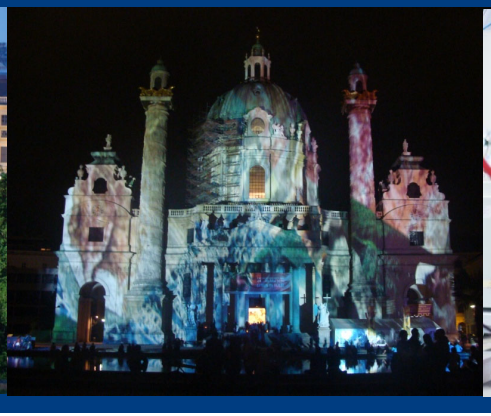
Control strategies for integrated continuous bioprocessing

Christoph Herwig

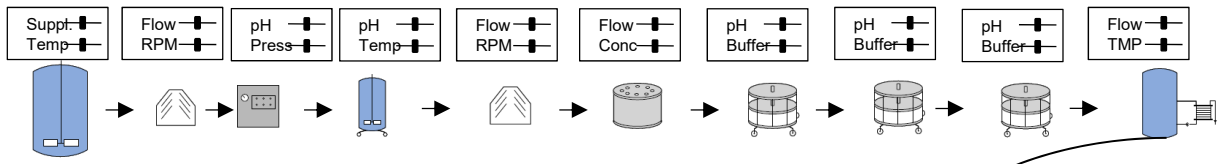
Control strategies for integrated continuous bioprocessing

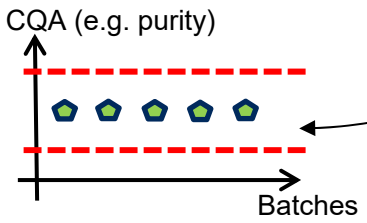
Christoph Herwig

Brewster, 9.10.2019


How to Manufacture Product with Consistently High Product Quality?

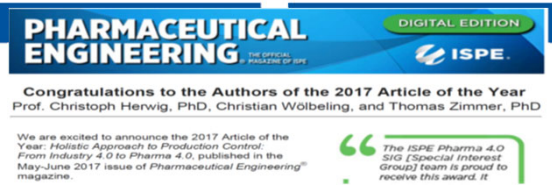




Critical Quality Attributes (CQAs):

- pH
- Particles
- Purity/ Content uniformity
- Impurities (Endotoxins, HCPs, DNA)
- …

ICH Q12 motivation: Life Cycle Management!
Need for Holistic control strategies

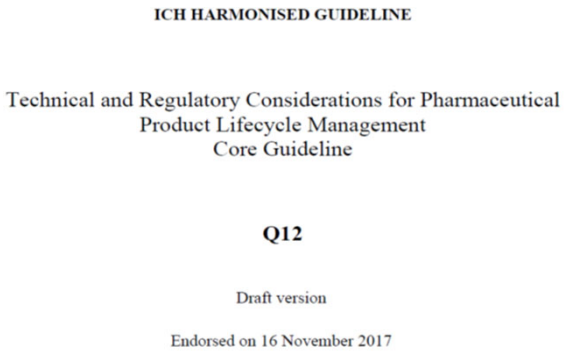

PHARMACEUTICAL ENGINEERING
DIGITAL EDITION
ISPE.

Congratulations to the Authors of the 2017 Article of the Year
Prof. Christoph Herwig, PhD, Christian Wölbeling, and Thomas Zimmer, PhD

We are excited to announce the 2017 Article of the Year: *Holistic Approach to Production Control: From Industry 4.0 to Pharma 4.0*, published in the May-June 2017 issue of *Pharmaceutical Engineering*® magazine.

The ISPE Pharma 4.0 SIG [Special Interest Group] team is proud to receive this award. It

ICH Q12: Established Conditions (ECs)



ICH HARMONISED GUIDELINE

Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
Core Guideline

Q12

Draft version

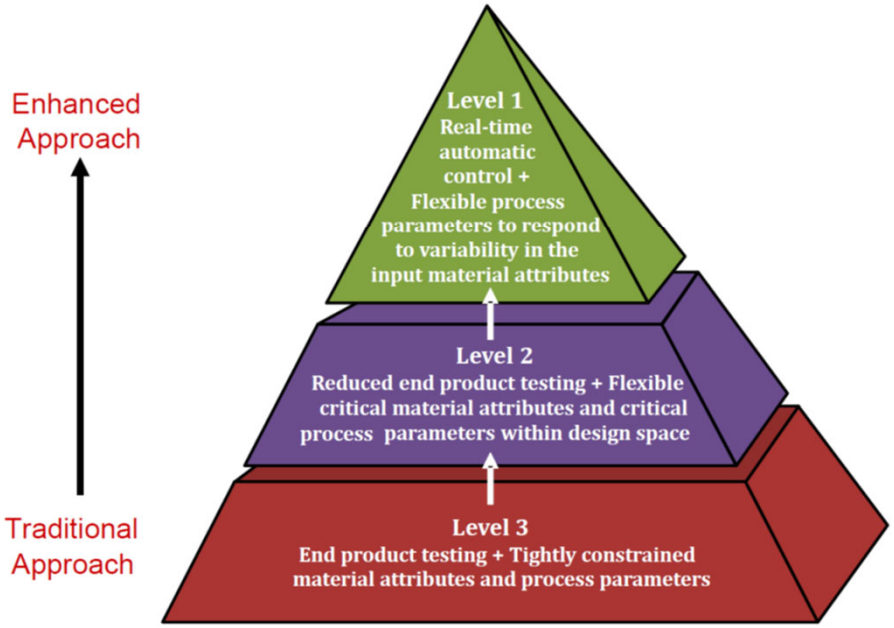
Endorsed on 16 November 2017

EC for Manufacture and Control are binding information or elements in the dossier concerning the manufacture and control of a pharmaceutical product

EC may vary in their level of detail:

- A **parameter based approach**, in which product development prior to regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process controls).
- An **enhanced approach** with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate.
- In certain cases, applying knowledge from a data-rich environment enables a **performance based approach** in which ECs could be primarily focused on control of unit operation outputs rather than process inputs (e.g., process parameters and material attributes). For example, a performance-based approach could be considered for manufacturing process steps with in-line continuous monitoring (e.g., using appropriate process analytical technologies such as NIR for the control of a blending process).

ICH Q12 Performance Based Approach: Process Control Strategies based on Digital Twins



Lawrence Yu
3rd PQRI/FDA Conference on Advancing Product Quality, March 22-24, 2017

Control Strategy Tasks

- Declare Established Conditions along ICH Q10 and ICH Q12 along the product life cycle

- Need for workflows for Digital Twin Generation and Adaptation

- Case Studies
  1. Benefits of Model Predictive Control (intensified Fedbatch)
  2. Obstacles for Continous Upstream Biomanufacturing
  3. Benefits of Digital Twins for Integrated Continuous Process Design

Your PE Article has been awarded the 2018 Roger F. Sherwood Article of the Year Award!

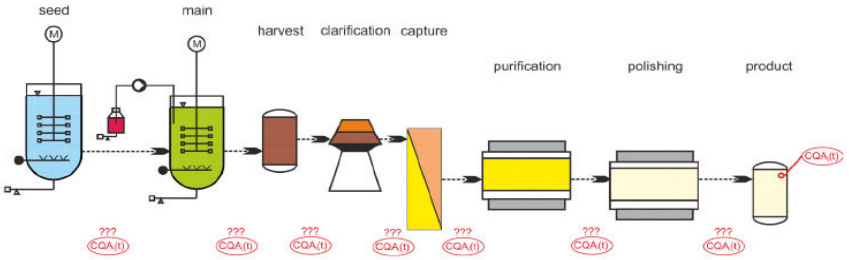
8.10.2019

Robert, Christoph, and Emilie,

Your article, "Continuous Manufacturing in Biotech Processes: Challenges for Implementation," has been named the 2018 Roger F. Sherwood Article of the Year!

Congratulations and thank you for your contribution to the industry and to ISPE.

https://ispe.org/pharmaceutical-engineering/about/article-year-award



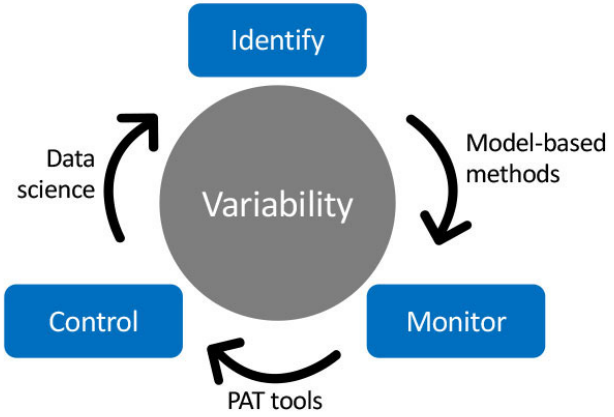
Thanks and congratulations again!

Best,

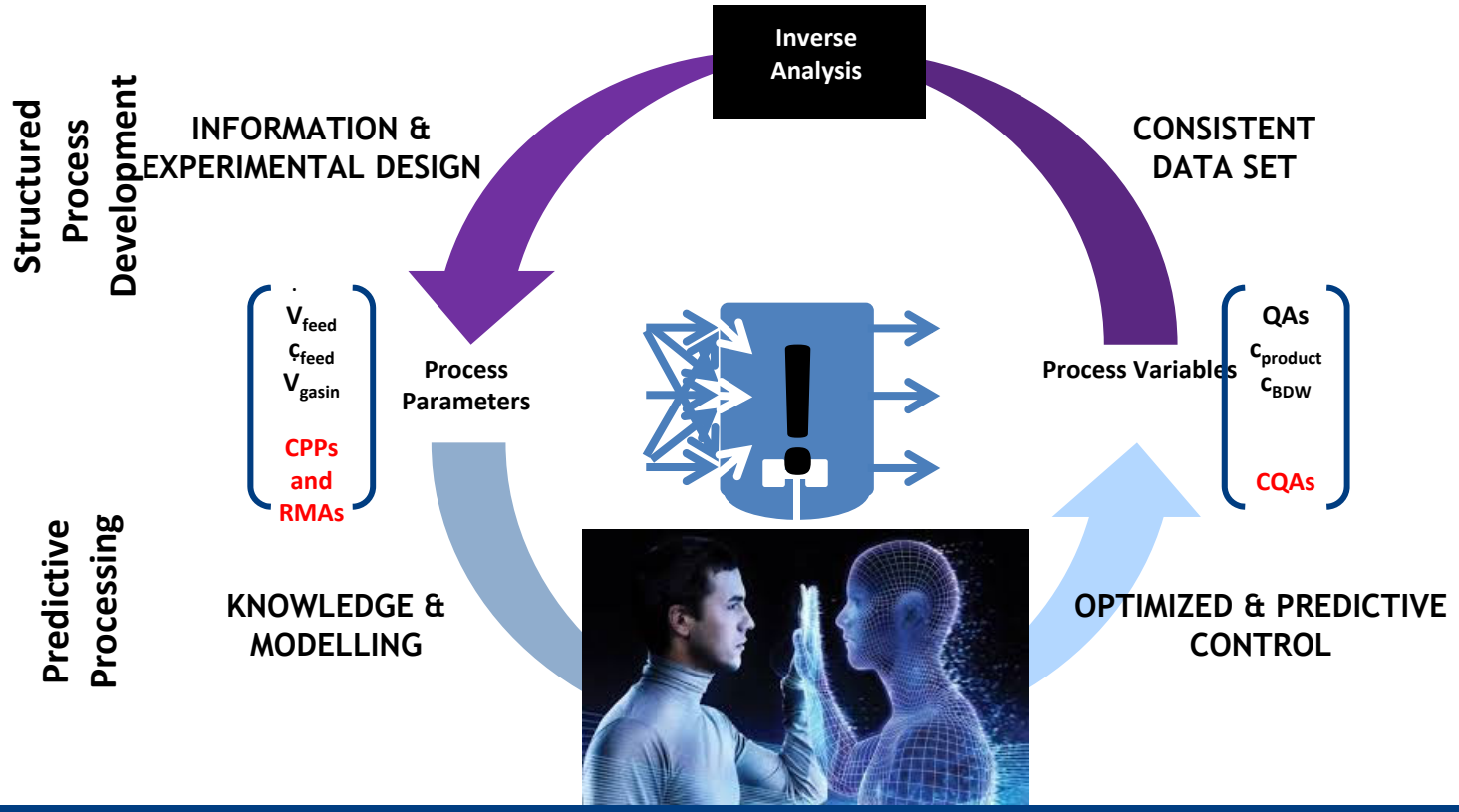
Susan F. Sandler

Senior Director, Editorial

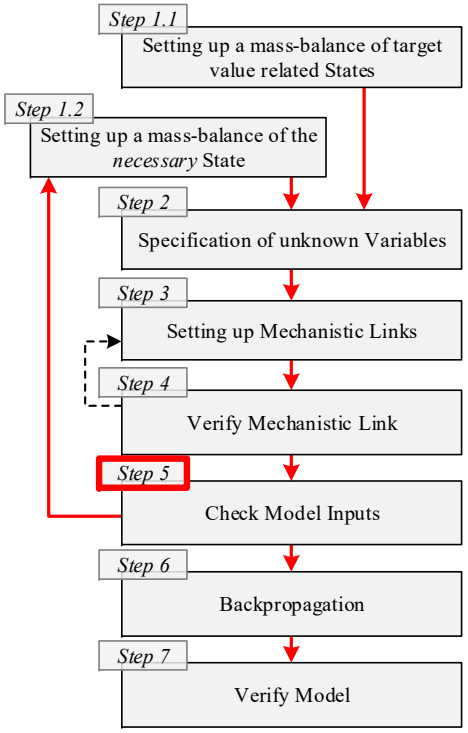
ISPE - Connecting Pharmaceutical Knowledge



Digital Twins as central tool to capture and provide knowledge



Workflow to control knowledge by Digital Twins: Minimum Model for VCC



$$\frac{dc_{VCC}}{dt} = (\mu - k_D) \cdot c_{VCC} - \sum_{j=1}^{n} \frac{\dot{V}_{in,j}}{V_R} \cdot c_{VCC}$$ [1]

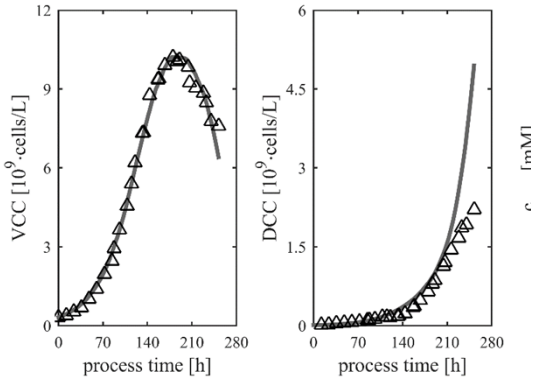
$$\frac{dc_{DCC}}{dt} = k_D \cdot c_{VCC} - \sum_{j=1}^{n} \frac{\dot{V}_{in,j}}{V_R} \cdot c_{DCC}$$

$$\frac{dc_{Asn}}{dt} = q_{Asn} \cdot c_{VCC} - \sum_{j=1}^{n} \frac{\dot{V}_{in,j}}{V_R} \cdot c_{Asn}$$

$$\mu = \mu_{max} \cdot \frac{c_{Asn}}{c_{Asn} + k_{Asn}}$$

$$k_D = k_{D,min} \cdot e^{\frac{k_{D,\mu}}{\mu}}$$

$$q_{Asn} = q_{Asn,max} \cdot \frac{c_{Asn}^n}{c_{Asn}^n + k_{Asn,2}}$$

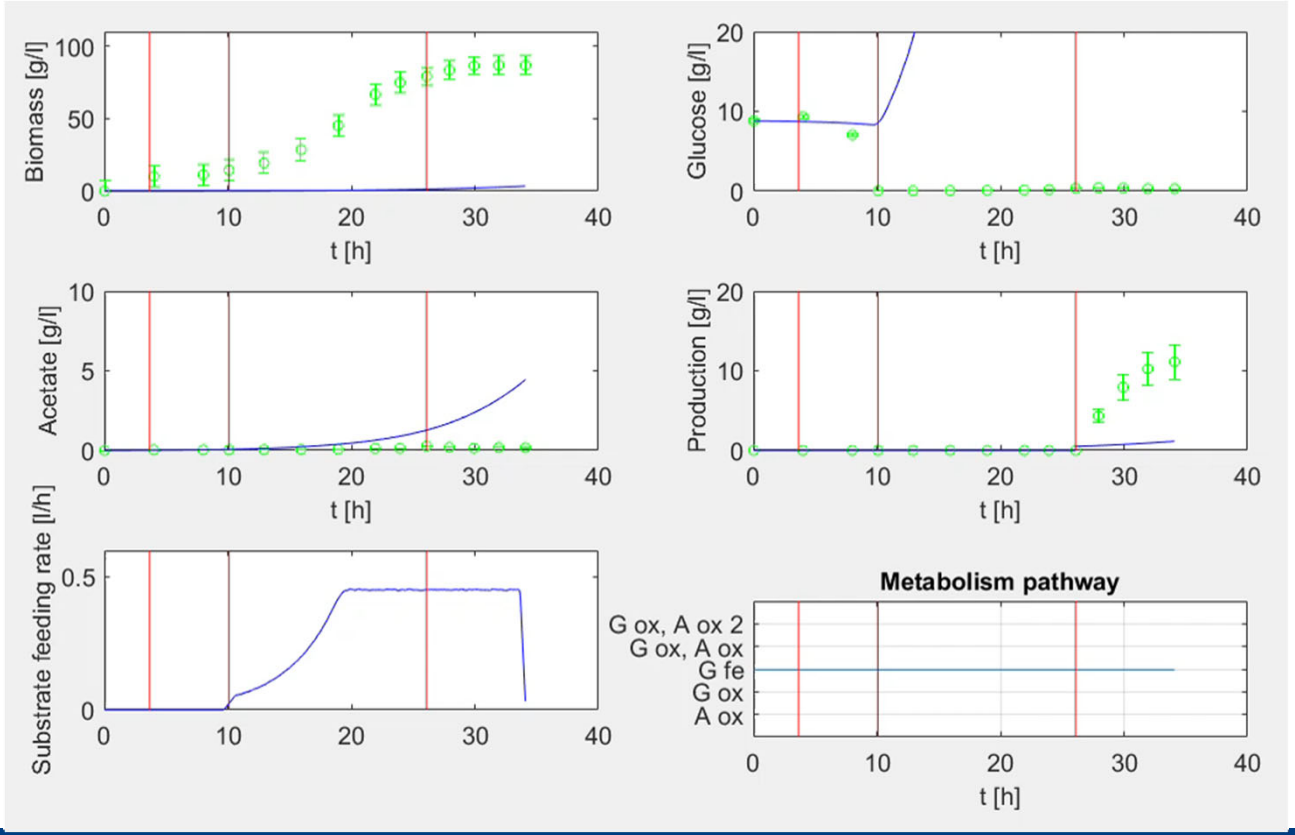


Contents lists available at ScienceDirect
Process Biochemistry
journal homepage: www.elsevier.com/locate/procbio

Workflow to set up substantial target-oriented mechanistic process models in bioprocess engineering

Paul Kroll[a,b], Alexandra Hofer[a], Ines V. Stelzer[a,b], Christoph Herwig[a,b,*]

Automated Model Adaptation Workflow



Extract data + Identify phases

Define states (Pathways)

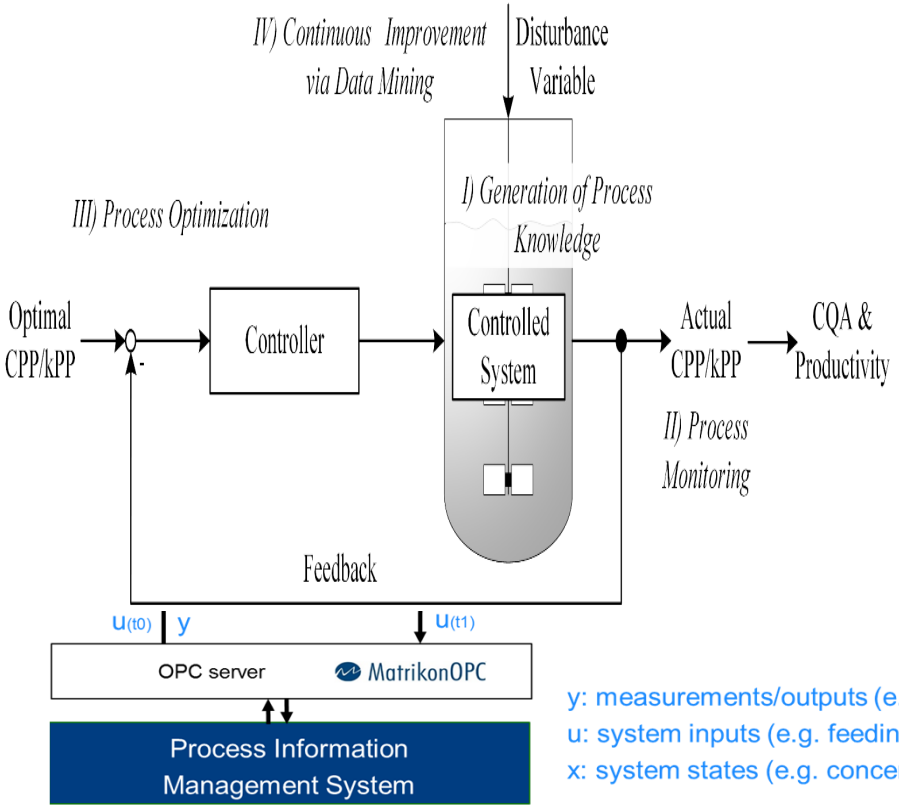
Select combination of kinetic links

Fit model to the data

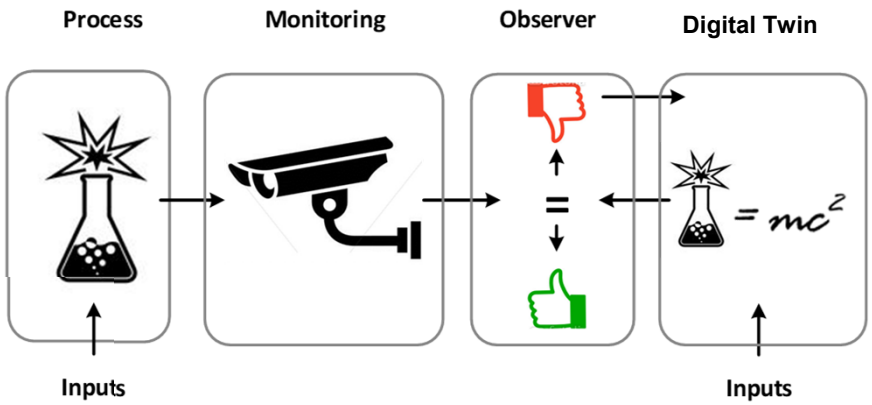
Optimal Parameters

Cross validation

Real Time Implementation of Digital Twins: Process transparency with meaningful parameters

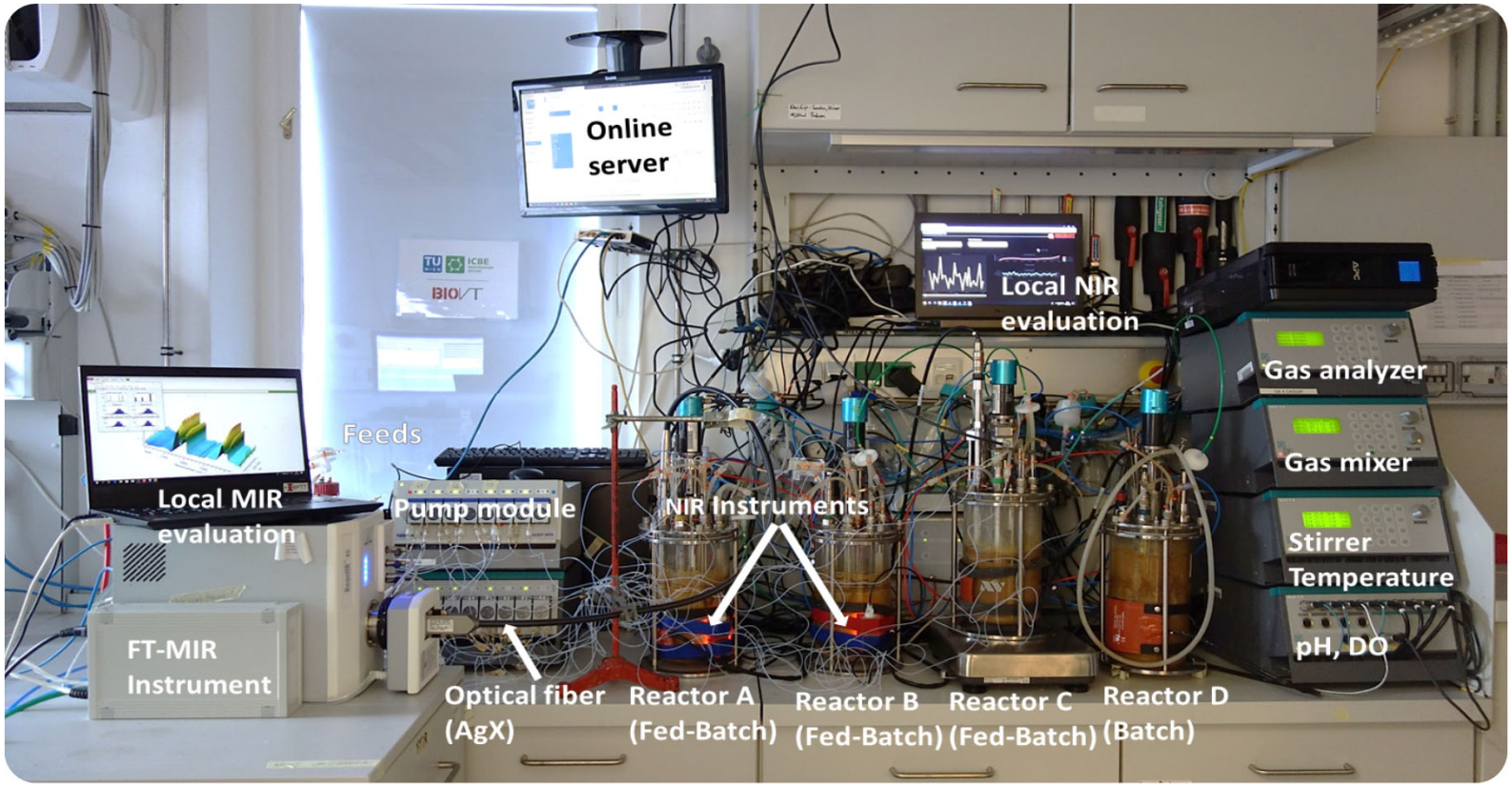


y: measurements/outputs (e.g. offgas)
u: system inputs (e.g. feeding rates)
x: system states (e.g. concentrations)

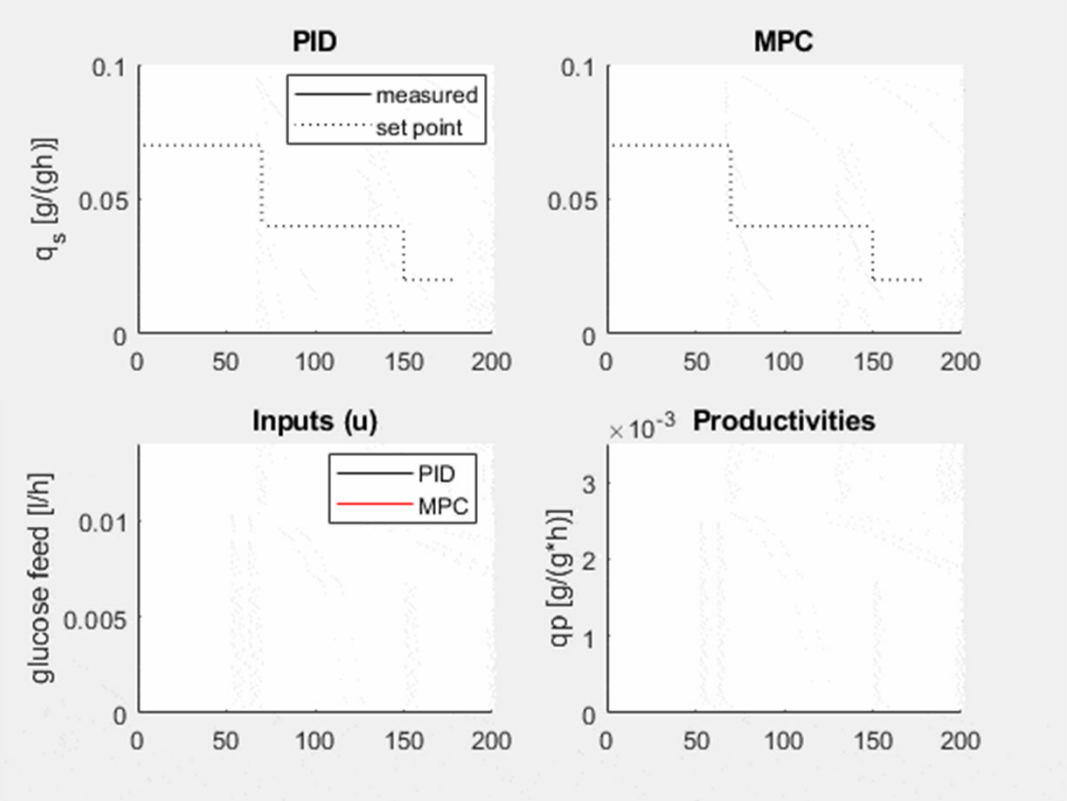


e.g:
Kalman Filter
Ext. Kalman Filter
Unscented Kalman Filter
Particle Filter…

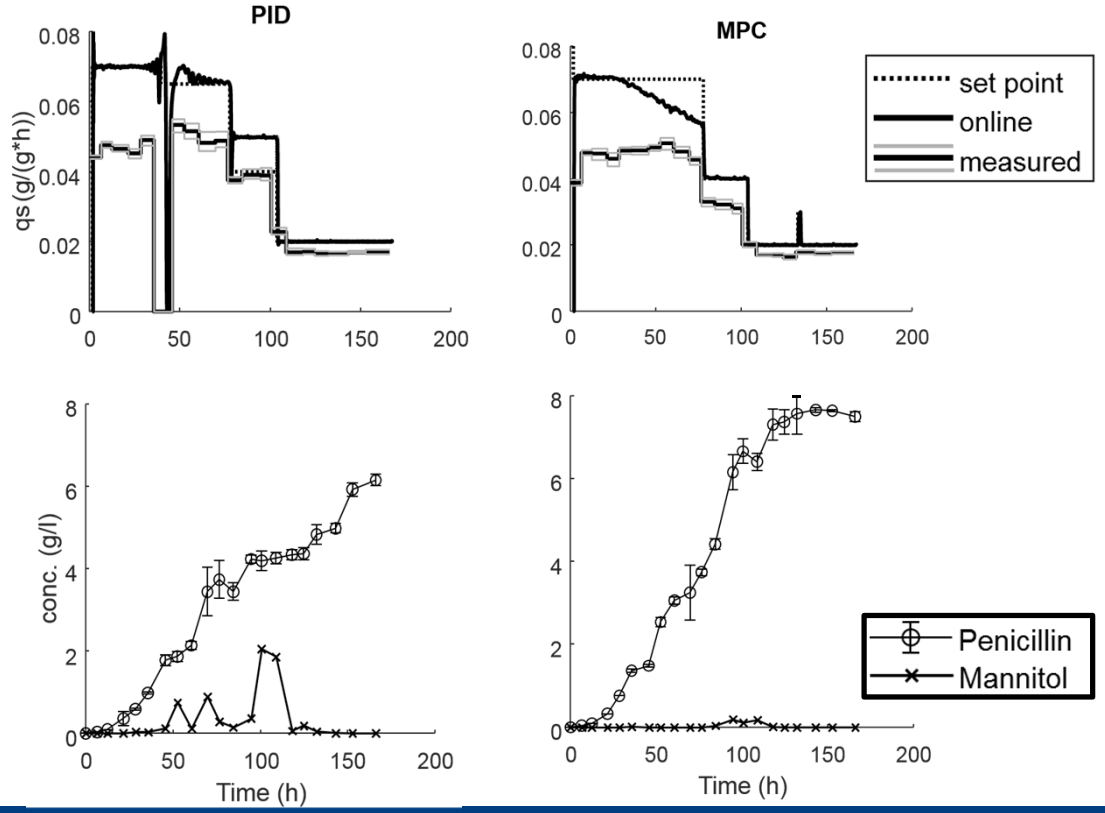
Advanced Control needs Digitized Laboratories



Digital Twin Based Advanced Control



Digital Twin Based Advanced Control

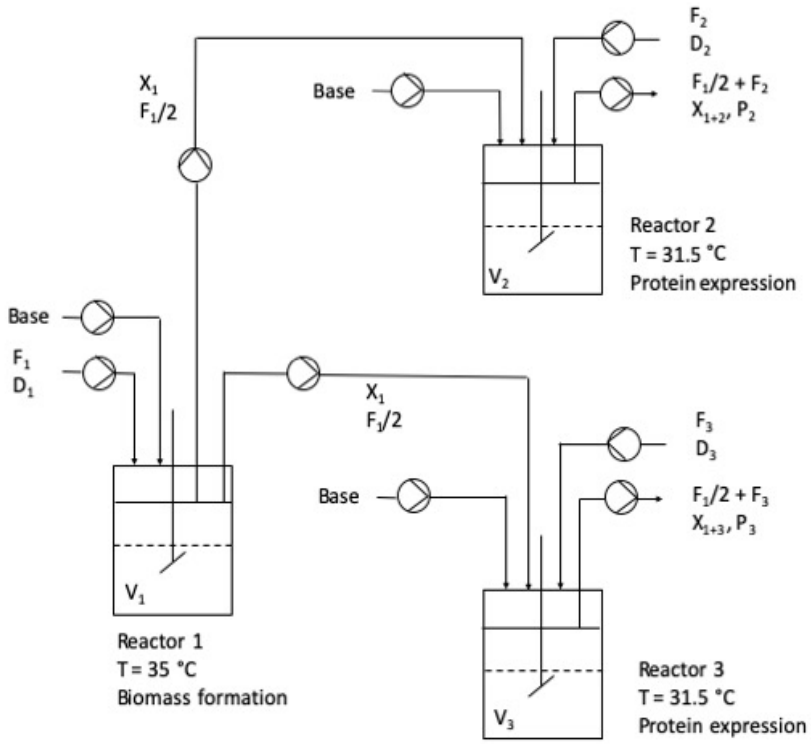


Kager, J., et al. (2019). Submitted
Ulonska, S., **Kager, J.,** et al. (2018). *Chemical Engineering Science*, *191*, 459-467.
Ulonska, S., **Kager, J.,** et al. (2018). In *Computer Aided Chemical Engineering* (Vol. 43).

Master DSP by Robust USP

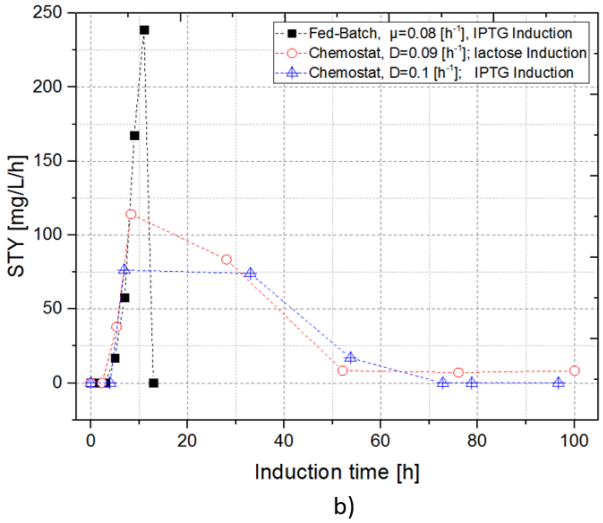
CASE STUDY ON TUNABLE PROMOTERS FOR CONTINUOUS UPSTREAM PROCESSING

Bioprocess Cascade Npro-BVS
Continuous *Cultivation scheme*

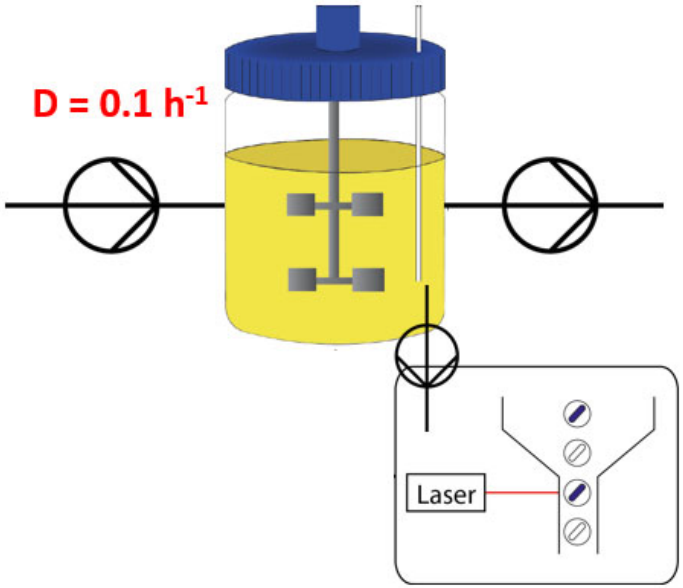


Population Analysis by Online Flow Cytometry

- Does an online FCM enable to monitor the drop in productivity?
- Can we gain more knowledge about populations with specific staining??

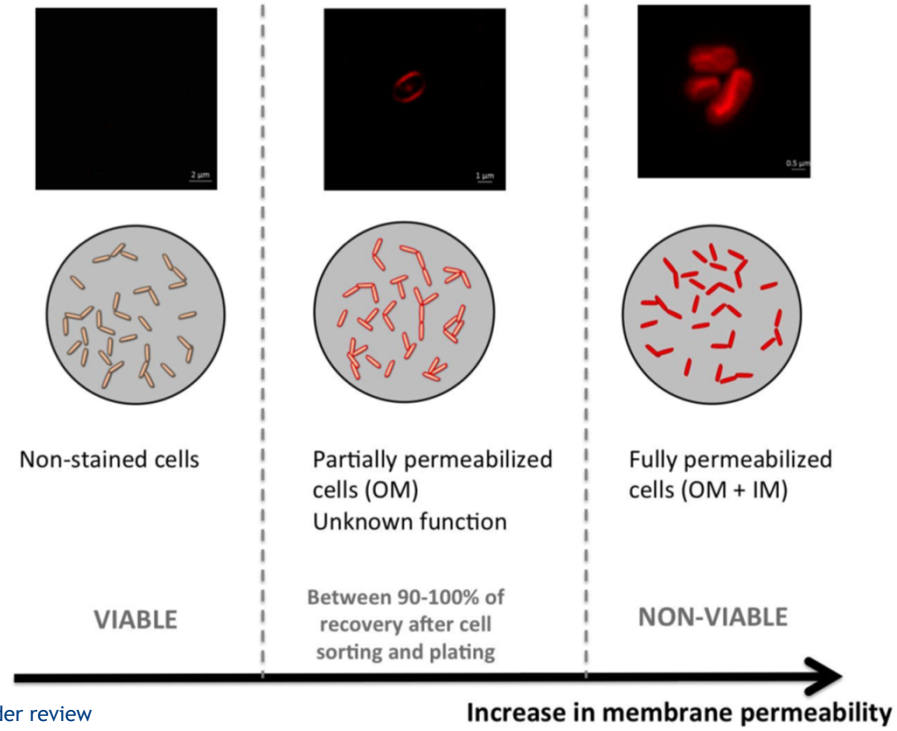


b)



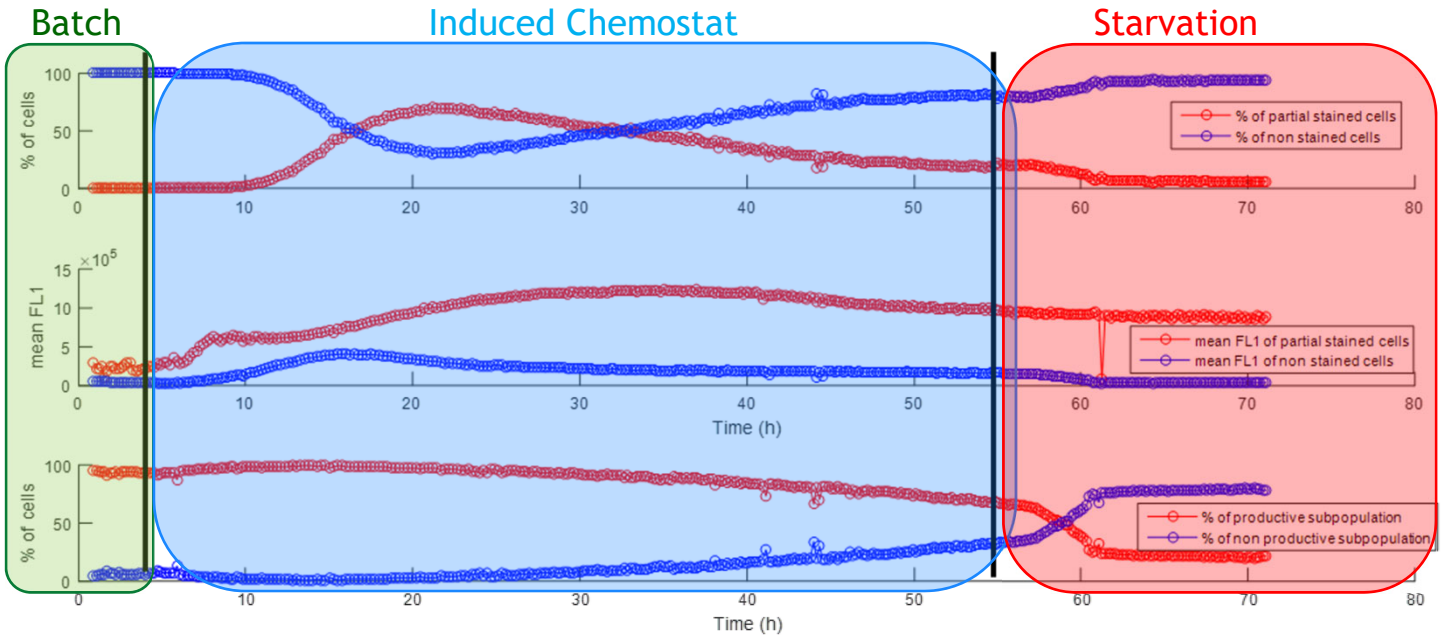
Population Analysis by Online Flow Cytometry

- FL3 vs FSC → PI staining commonly used for live-dead determination but…



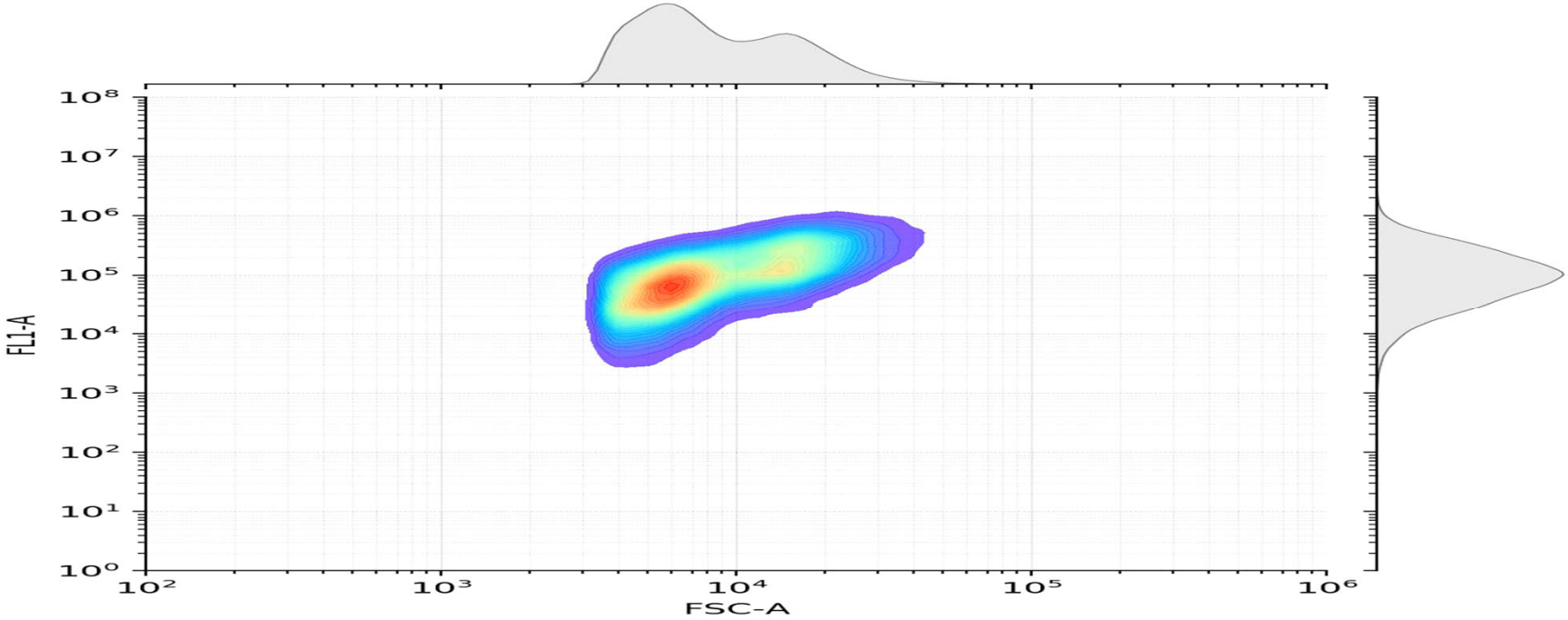
Sassi & Delvigne; under review

Population Analysis by Online Flow Cytometry



High dynamics in subpopulations lead to decrease in productivity…

Population Analysis by Online Flow Cytometry



High dynamics in subpopulations lead to decrease in productivity…

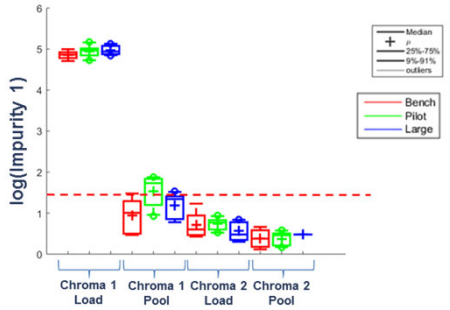
MANUFACTURING CONTROL STRATEGY: DEMONSTRATE MANUFACTURING CAPABILITY

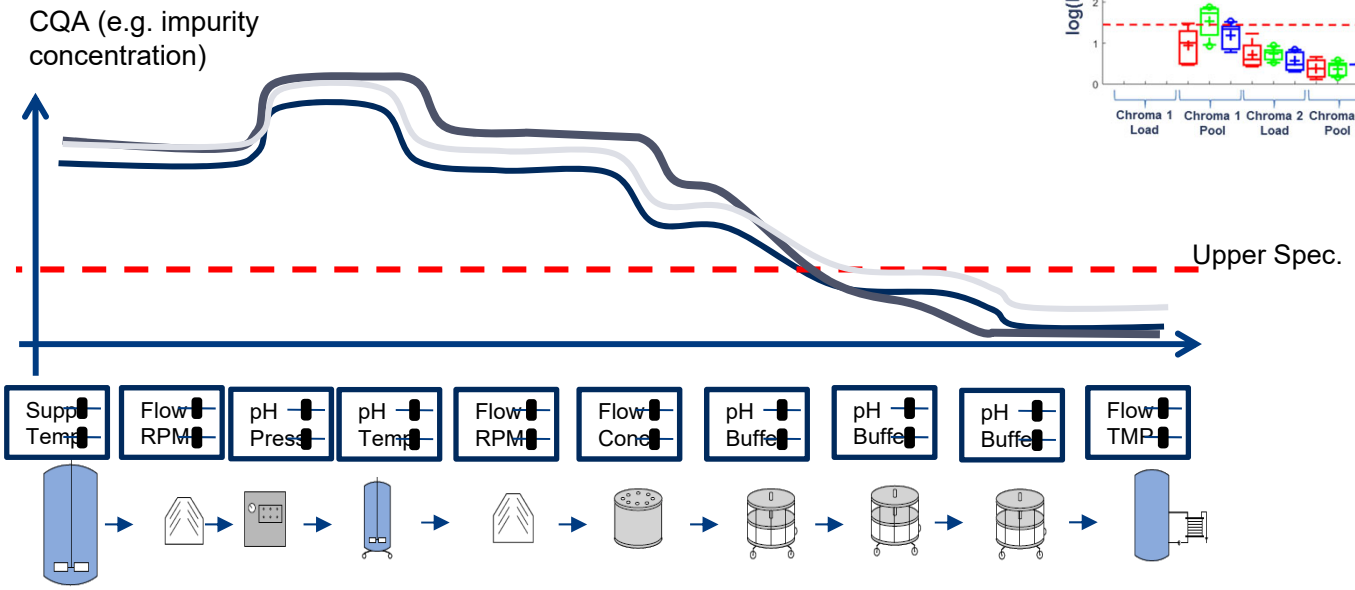
Identify robust operating ranges PARs and NORs

Identify holistically critical process parameters

Why integrated process modelling (IPM)?

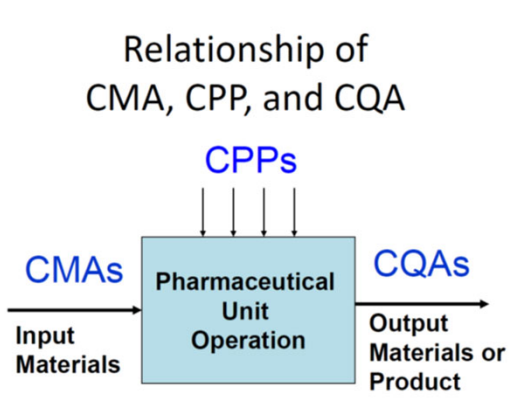
- Model impurity clearance over multiple unit operations
- Meet the target with highest probability!





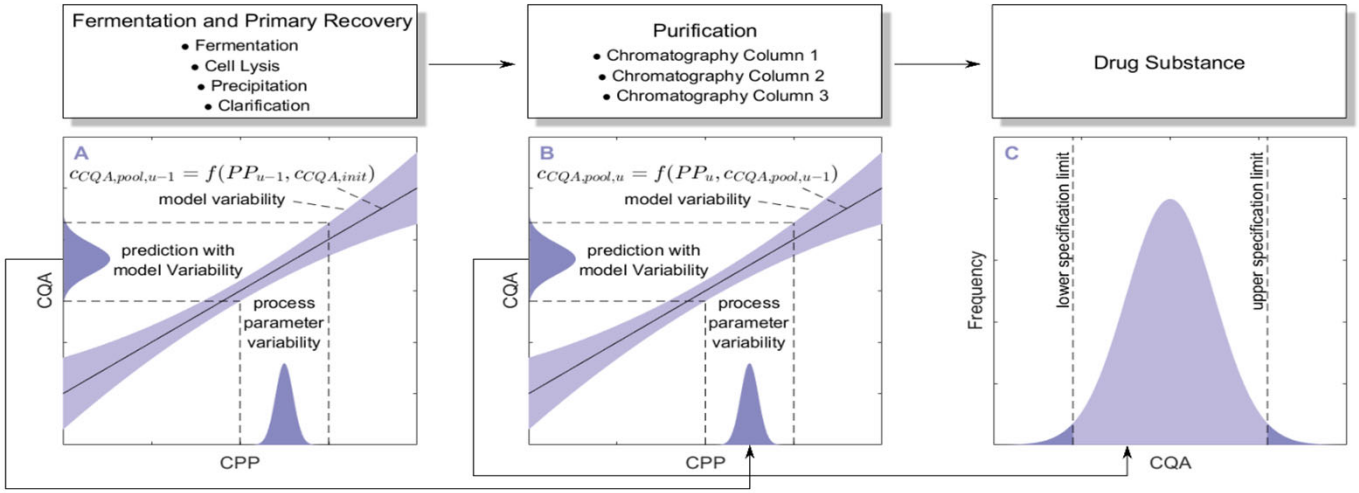
How to achieve IPMs?

- Two sources of variance per unit operation:
  - Variance in load
  - Variance in process parameters



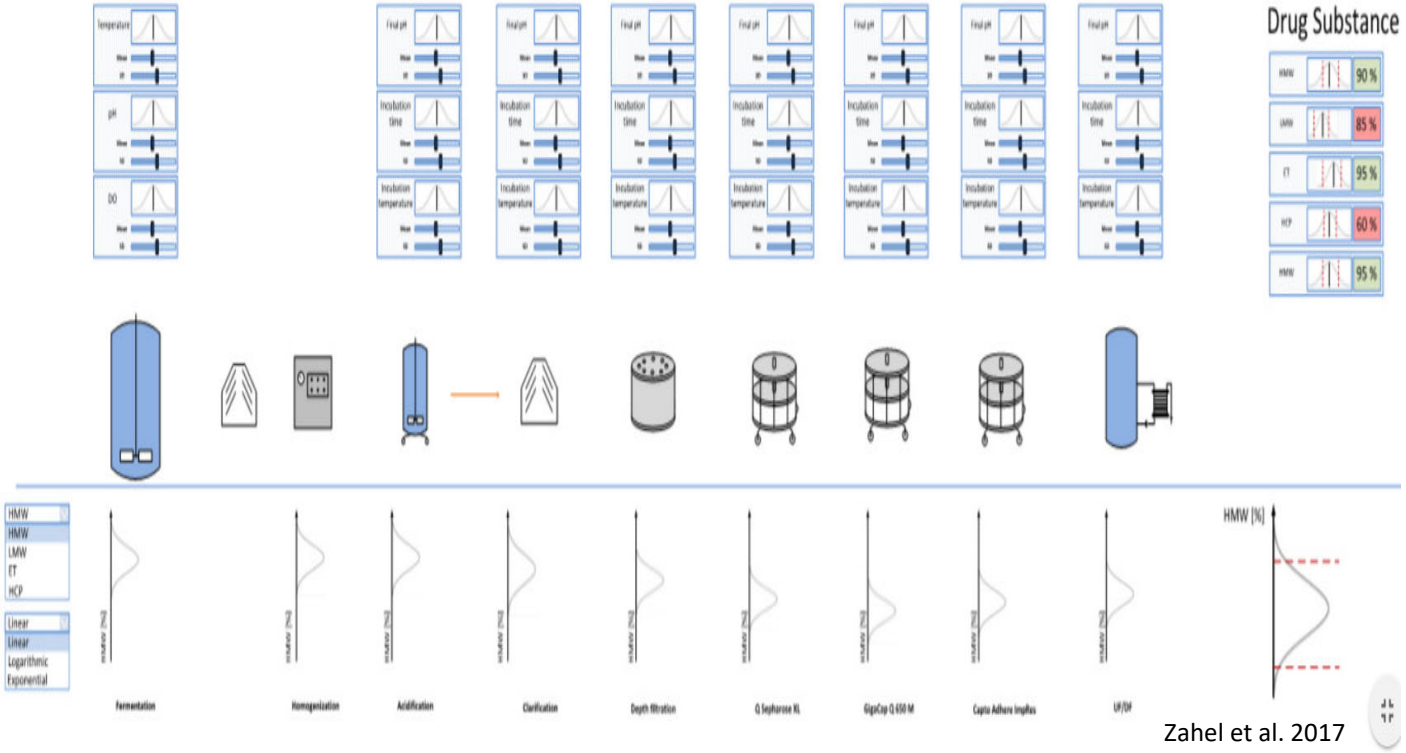
Lawrence Yu
3rd PQRI/FDA Conference on Advancing Product Quality, March 22-24, 2017

A CQA of an output material may become a CMA if it becomes an input material of another unit operation



Integrated Process Modelling as integral part of PCS

exputec
Boehringer Ingelheim



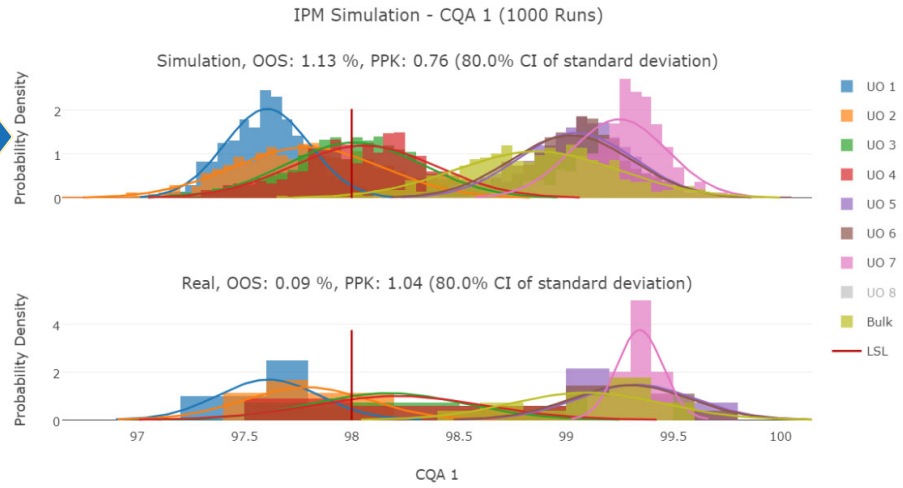
Zahel et al. 2017

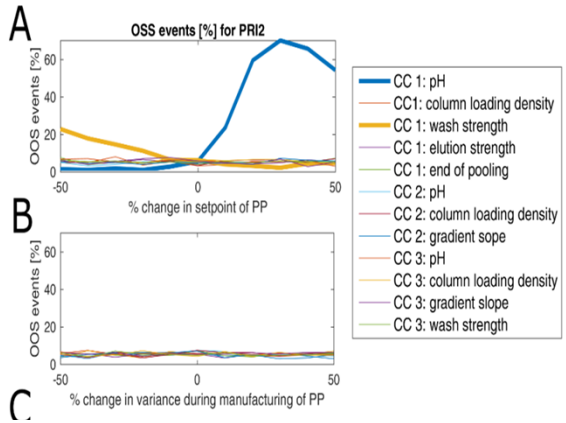
Results of Integrated Process Modelling

exputec
Boehringer Ingelheim

Concatenated Predictive Models

Real historical data





bioengineering
MDPI

Article

Integrated Process Modeling—A Process Validation Life Cycle Companion

Thomas Zahel [1], Stefan Hauer [1], Eric M. Mueller [2], Patrick Murphy [2], Sandra Abad [3], Elena Vasilieva [3], Daniel Maurer [3], Cécile Brocard [3], Daniela Reinisch [3], Patrick Sagmeister [1] and Christoph Herwig [1,*]

→ Integrated process modelling identifies PPs that are holistically critical
→ Impose a sufficient & holistic control strategy

Control Strategy Tasks

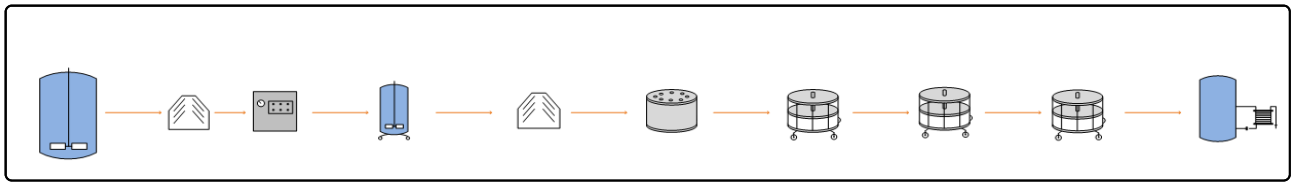
Declare Established Conditions along ICH Q10 and ICH Q12 along the product life cycle

- Process control strategy comprising
  - Control single unit operations
  - Control transitions between unit operations
  - Control for constant product output along the full process chain
  - Use Data Science when PAT is not feasible

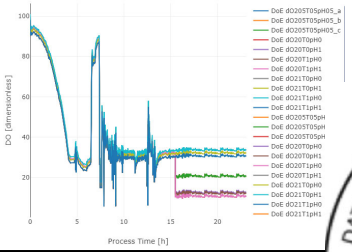
- Demonstrate Manufacturing Capability
  - Identify robust operating ranges NORs
  - Identify holistically critical process parameters

Data Fusion and Data Integrity

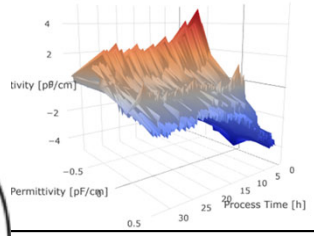
BLOCKCHAIN

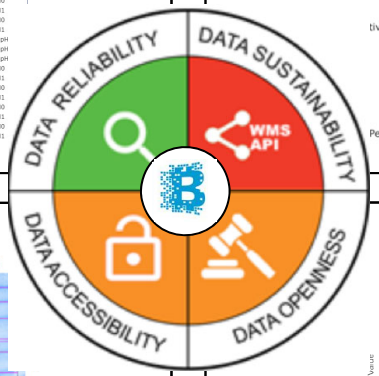


… data from Sensors

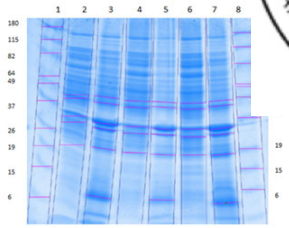


… data from PAT equipment

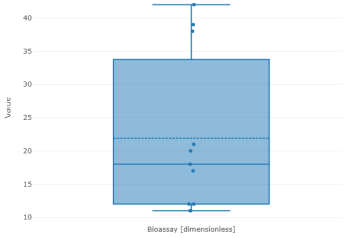




… images



… data from quality



PDA Journal of Pharmaceutical Science and Technology

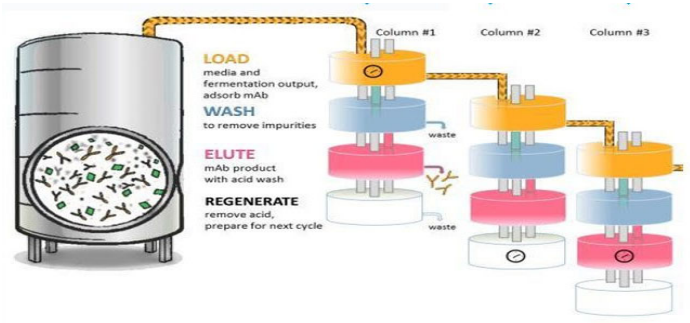
Provable Data Integrity in the Pharmaceutical Industry based on Version Control Systems and the Blockchain

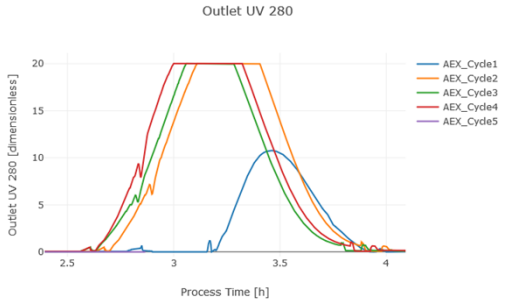
Valentin Steinwandter and Christoph Herwig

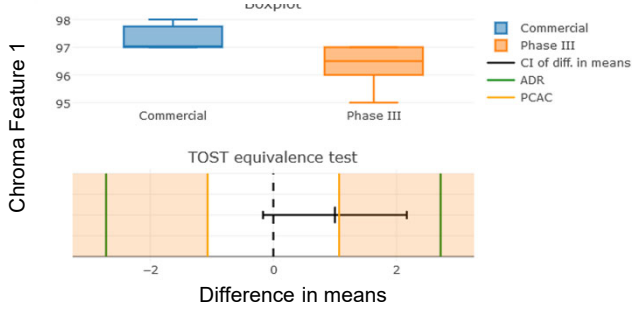
PDA Journal of Pharmaceutical Science and Technology **2019**,
Access the most recent version at doi:10.5731/pdajpst.2018.009407

Control Strategy via Similarity Analysis

- **Aim:**
  - Analyze elution profiles from different cycles







Equivalence testing approach prevents

→ Direct assessment of suitability for pooling of cycles

→ Let detect degradation effect in continuous operations

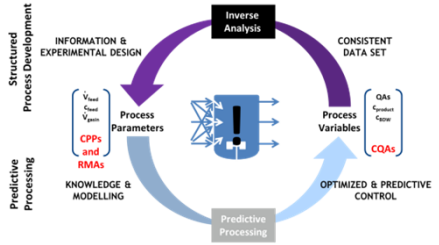
Q12 Digitalization enablers for the product life cycle

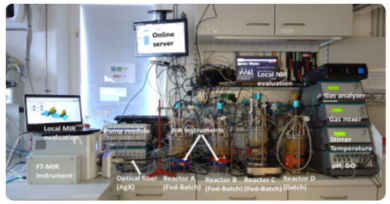
Digitalization

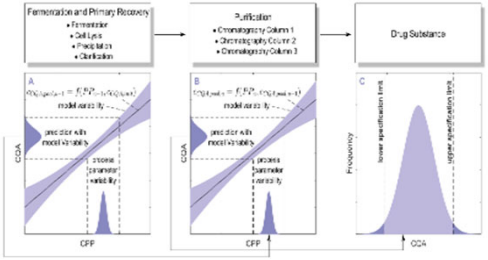
- Connectivity
- Data Science
- Knowledge Share

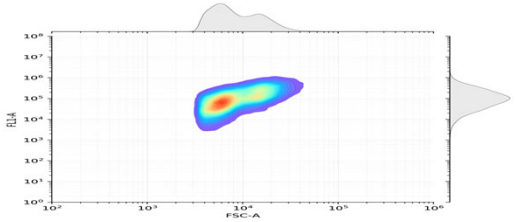
Process Characterization

- Scale down models









PAT & Controls

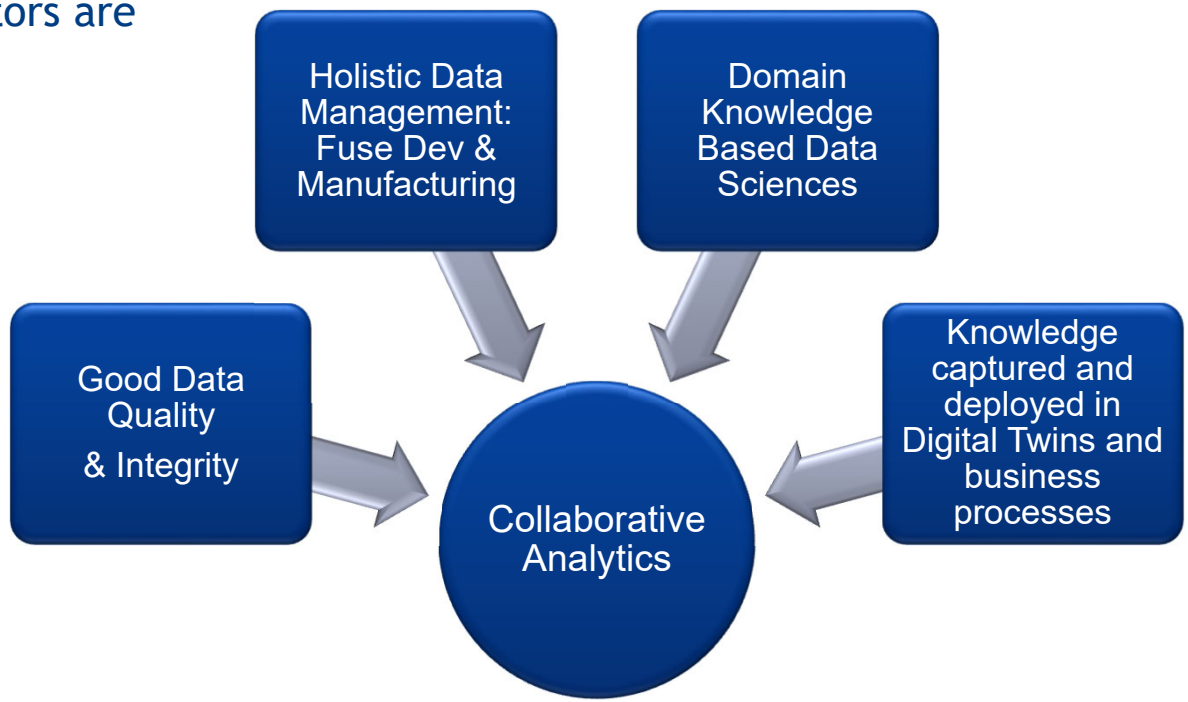
- MPC
- Data Science

Digital Twins

- Efficient tools to capture and provide knowledge

Common denominators:
Collaborative Analytics for successful control strategies

- Digitalization is not enough to achieve control strategies
- Common Denominators are



Thank you
for your attention!

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exputec

FWF Der Wissenschaftsfonds.

bmwfi Bundesministerium für Wirtschaft, Familie und Jugend

FFG

arbeitskreis prozessanalytik

Gedeon Richter

Roche

HOOKIPA BIOTECH

Boehringer Ingelheim

SIEMENS

SANDOZ A healthy decision

BILFINGER

BIRD-C bacterial ghost platform technology

Lonza