An Advanced Process Control Framing to Application of Analytics and Modeling for Biopharm Manufacturing

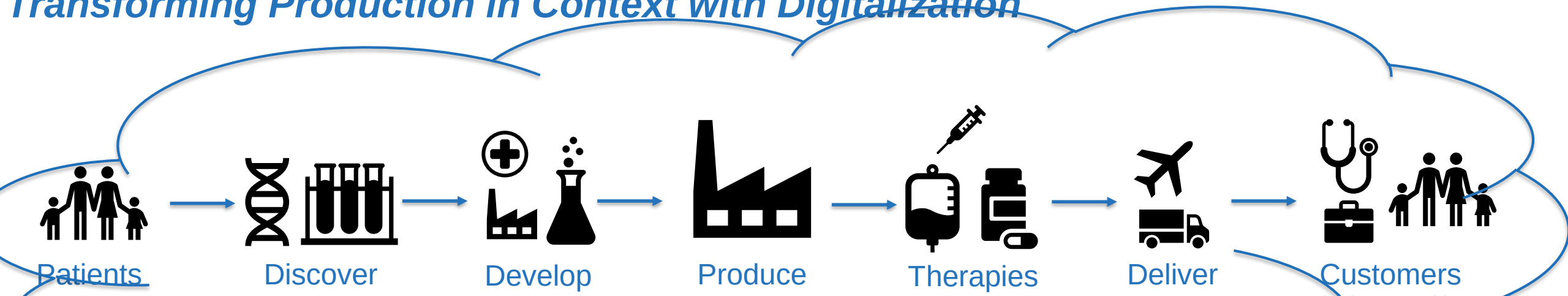
Robert D. Guenard, Ph.D., Sr. Director, *Global Process Analytics, Biogen*

Coauthors: Saly Romero-Torres, Jun Ren, Syed Kaschif Ahmed

WCBP 2019 - Use of Advance Computational Tools in the Biopharmaceuticals and Vaccines Industries Session

Customer-centric Biopharm Modernization

Transforming Production in Context with Digitalization



Customer Insights, Regulatory Compliance, Science and Technology, etc

Digitalization is enabling transformation in each part of the value chain and connecting them together.

Production:
Step change needed in
Quality
Speed/agility/adaptability
Cost
Predictability/Reliability

Biogen

Intelligent Manufacturing Starts in Development! Design for X (Quality, Cost, Reliability, etc.)*

Patients

Providers

Payors

Voice of the Customer

Customer Domain

Customer Requirements (WHAT)

Functional Requirements (HOW)

First House Of Quality

High Priority CTQs
The NUDs

Functional Domain

Functional Requirements (WHAT)

Product Characteristics (HOW)

Second Houses Of Quality

Key Product Characteristics

Physical Domain

Product Characteristics (WHAT)

Process Variables (HOW)

Third Houses Of Quality

Critical Process Factors

Voice of the Process

Process Domain

Process Variables (WHAT)

Process Controls (HOW)

Fourth Houses Of Quality

Control Strategy

A systematic knowledge driven process

*Credit: QfD Model Anando Chowdhury, Merck

Modern Control Strategy Element: Advanced Process Control (APC)

APC is commonly defined as Model-Based Process Control plus Fault Detection and Classification

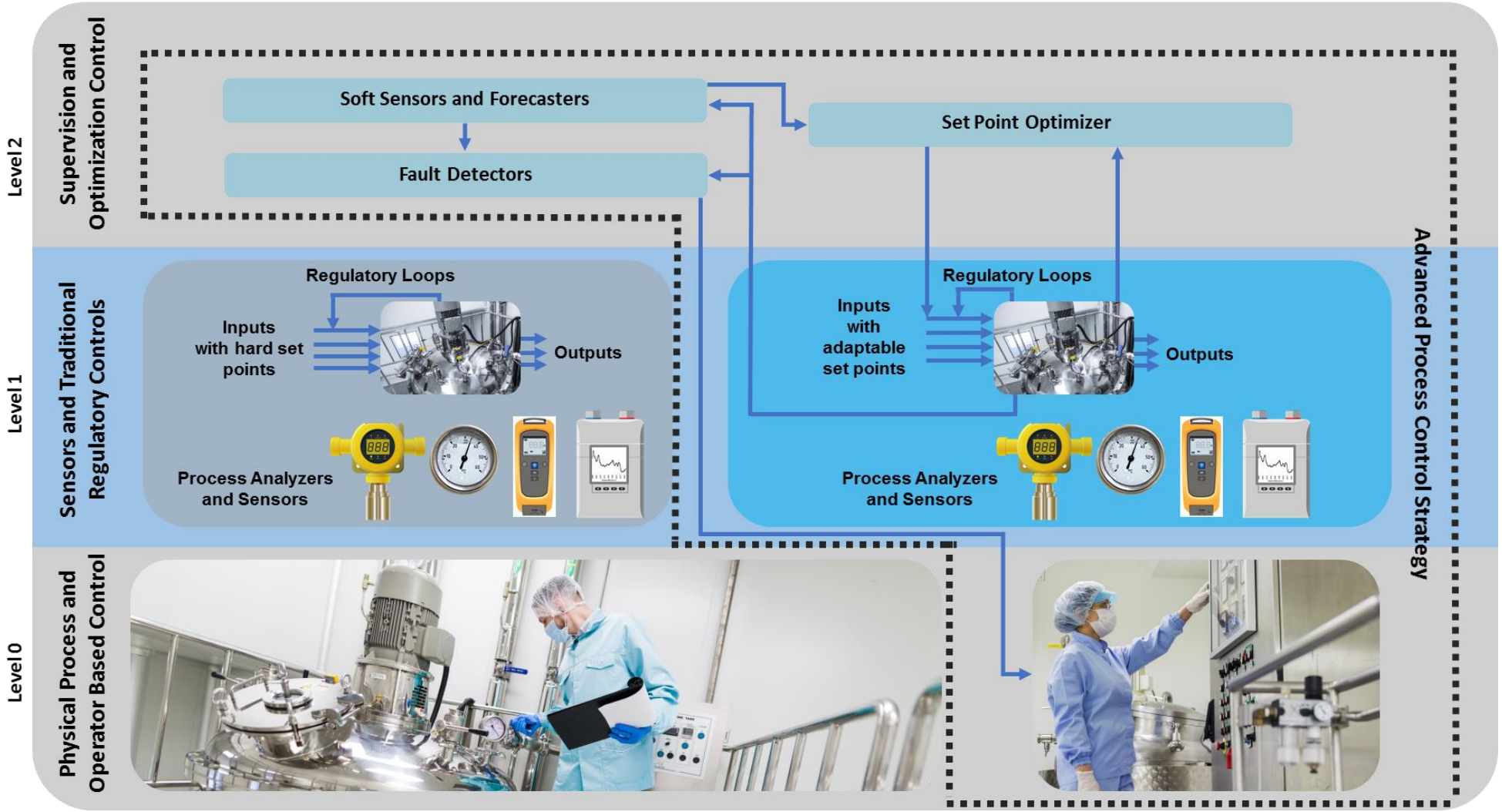
APC = MBPC + FDC

Handbook of Semiconductor Manufacturing Technology, Second Edition /Yoshio Nishi and Robert Doering

- **Model Based Process Control (MBPC) :** "The technique of **modifying the selection of control parameters between runs** to improve process performance."
- **Fault Detection (FD):** the technique of **identifying changing conditions** within equipment and/or process.
- **Fault Classification (FC):** analyzing available data to **determine the root cause** of a fault
- **FDC = FD + FC**

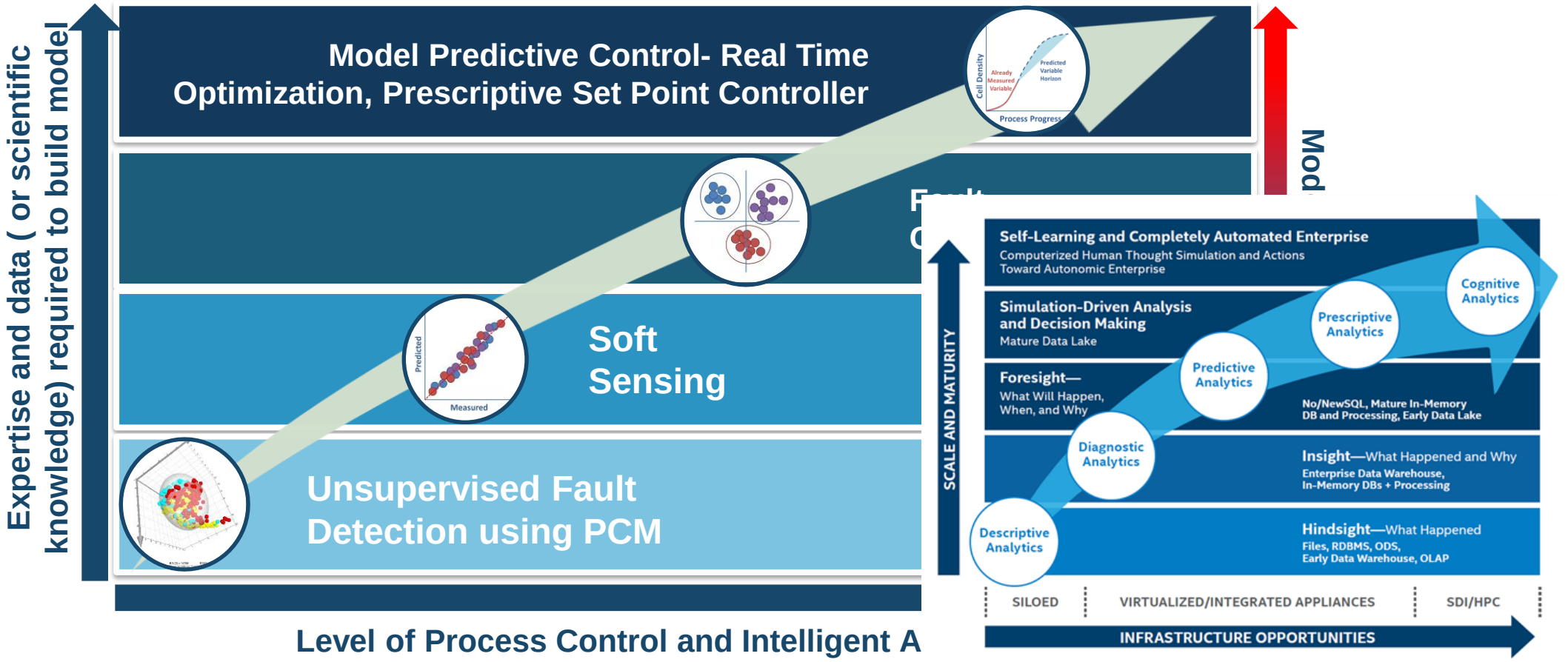
Biogen

APC Resides at Level 2 of ISA S-95*



*ISA = International Society of Automation

Biopharm Process Model Continuum for APC*



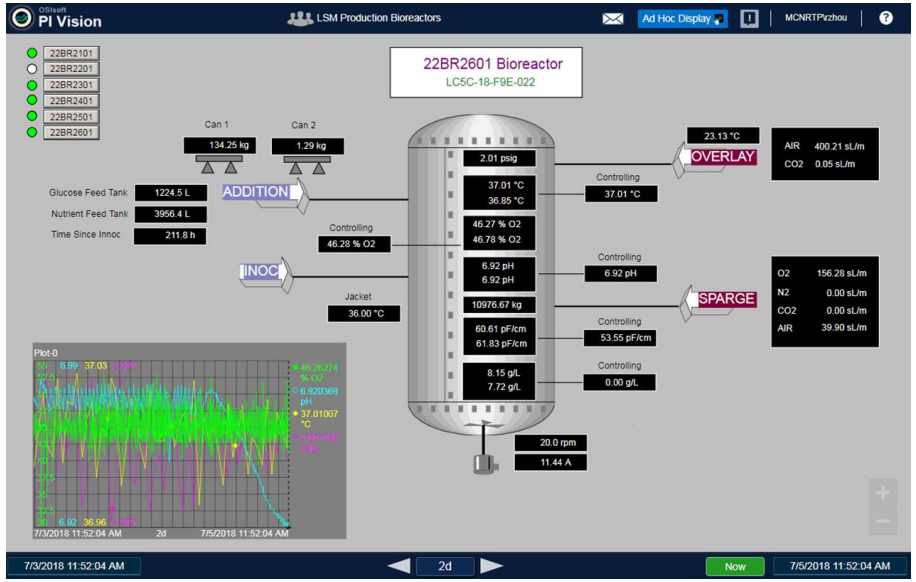
*S. Romero-Torres, et al, *Pharm. Rev*. May/Jun 2018, p 62-71

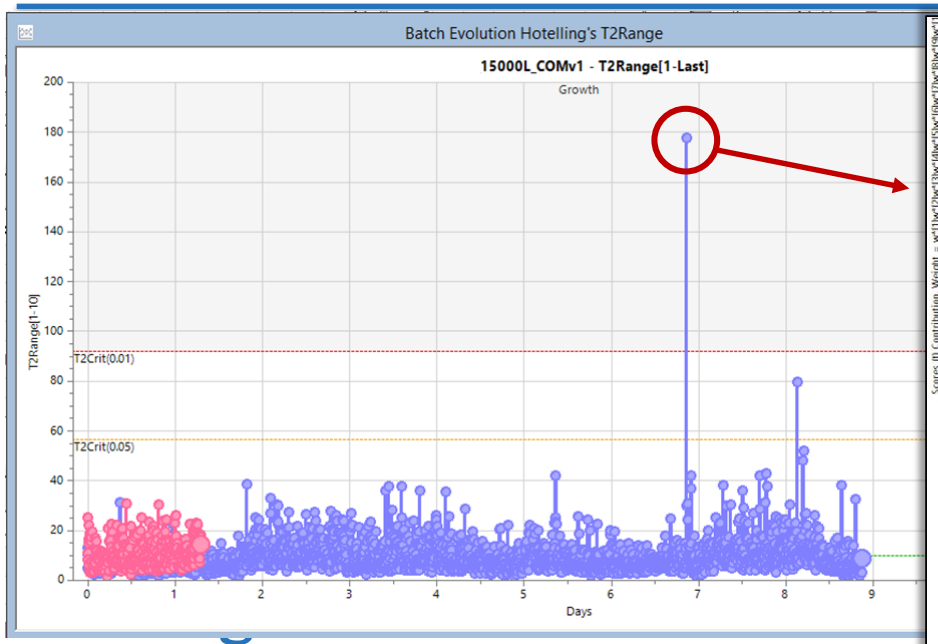
Fault Detection – Process Condition Monitoring

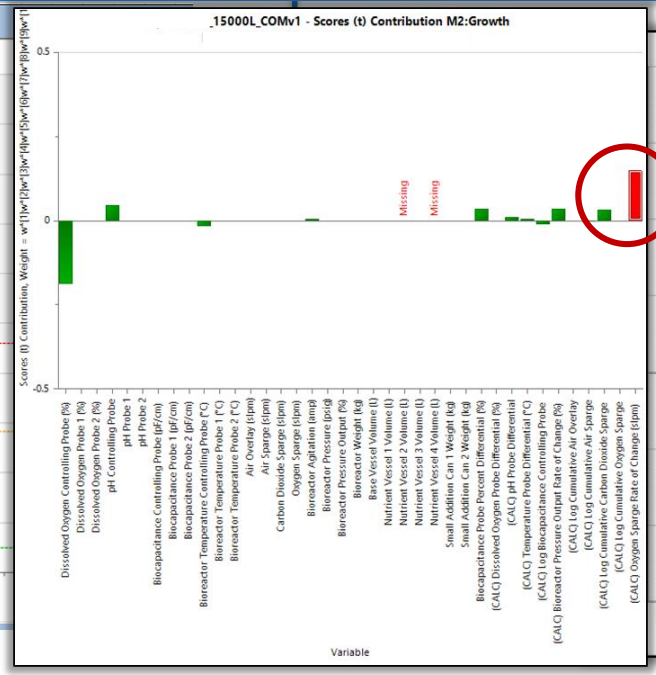
What? Multivariate real-time process monitoring of equipment and state variables.

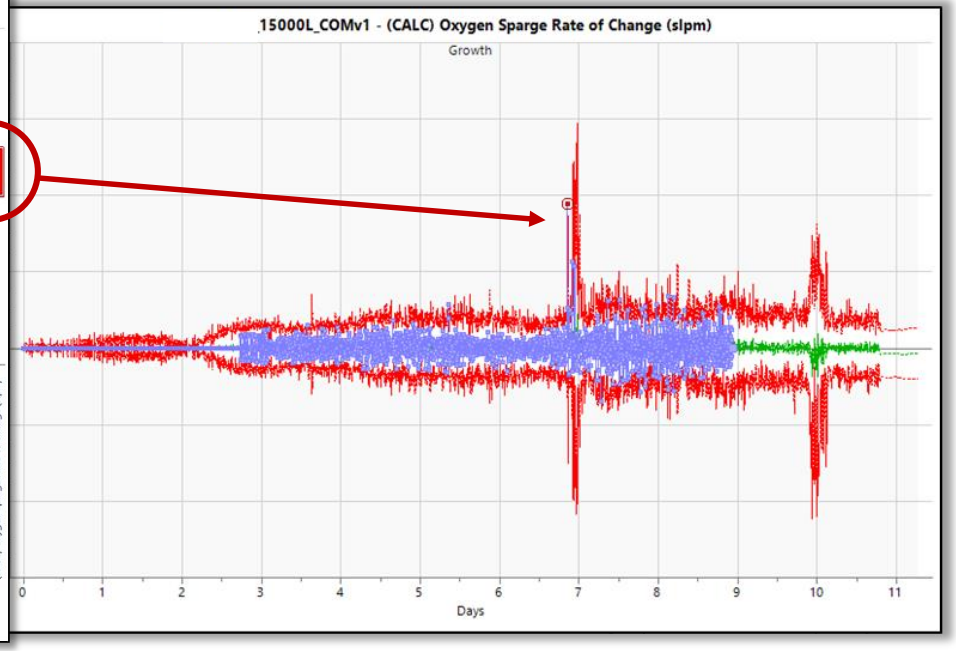
How? Utilize SIMCA On-line and unsupervised multivariate models.

Why? Provide production floor with process health monitoring capability and ability to diagnose root causes of process disturbances and faults.







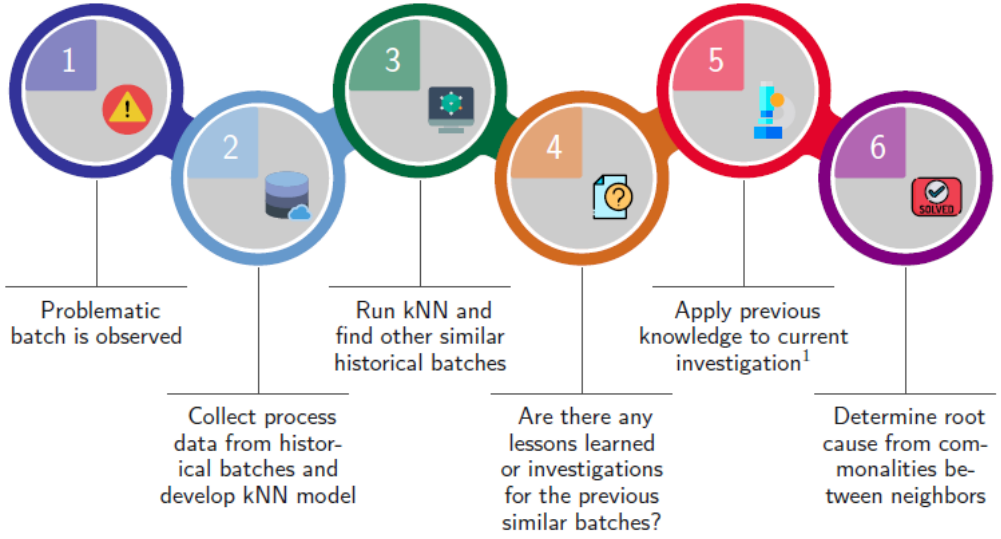


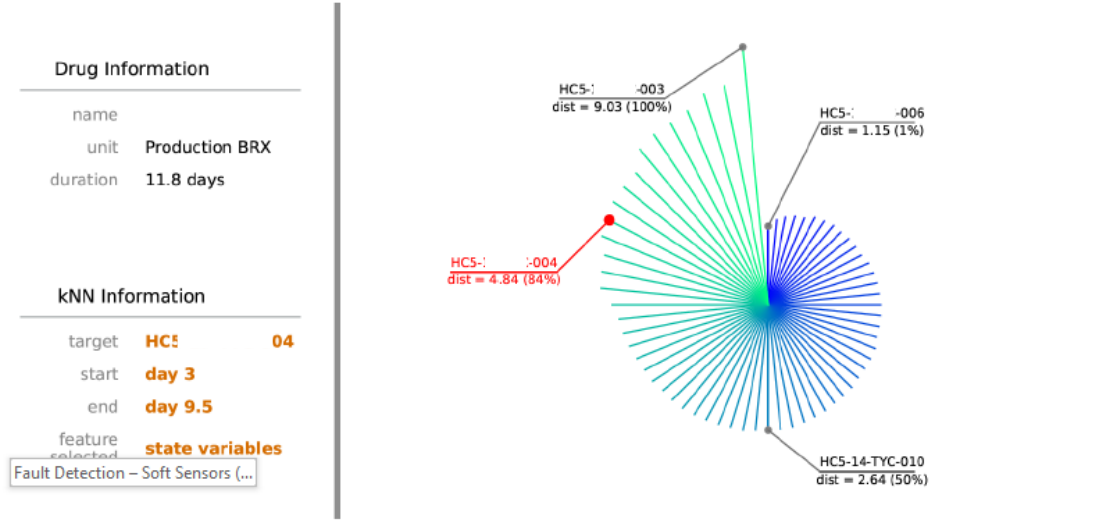
Fault Detection – K-Nearest Neighbors (KNN)

What? Innovative solution to support root cause analysis and process performance evaluation

How? Through inter-batch similarity analysis using KNN based method.

Why? Long-term resource and time saving during process investigations and evaluations





Similarity analysis can be used to calculate the distance/deviation of a batch to the historical average. Therefore, the tool can also help select representative or 'golden' batches.

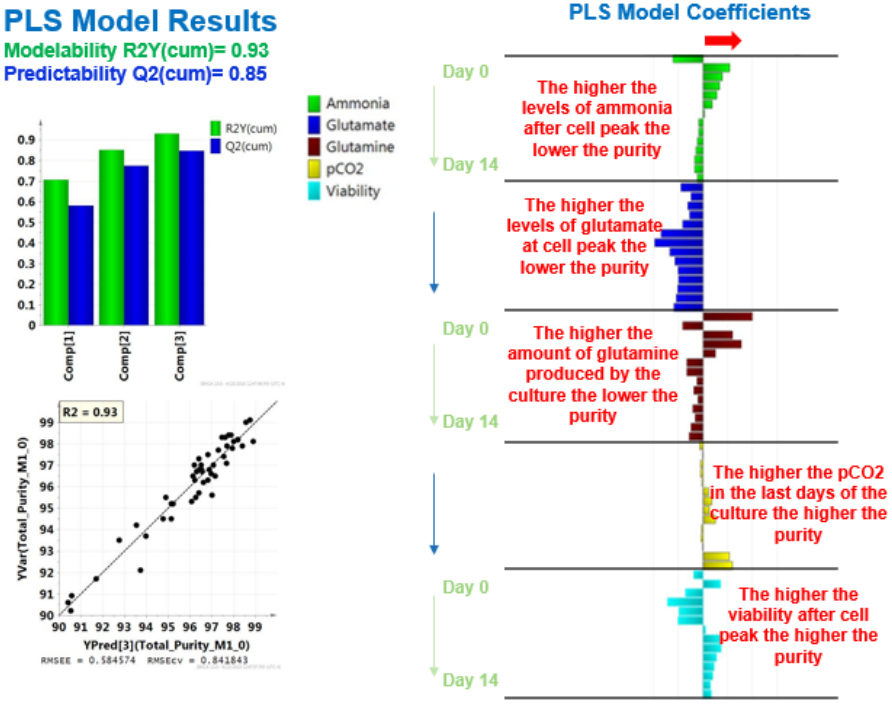
Fault Detection – Soft Sensors

(estimators)

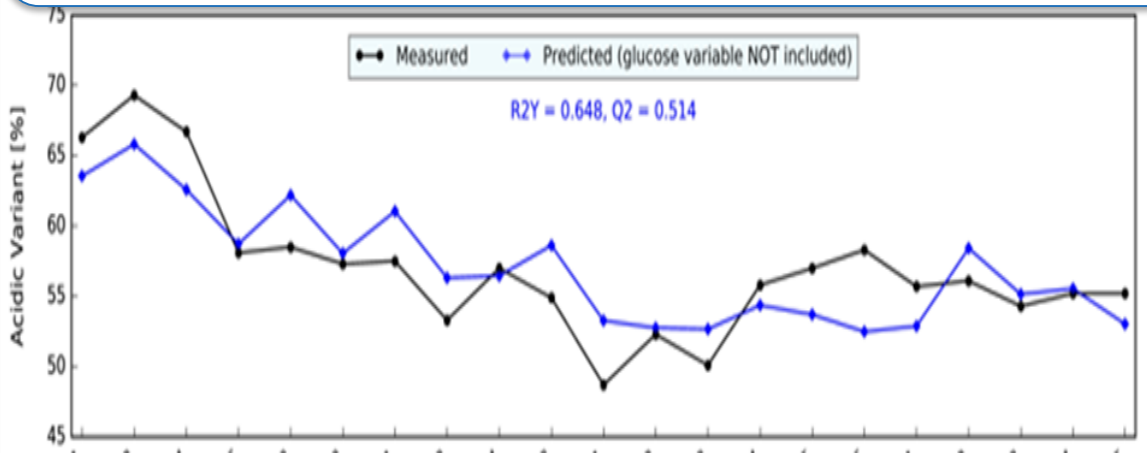
What? Develop quantitative soft sensors to estimate quality attributes based on state variables.

How? Apply MLR and PLS to build supervised models using an empirical approach.

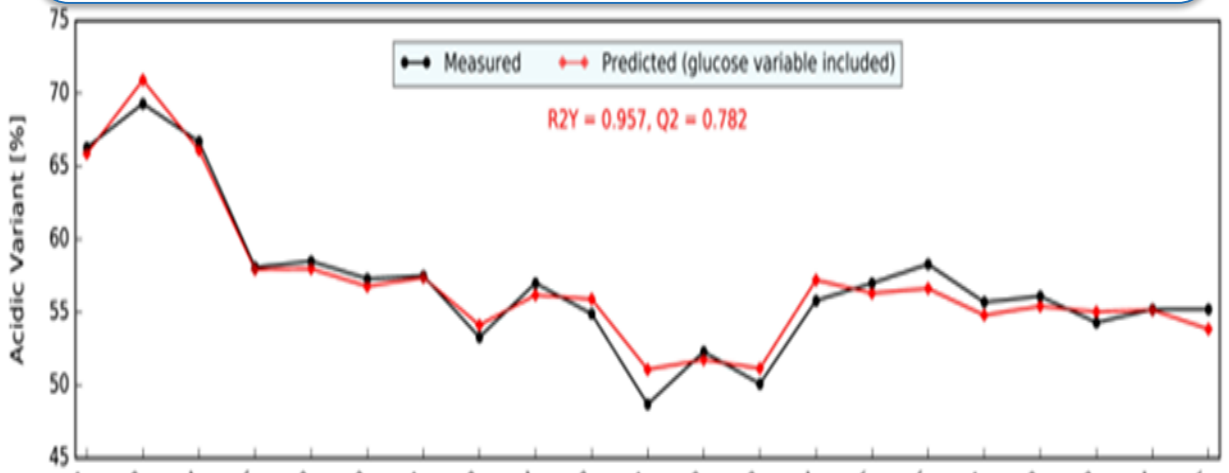
Why? Fault detection/real time quality & gain valuable process understanding.



Quality attribute estimator using traditional process sensing.
R2=0.65



Quality attribute estimator using traditional process sensing and in-line Raman.
R2=0.96

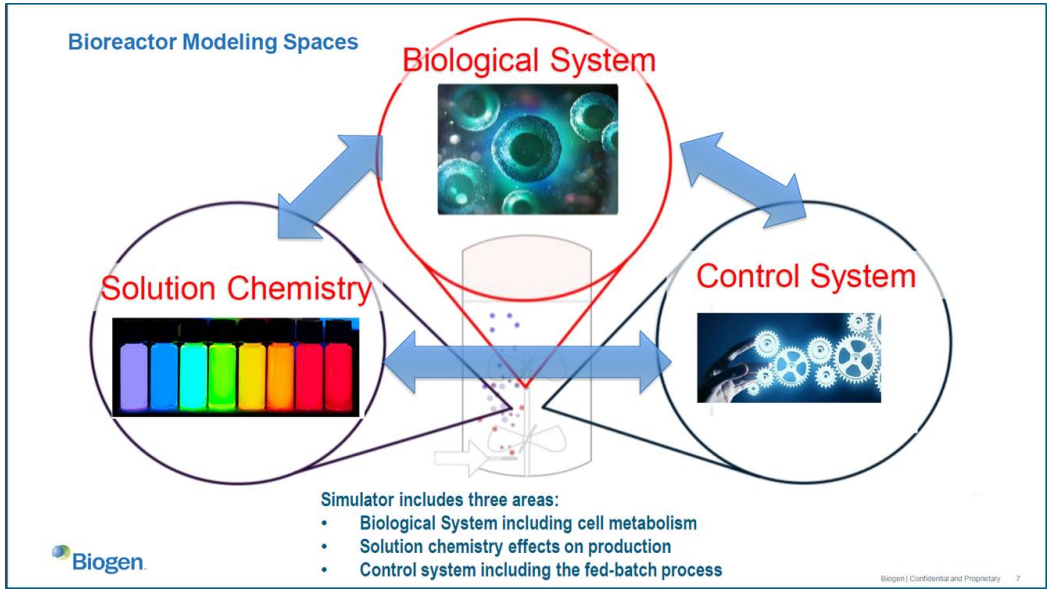


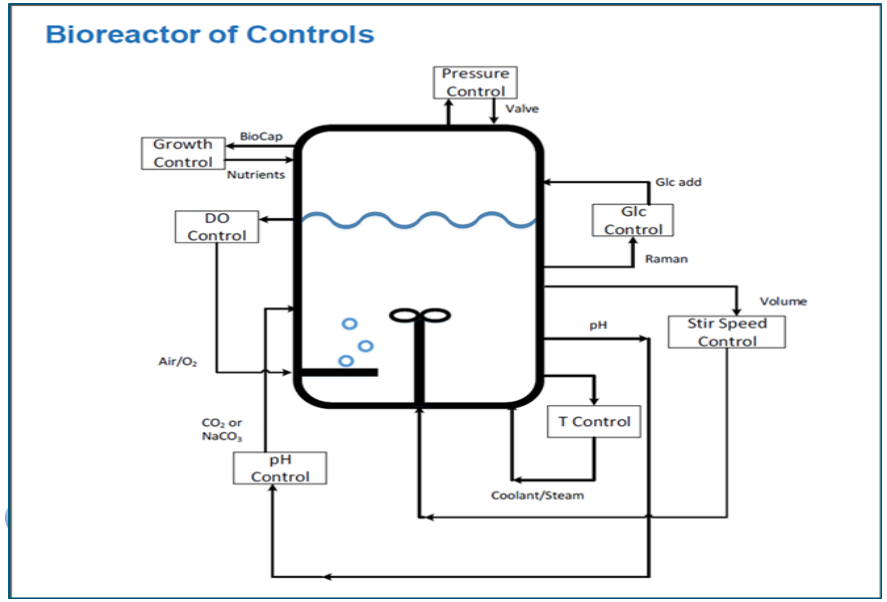
Model-Based Control – Bioreactor Simulator (digital twin)

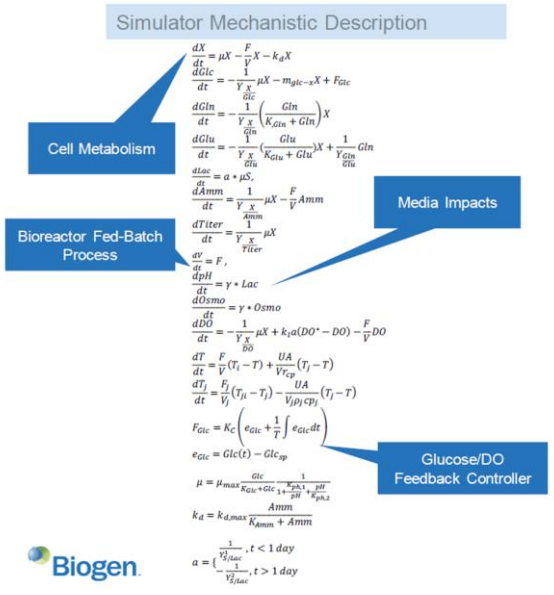
What? A bioreactor simulator that incorporates mechanistic and machine learning modeling strategies.

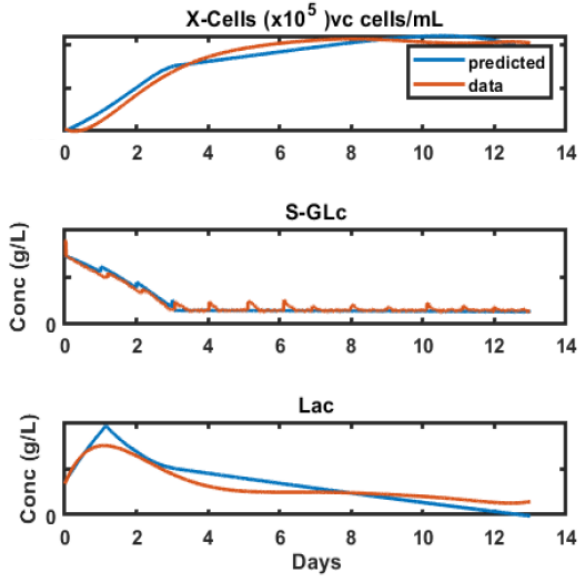
How? By utilizing fundamental principles found in the literature, DOEs and manufacturing data sets

Why? To capture mechanistic understanding (and data patterns) in support of process development/, improvements & advanced controls.



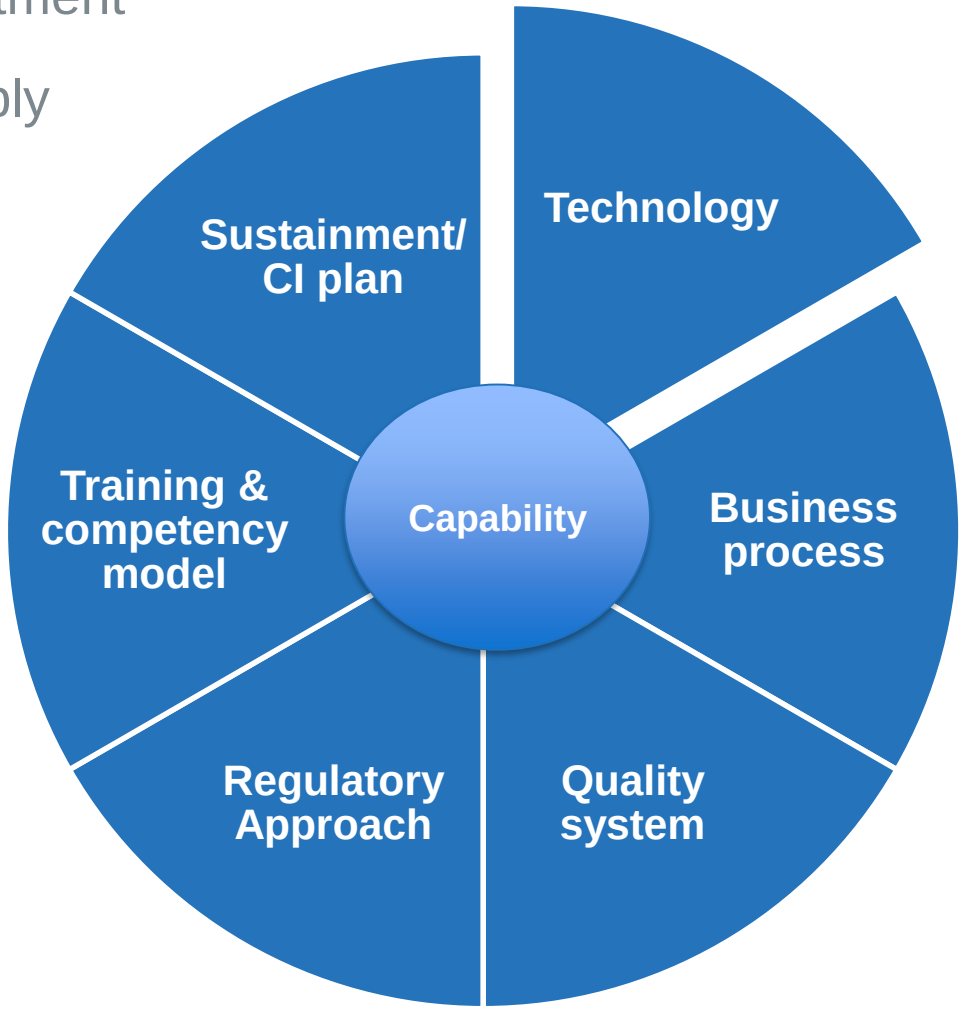






APC Journey: Lessons and Guiding Principles so far…

- Sponsorship is key – transformation takes vision and investment
- Innovate for unmet needs and drivers in the context of supply chain to patient
- Turn technologies into capabilities
- It takes a diverse village of partners: co-creation!
- No AI without IA – need data systems & architecture.
- Models create a virtuous learning loops
    - *Takes knowledge to build them*
    - *Gain knowledge by using them*
- We are just scratching the surface!



Biogen

Summary

- Demands are increasing on manufacturing to improve supply chain performance and patient access
- Digitalization is enabling a disruptive change across the value chain and production
- Use of process control approaches like APC will help modernize production.
- Must build capabilities from disruptive technologies
- “The future is here now…it’s just not yet evenly distributed”

Fred Miller – Kaleel Jamison Consulting Group

Biogen

Acknowledgements

Development Team

An Zhang

Bassam Nakhle

Brad Stanley

Devin McCann

John Paul Smelko

Kelly Wiltberger

Le Ly

Li Zhang

Sarwat Kahttak

Rashmi Kshirsagar

Valerie Tsang

MS/GPA Team

Bill Welsh

Canping Jiang

Chao Shi

Dan Hill

Dave Kolwyck

Gitanjali Talreja

Greg Stromberg

Jun Ren

Mike Farrow

Oliver Steinhof

Rebekah Wilson

Saly Romero-Torres

Thomas Matthews

BES/IT Team

Bill Rusin

Bob Song

Frank Mastellone

Jim Kenyon

Jyotika Sharma

Mike Stroz

Rich Snoddy

Tim Alosi

Yvonne Ledford

Quality/Regulatory Team

Cassandra Braxton

Enoc Henry

Diane Wilkinson

Greg Pittman

John Armando

Kim Wolfram

Sofi Fexby

Stacey Traviglia

Engineering Team

Chris Antinou

James Wright

Scott Billman

Sponsors

Paul McKenzie

Rohin Mhatre

Steve Doares

Eliana Clark

Besu Alemayehu

John Reusch

Brian Fahie

Adam Kroft

Michael Pohlscheidt

Biogen

Thank you!!!