Advancing Industry 4.0 in Pharmaceutical Manufacturing:

Integrating the Process Safety Perspective

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P2SAC Meeting – Spring 2019

150 YEARS OF GIANT LEAPS™

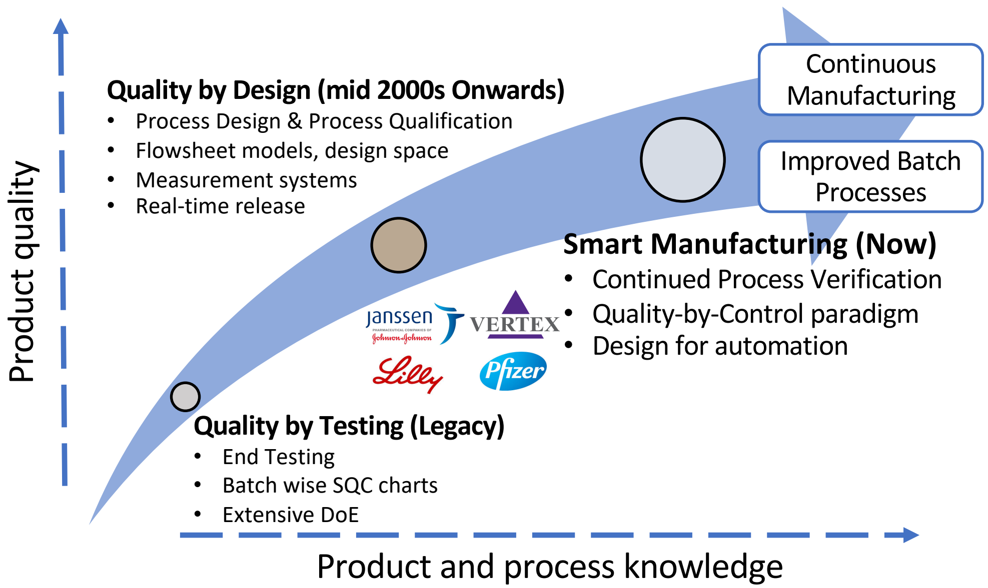
PURDUE UNIVERSITY

Vision

Science and risk based manufacturing for improved patient reach & healthcare supply chains

Goal

Real-time release testing in oral solid dose
Continuous manufacturing systems



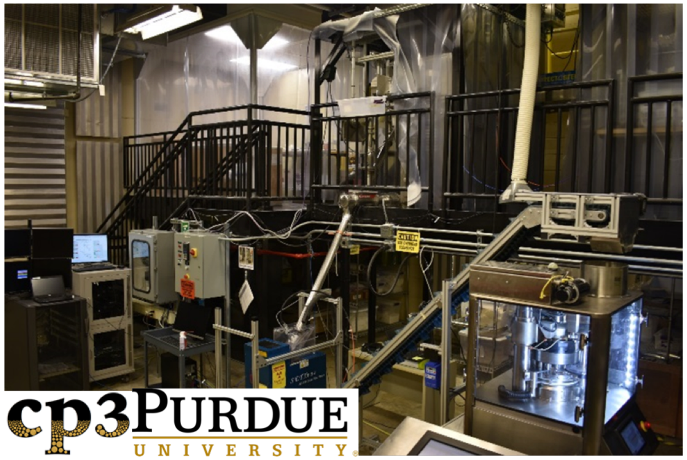
Talk Agenda

- QbD to Operational Excellence
- Process Automation
- Condition Based Maintenance
- Sensors & Systems Integration

Continuous OSD Manufacturing

Journey from QbD to Operational Excellence

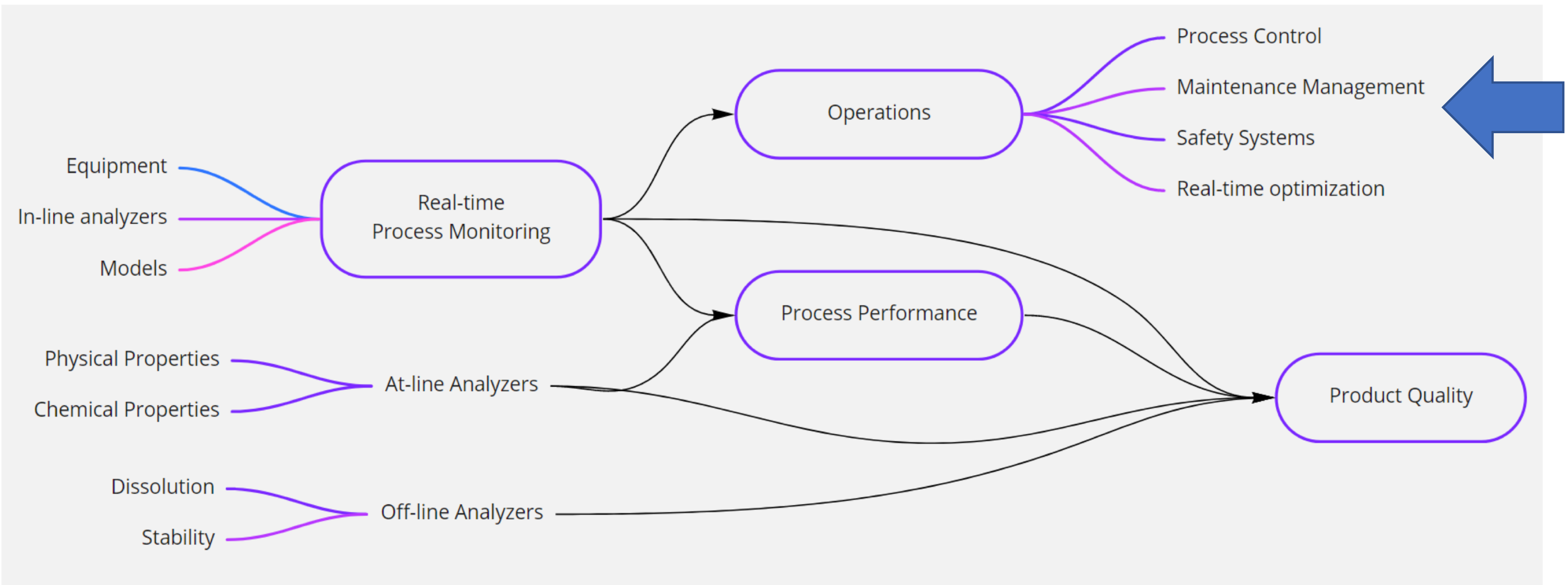
Material Characterization	• Solid handling • Effect of unit operations
Process Modeling	• Mechanistic understanding • Quality by Design
Pilot Plant Studies	• Dry Granulation, Tablet Compaction • PAT measurements
Integrated Systems	• Product quality, process robustness • Real-time release strategies
IIoT, Analytics & Control	• Data-driven insights for strategizing operations for 6σ systems



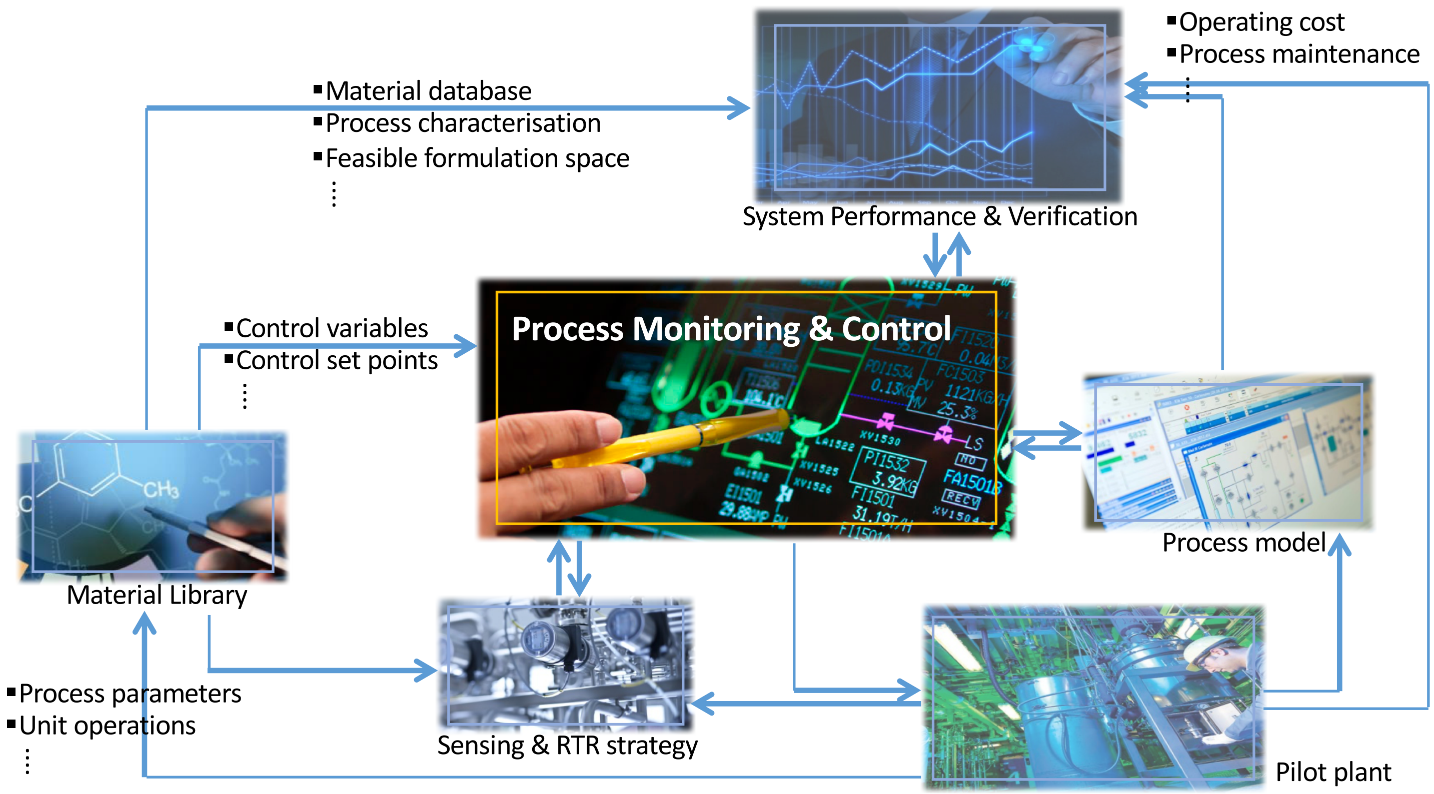
schenck process · Alexanderwerk · Innopharma · sotax Solutions for Pharmaceutical Testing · MATLAB · Gericke · NATOLI · DeltaV · KEPServerEX · En'Urga Inc. · TECH4IMAGING · OSIsoft · APPLIED MATERIALS

Quality by Design & Real-Time Release Testing

Operational Excellence using Data, Models and Automation

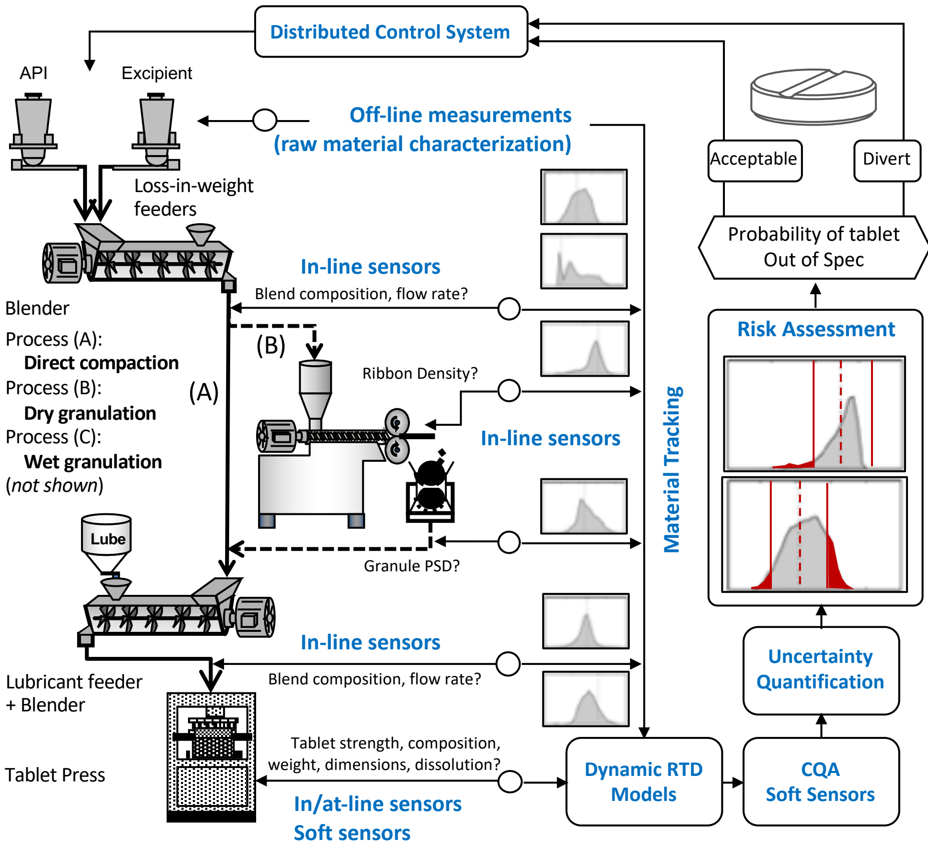


Process Design & Risk Assessment



Su Q, Moreno M, Giridhar A, Reklaitis GV, Nagy ZK. A systematic framework for process control design and risk analysis in continuous pharmaceutical solid-dosage manufacturing. *Journal of Pharmaceutical Innovation*. 2017;12: 327-346.

Compaction Modeling for Material Tracking



$$\bar{W} \sim \mathcal{N}(\mu_{\bar{W}}, \sigma^2_{\bar{W}})$$

$$\mu_{\bar{W}} := \frac{\rho_b \pi D^2}{4} H^{\text{fill}} \left(1 - \xi_1 \frac{n_{\text{T}}}{n_{\text{F}}} + \xi_2 \frac{H^{\text{fill}}}{D}\right)$$

$$\sigma_{\bar{W}}/\mu_{\bar{W}} := s_{\text{MCC}}(1 - x_{\text{APAP}}) + s_{\text{APAP}} x_{\text{APAP}}$$

$$\sigma_{\text{punch}} = \frac{4F_{\text{punch}}}{\pi D^2}$$

$$\bar{\rho}(x_{\text{APAP}}, H, W) := \frac{4W}{\pi D^2 H \rho_t}$$

Kawakita model[2]

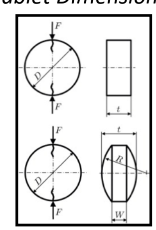
$$\bar{\sigma}_{\text{punch}}(x_{\text{APAP}}, \rho^{\text{in-die}}) := \frac{\rho^{\text{in-die}} - \tilde{\rho}_b}{[\rho^{\text{in-die}}(a-1) + \tilde{\rho}_b]\, b}$$

Elastic recovery

$$\bar{\rho}^{\text{tablet}}(x_{\text{APAP}}, \rho^{\text{in-die}}) := \rho^{\text{in-die}}(1 - \epsilon_\rho)$$

$$\epsilon_\rho = \epsilon_0 \frac{\rho^{\text{in-die}} - \rho_{c,\epsilon}}{1 - \rho_{c,\epsilon}}$$

Tablet Dimensions



Leuenberger model[1]

$$\bar{\sigma}_t(x_{\text{APAP}}, \rho^{\text{tablet}}) := \sigma_{t,0}\left[1 - \frac{1 - \rho^{\text{tablet}}}{1 - \rho_{c,\sigma}} e^{(\rho^{\text{tablet}} - \rho_{c,\sigma})}\right]$$

Monitoring Product Quality & Process Health

Data Sources

Equipment — Process Parameters

- Vibrations, lubrication frequency, Oil levels
- Device alarms, electrical system status

Analyzers — Quality Attributes

- Device setup and operating conditions
- Device life – light source intensity, white/dark references, calibration history

Soft Sensors — Operational Data Analytics

- Process & statistical models
- Heuristics

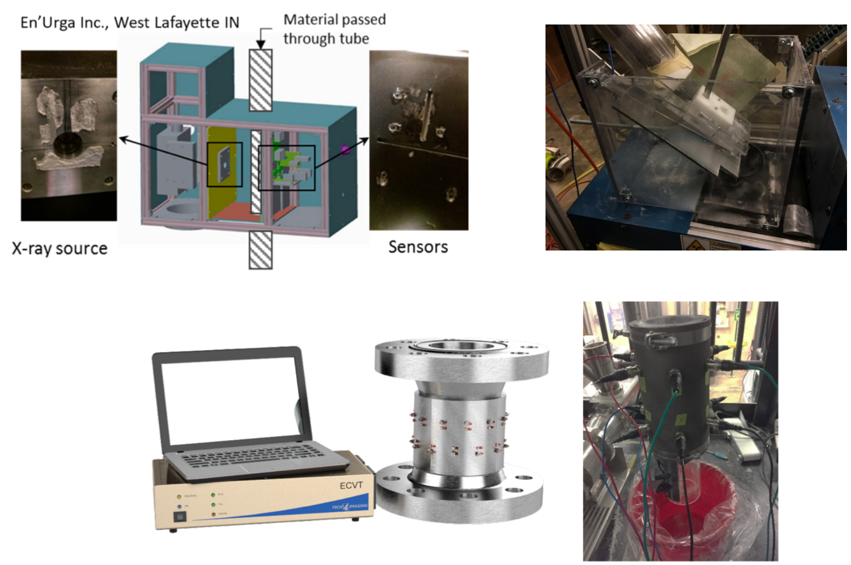
Monitoring Product Quality & Process Health

Data Sources

Equipment

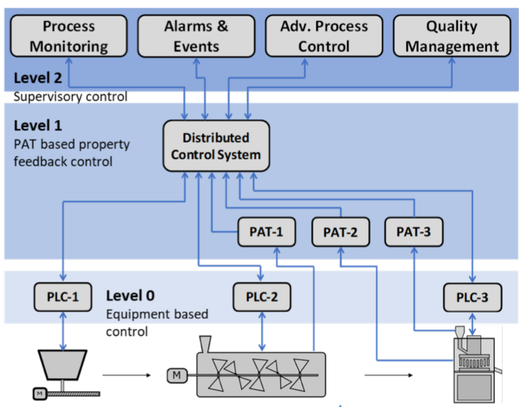
Material analyzers

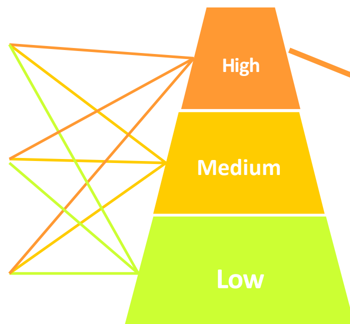
Mass flow sensors



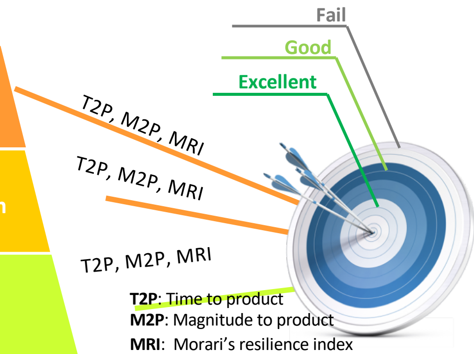
Process Control

Hierarchical control architecture





Risk levels & failure mode



Evaluation & regulatory filling

- Sensor accuracy, precision, sampling time
- Sensor location
- Control architecture reconfiguration
- Control method
- Controller tuning

⋮

Continuous improvement

- Process verification
- Formulation optimization
- Process reconfiguration
- ⋮

e.g. GMP guidelines

- Design & qualification

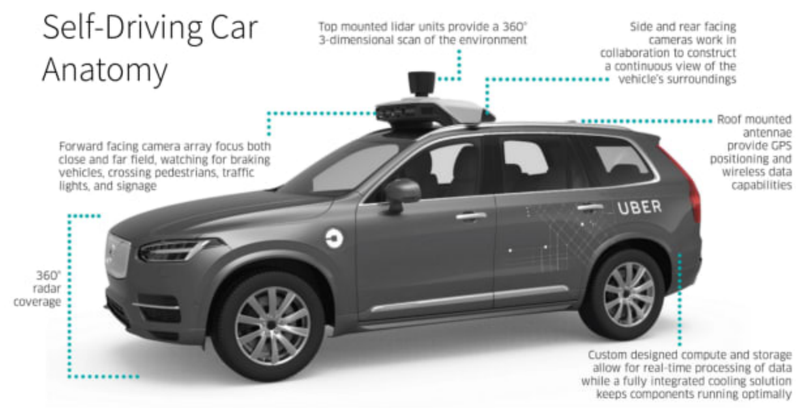
⋮

Complex System of Systems

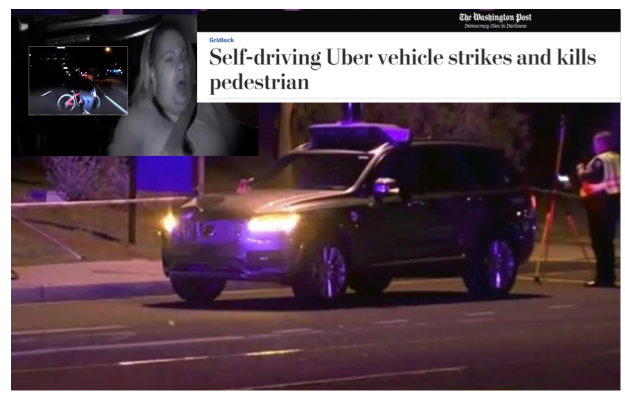
- Product Quality
- Process Safety
- Control Systems
- Information Technology
- Design Space
- Process Control
- Alarms
- Equipment
- Instruments
- Models

Failures Impact Quality & Safety

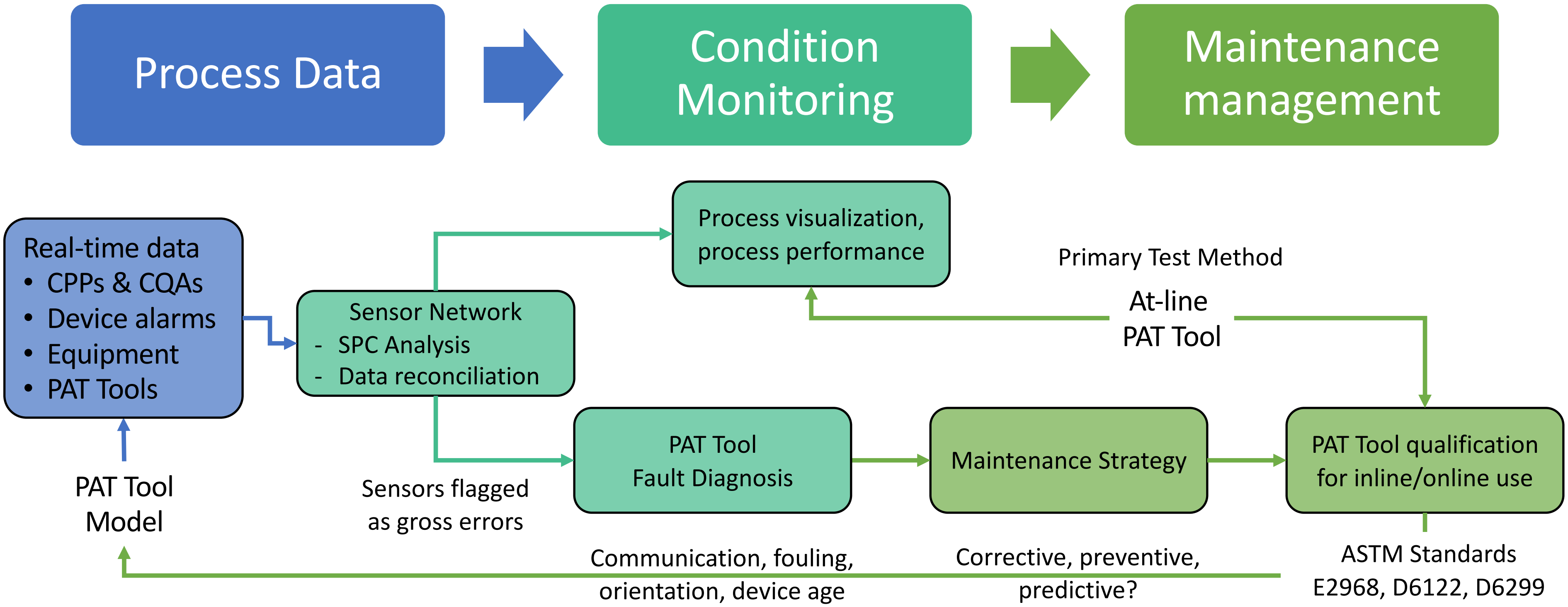
- Increased offline quality testing
- Diminished competitive advantage
- Limits & Questions use of technology



What if… these complex systems fail?



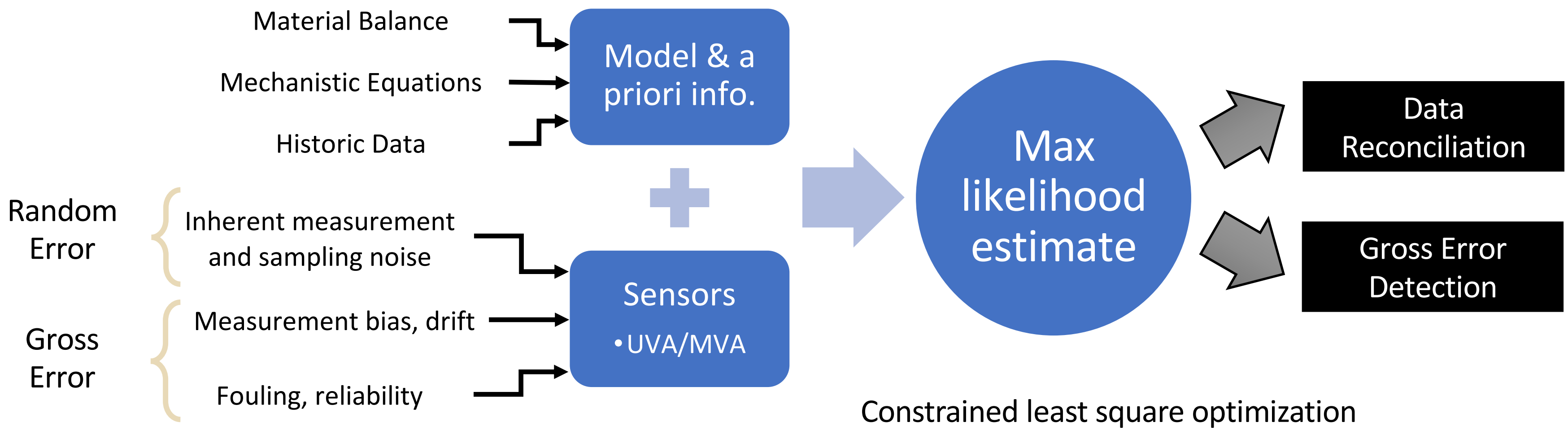
Sensor Network Condition Based Maintenance



S. Ganesh, G. Reklaitis et al. Maintenance Management for the Sensor Network in Continuous Pharmaceutical Systems, Talk 171e, AIChE Annual 2018
S. Ganesh et al. Condition based maintenance for monitoring reliability in continuous tablet manufacturing (in preparation)

Utilizing Sensor Network Redundancy

Data Reconciliation and Gross Error Detection



- ❑ Contextualize direct measurements
- ❑ Flag faulty sensors
- ❑ Estimate unmeasured variables
- ❑ Validate model parameters

Constrained least square optimization

$$\min_{x,z} J = v^T Q^{-1} v$$

$$s.t. \quad h(x, z, \theta) = 0$$

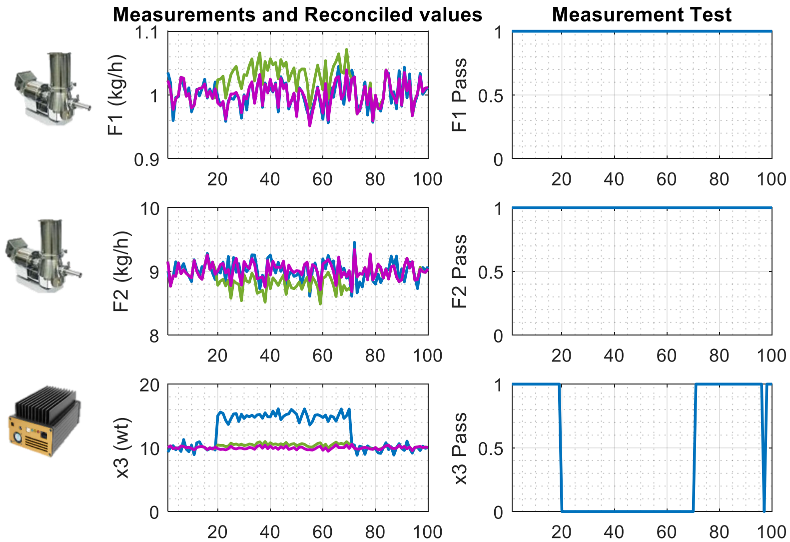
$$x^+ - x = v$$

- x^+ vector of measurements, $\Re^n$
- x vector of reconciled values, $\Re^n$
- v vector of errors, $\Re^n$
- z vector of unmeasured states, $\Re^m$
- Q covariance matrix, $\Re^{n \times n}$
- θ vector of system parameters, $\Re^p$
- h algebraic equations, $\Re^{m+n} \rightarrow \Re^k$

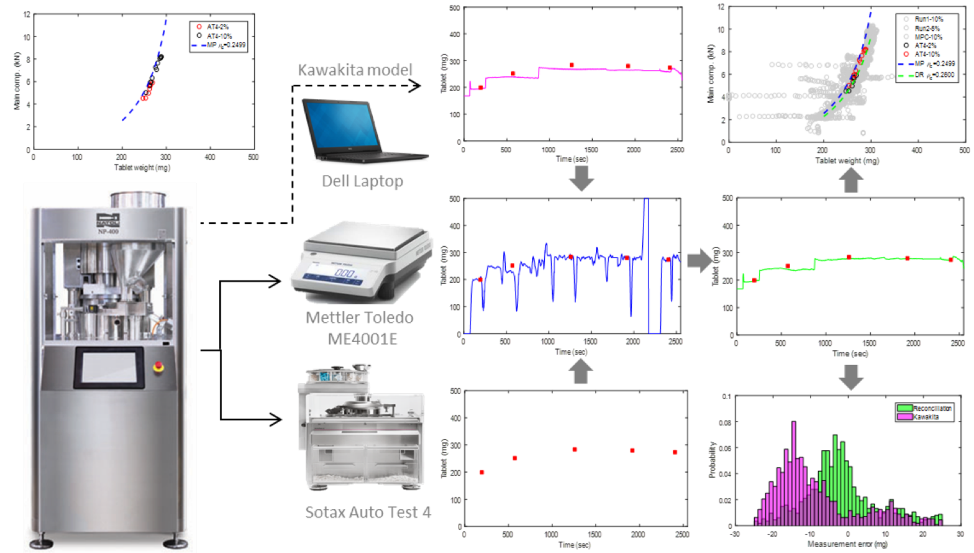
Narasimhan & Jordache (2000)
M. Moreno, G. Reklaitis et al. J. Pharm. Innov. (2018)
J. Liu, C. Laird, G. Reklaitis et al. Chem. Eng. Res. Des. (2018)

Data redundancy for actionable insights

Gross error detection, parameter estimation, CQA validation in real-time



Process – 2 feeders, blender, RC



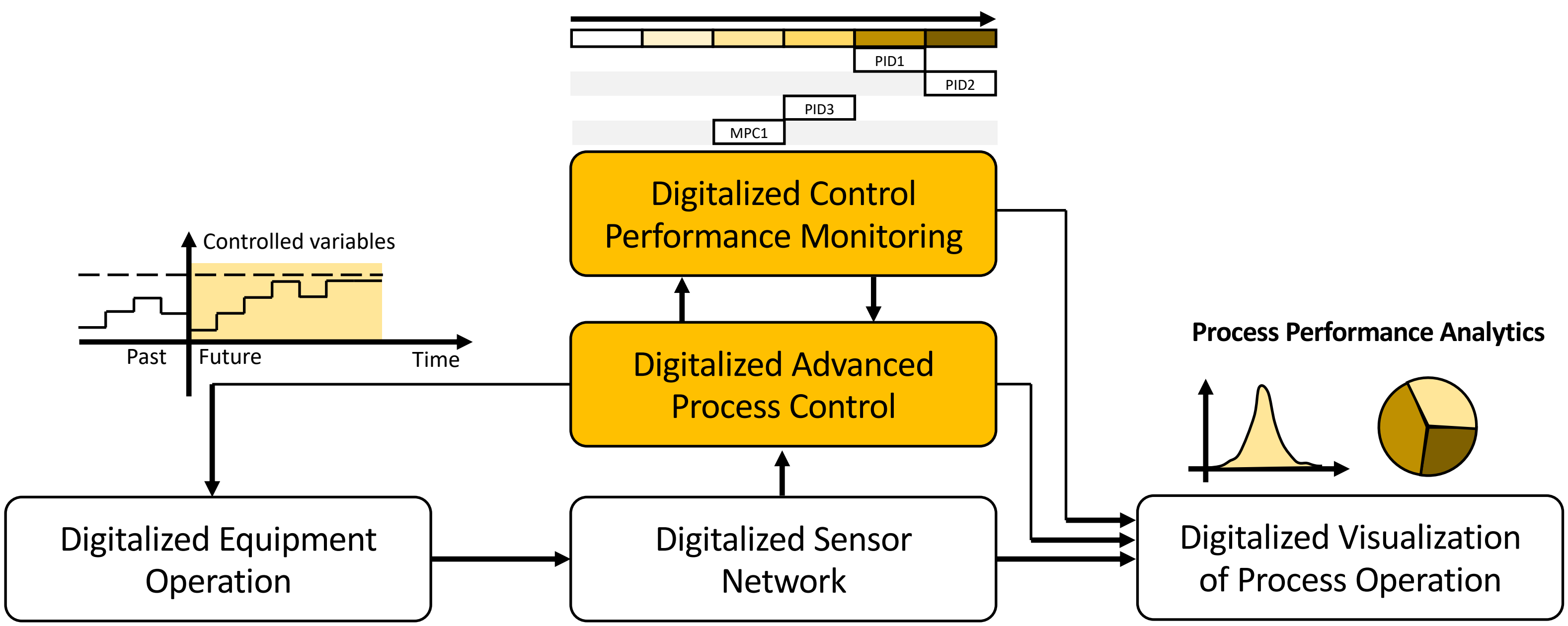
M. Moreno, S. Ganesh et al., *Sensor Network Robustness using Model-based Data Reconciliation for Continuous Tablet Manufacturing*, J. Pharm. Sci. (2019)

Q. Su, S. Ganesh, et al., *A perspective on Quality-by-Control in pharmaceutical continuous manufacturing*, Comp. & Chem. Eng. (2019)

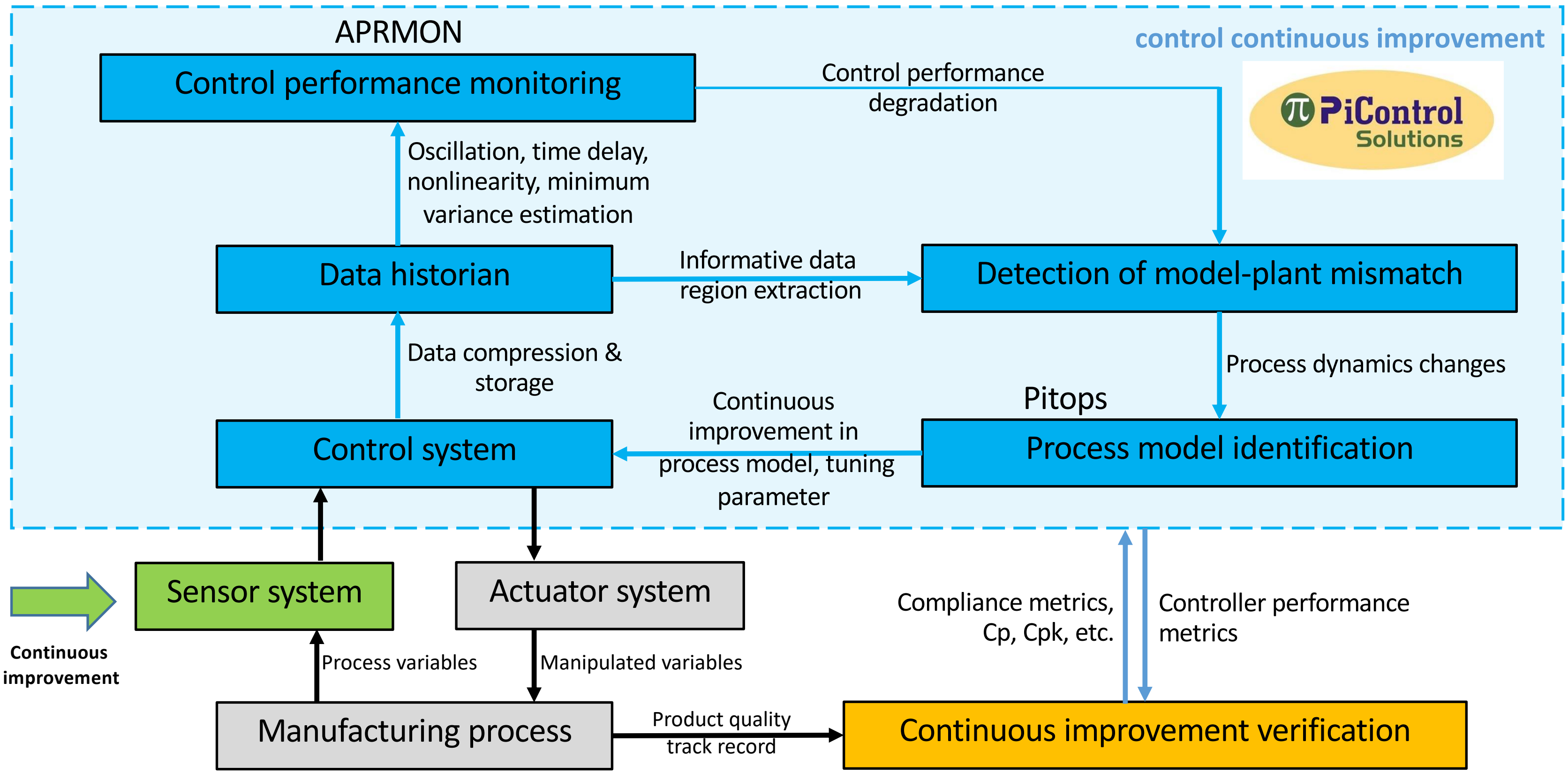
Q. Su, S. Ganesh et al., *Data reconciliation in the Quality-by-Design (QbD) implementation of pharmaceutical continuous tablet manufacturing.* Int. J. Pharm. (2019)

Operational Digital Twins

Data-driven & model-based insights for process health monitoring

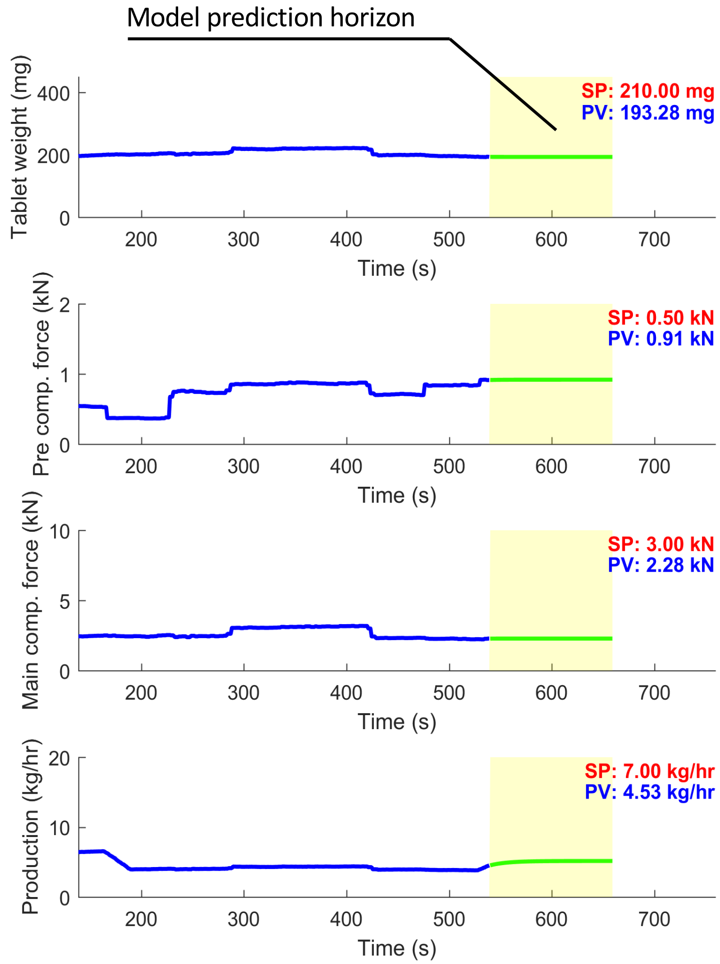


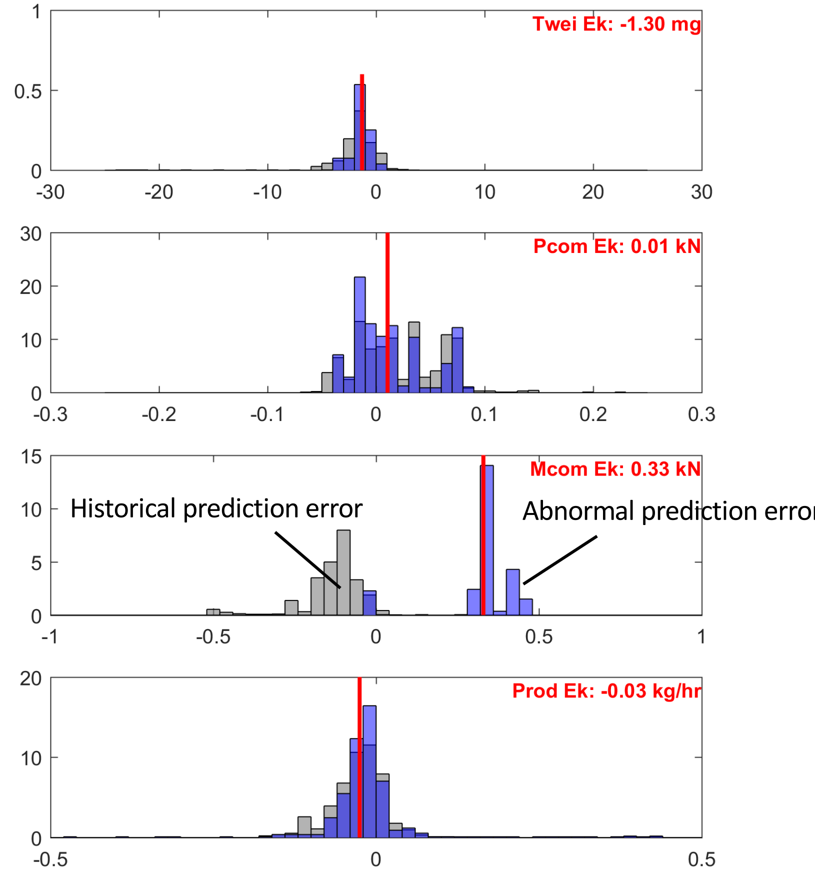
Process Control Performance Monitoring and Improvement



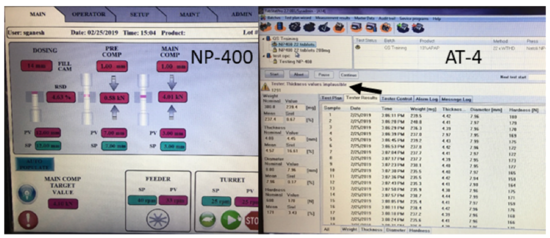
Q. Su, S. Ganesh, …, G. Reklaitis, Z. Nagy. A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing. (Comp. & Chem. Engg., 2019)

Natoli NP400

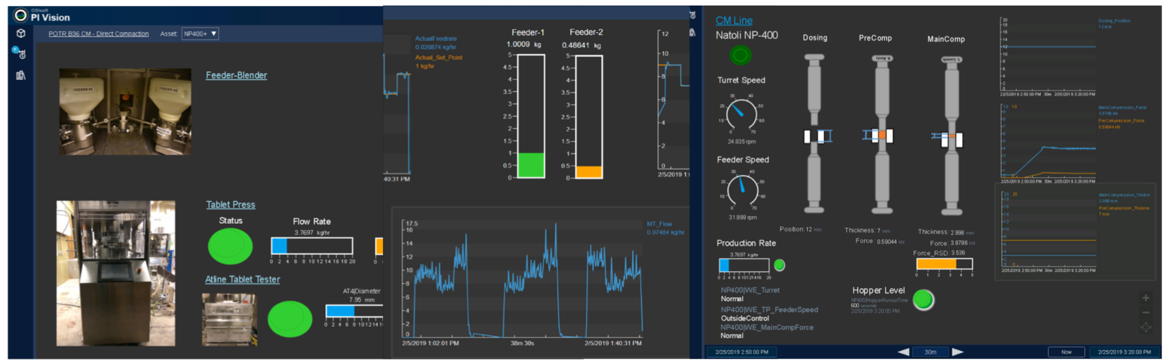


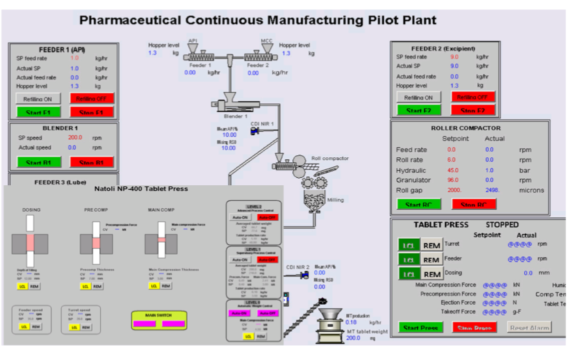


From Device Data to Actionable Insights

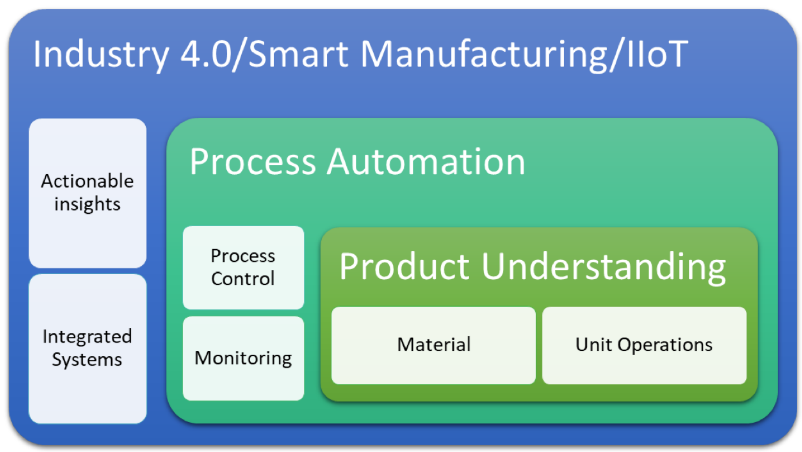


Individual equipment & sensors

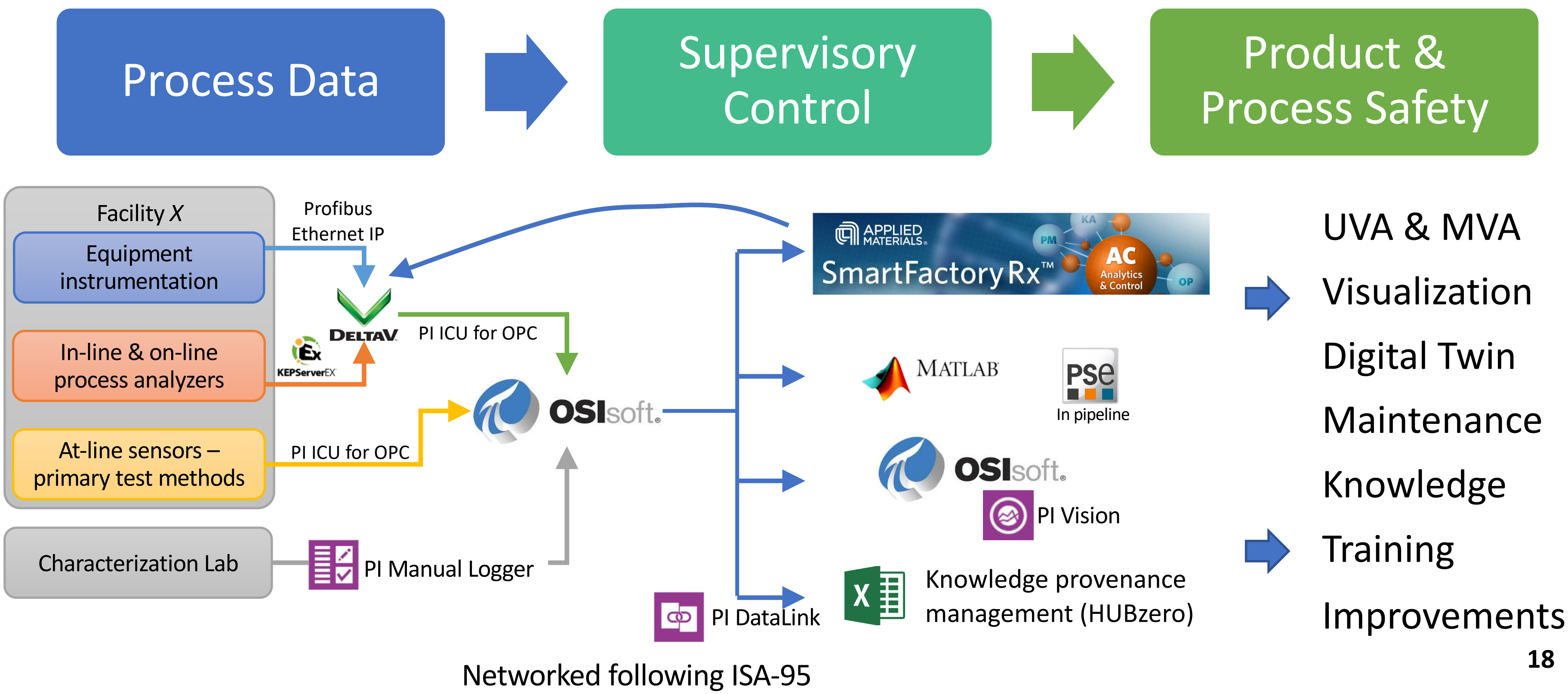




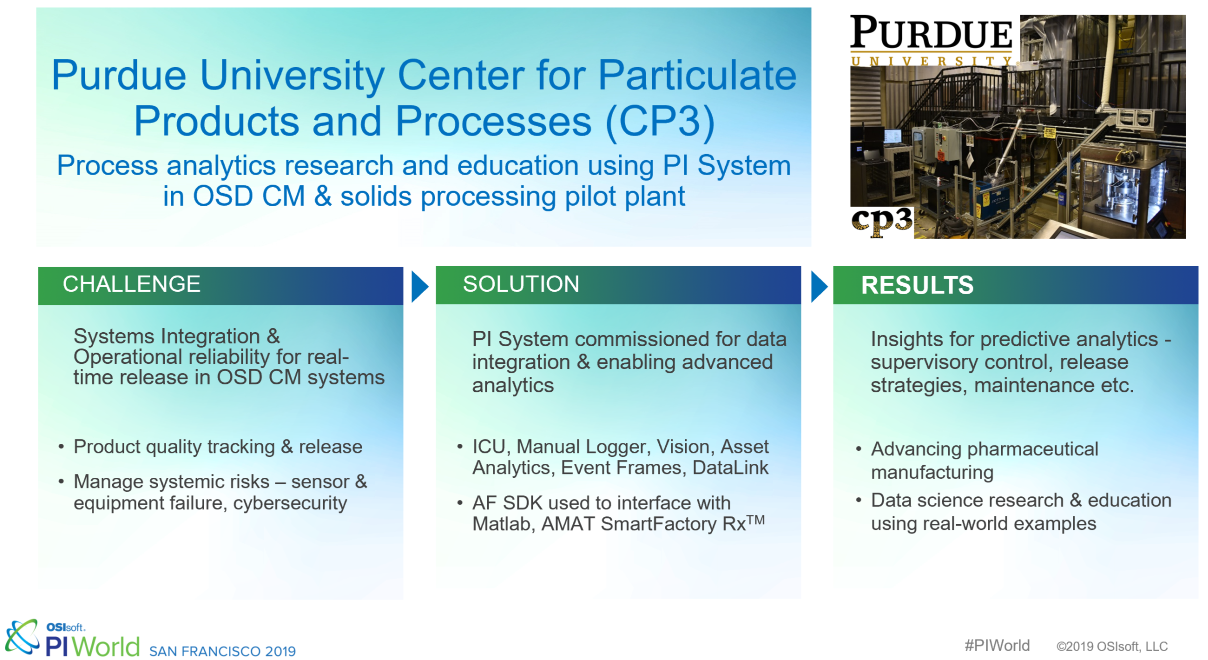
Operations configuration & control using DeltaV

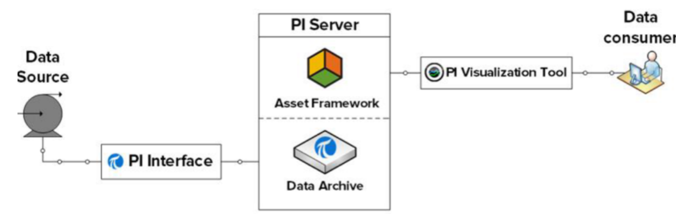


Real-time operations mgmt. infrastructure



OSIsoft PI System





- Process data integration, time-series historian &contextualization
- Enables data-driven analytics for process and business decisions
- Focus: Real time decision support
- Linkage with AMAT Smart Factory tools

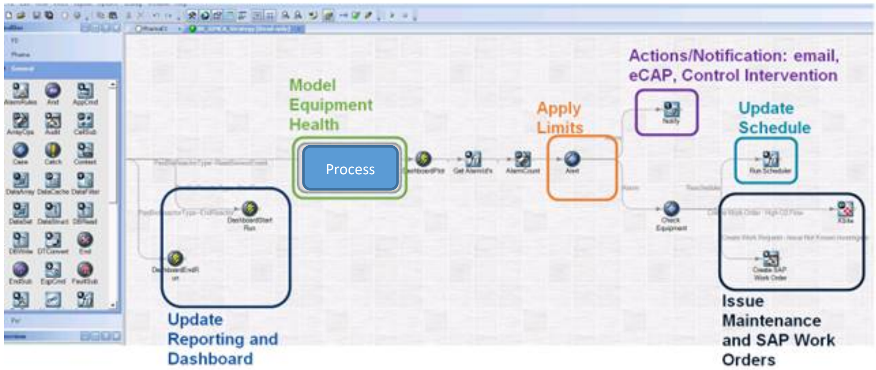
Applied SmartFactory Rx

➢ Information workflows for data-driven & model-based analytics

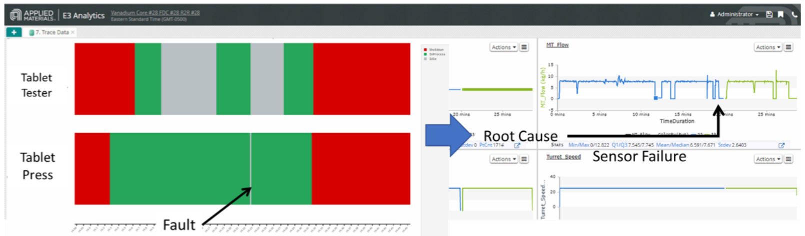
➢ Maintenance management

➢ Data life cycle management

➢ Visualization
- Annotate & manage faults, events
- Track lots & process states, product quality
- Configure release strategies



Applied SmartFactory dashboard for configuring strategies (representative example)



J. Moyne et al., *A software-defined framework for the integrated management of smart manufacturing systems*, Manufacturing Letters 2018

Safety by Design in OSD CM

Product & Material
- Traceability
- Contamination
- Containment

Process & Facility Safety
- Equipment hazards – moving parts, compaction, temperature
- Dust handling
- Leaks, blockage, overflows

Design & Operational Safety

The Human Factor
- Operator HMI
- Alarm Management
- Training and preparedness

Cybersecurity
- Smart sensors, PLCs, DCS, MES, LIMS, ELN, Reporting systems
- Computer literate operators
- Malicious intent

- Risk assessment
- Sensor networks
- Automation
- Information systems
- Operational digital twins
- Culture & Education

Integrated approach to safety…
of products, processes and people

Collaborative Approach

- Develop conceptual designs for coupling RTPM & safety systems
- Identify relevant incidents, implement case studies, assess effectiveness

Integrated Process Operations Management

- Product quality *and* process safety focused regulatory & supervisory control
- Asset health monitoring & condition based maintenance
- Systems integration for Safety & Quality by Design

Teamwork makes the dream work…

- Purdue Team
  - Sudarshan Ganesh, Dr. Qinglin Su, Yasasvi Bommireddy, Yan-Shu Huang, Sumit Kumar
  - UG RAs (2018-19) – Ben Rentz, Dan Vo Bao Lee, Nolan Pepka, Alessandra Lewis
  - Faculty – Profs Rex Reklaitis, Zoltan Nagy, Marcial Gonzalez
  - Purdue CP3 – Dr. Dhananjay Pai, Prof. Carl Wassgren
  - Former group members – Dr. Mariana Moreno, Dr. Jianfeng Liu, Yash Shah
- Purdue Engineering Computer Network – Joshua Harley, Shawn Whitaker, Sundeep Rao
- Rutgers Team

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Chris Zucarelli
Qussai Marashdeh

En'Urga Inc.
Jongmook Lim
Y. Sivathanu

& the community interactions …

Thank You! Questions?