Data Integration and Integrity Starts in the Basement

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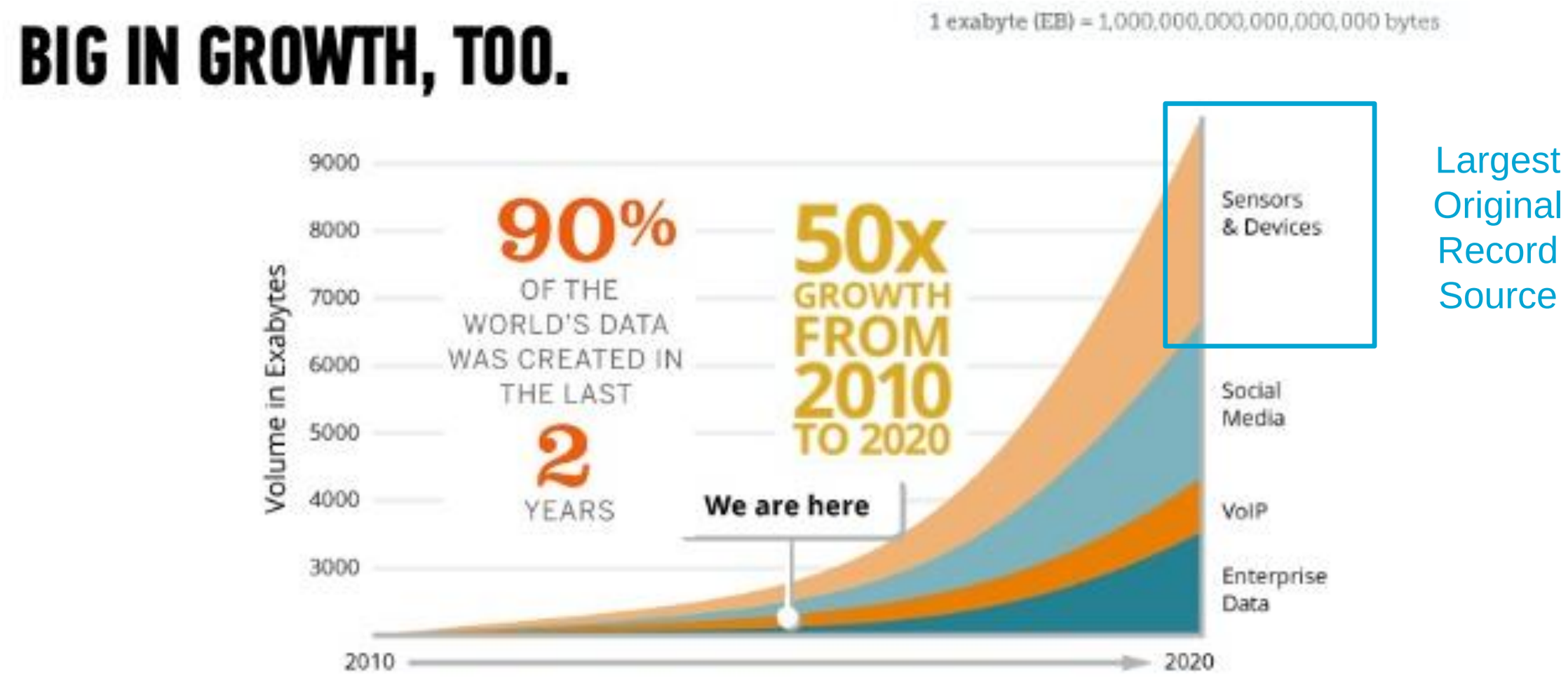
Life Science Manufacturing Produces:

Product **+ Paperwork** **+ Data**

Message from IFPAC (and other sources)



Largest Original Record Source

Original Records Have New Data Integrity Requirements

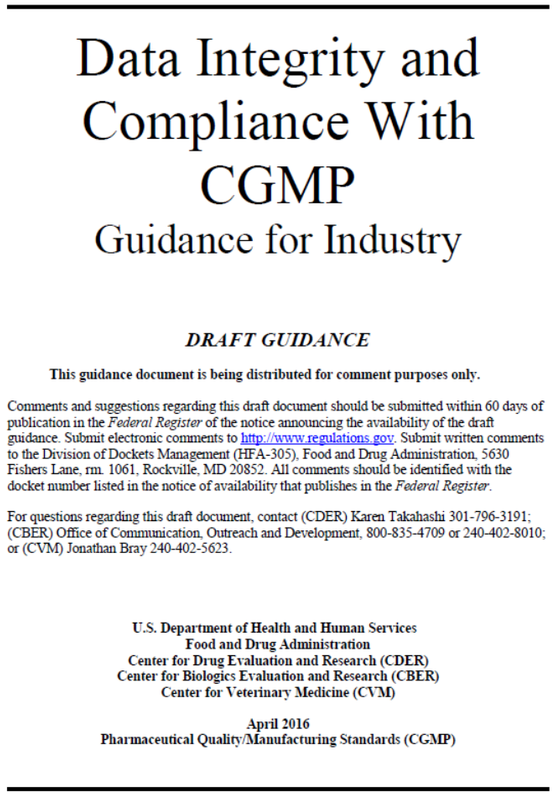
Data Integrity

- Completeness, consistency, and accuracy of data.

- Attributable
- Legible
- Contemporaneous
- Original (or true copy)
- Accurate

ALCOA +

- Enduring
- Complete
- Consistent
- Retrievable



Data Integrity and Compliance With CGMP

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Karen Takahashi 301-796-3191; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CVM) Jonathan Bray 240-402-5623.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

April 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

FDA Guidance:
What is Metadata?

Contextual information required to understand data

– A data value by itself is meaningless without additional information about the data

Structured information that describes, explains, or otherwise makes it easier to retrieve, use or manage data

Data should be **maintained throughout the record's retention period with all associated metadata required** to reconstruct the CGMP activity

The relationships between data and their metadata should be preserved in a secure and traceable manner

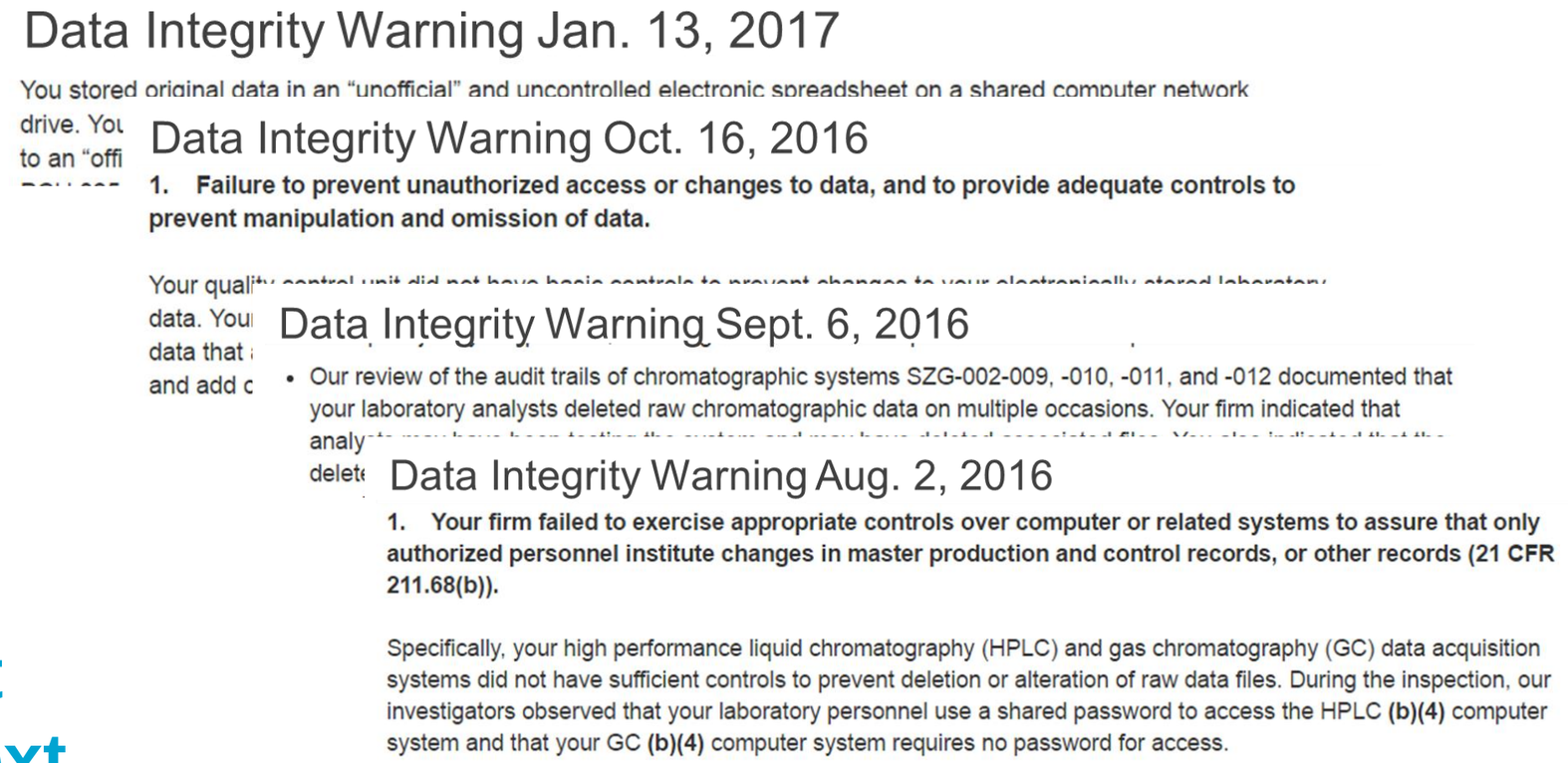
Meta Data and Context are Key Integrity Concepts

Warning Letters on Electronic Data Integrity

Key Issues Today:

- Shared Passwords
- Electronic records editable
- Electronic records deleted / didn't keep raw data files
- Original data in uncontrolled spreadsheet

Nothing yet about metadata and context



Data Integrity Warning Jan. 13, 2017

You stored original data in an "unofficial" and uncontrolled electronic spreadsheet on a shared computer network drive. You to an "offi

Data Integrity Warning Oct. 16, 2016

1. **Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.**

Your quali
data. You
data that
and add c

Data Integrity Warning Sept. 6, 2016

- Our review of the audit trails of chromatographic systems SZG-002-009, -010, -011, and -012 documented that your laboratory analysts deleted raw chromatographic data on multiple occasions. Your firm indicated that analy
delet

Data Integrity Warning Aug. 2, 2016

1. **Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).**

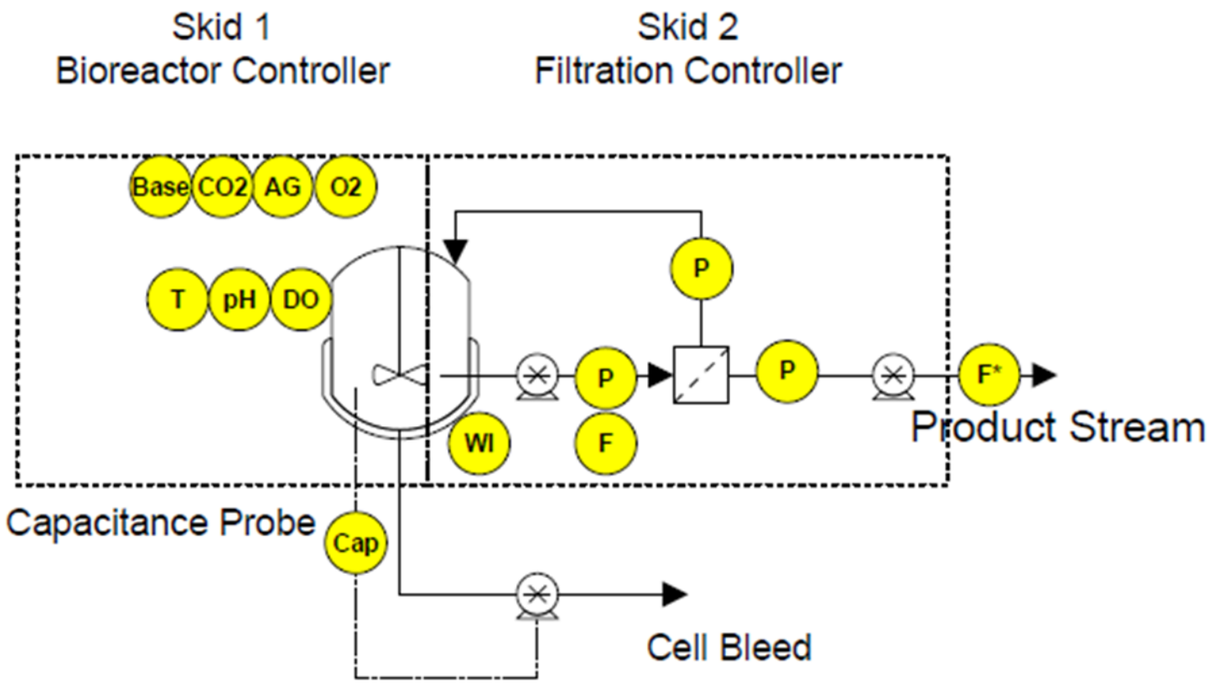
Specifically, your high performance liquid chromatography (HPLC) and gas chromatography (GC) data acquisition systems did not have sufficient controls to prevent deletion or alteration of raw data files. During the inspection, our investigators observed that your laboratory personnel use a shared password to access the HPLC **(b)(4)** computer system and that your GC **(b)(4)** computer system requires no password for access.

FDA is Looking for Data Integrity Issues

So What is “Context” for Life Science Manufacturing?

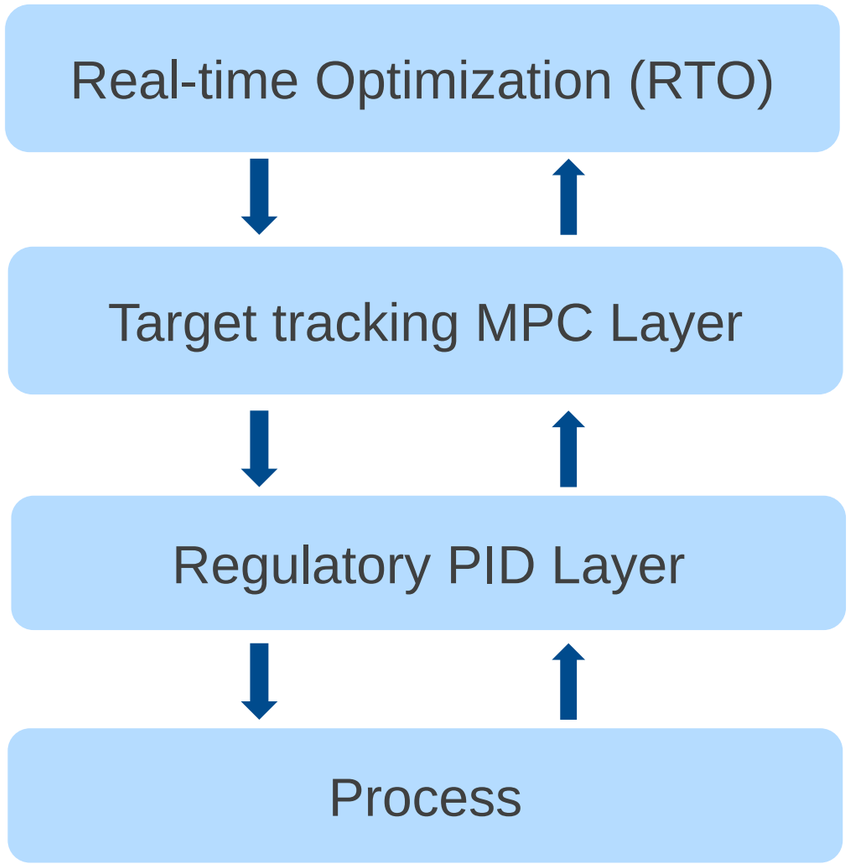
Context Today

- Example Continuous Bioreactor PFD



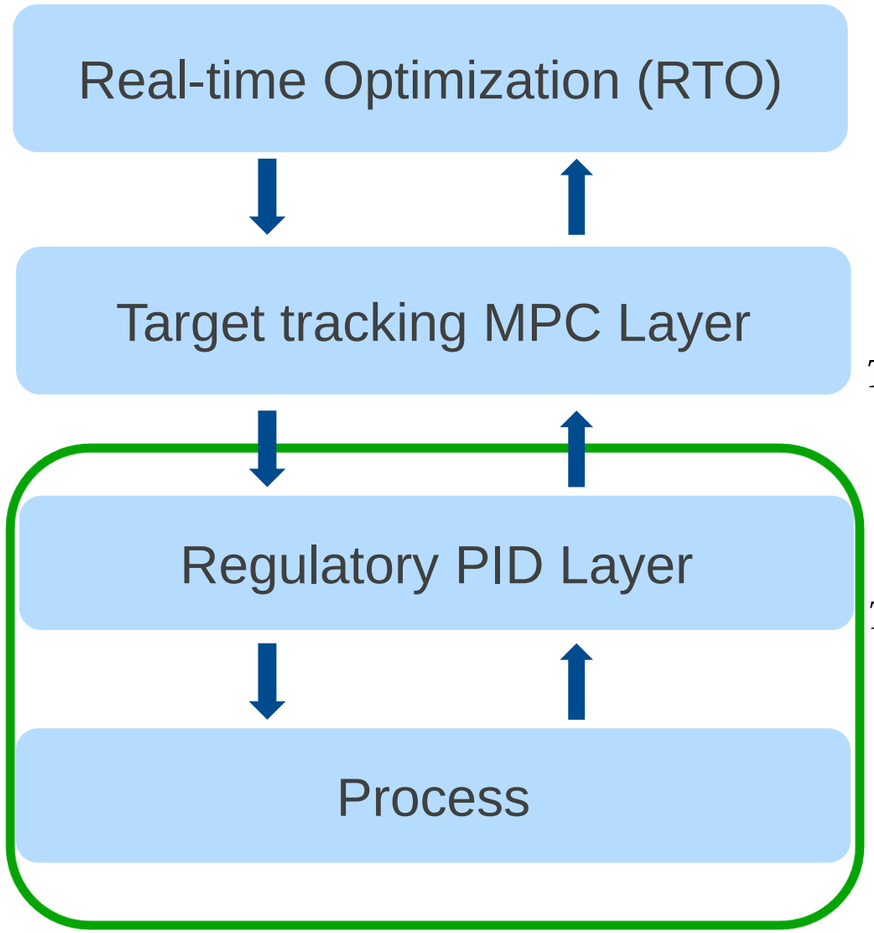
- Unit name / identifier
- Transmitter / sensor tags
  - Range / Units for tag
- Motor / rotating equipment names
  - Possible motor measurement (amps, rotations, etc.) with units
- Analyzer name / identifier
  - Measured value / units
  - Analyzer status
- Weigh scale name / identifier
  - Measured value / units
- Order / Batch ID number
  - When equipment was used as part of an order
- Other as required

Continuous Manufacturing Requires Comprehensive Control Solutions

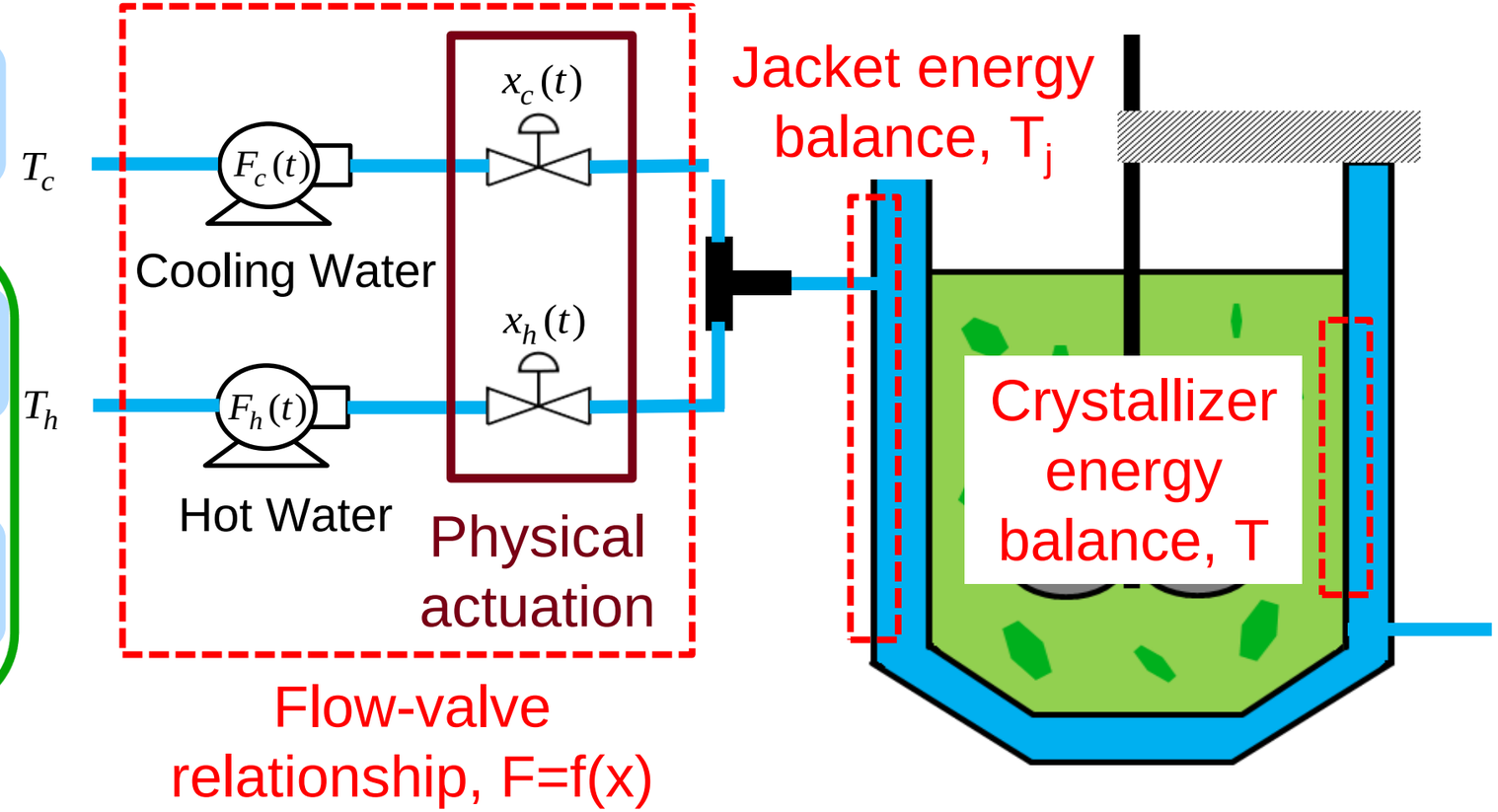


- Continuous Regulatory Control for minimum Variability
  - PID Control is the workhorse
- Advanced Control for Constraint Optimization
  - Multivariable Control
  - Control of Difficult Dynamics
  - Inferential Control
  - Optimization Objectives
- Statistical Process Control
  - Multivariate
    - Principle Component Analysis
    - Partial Least Squares

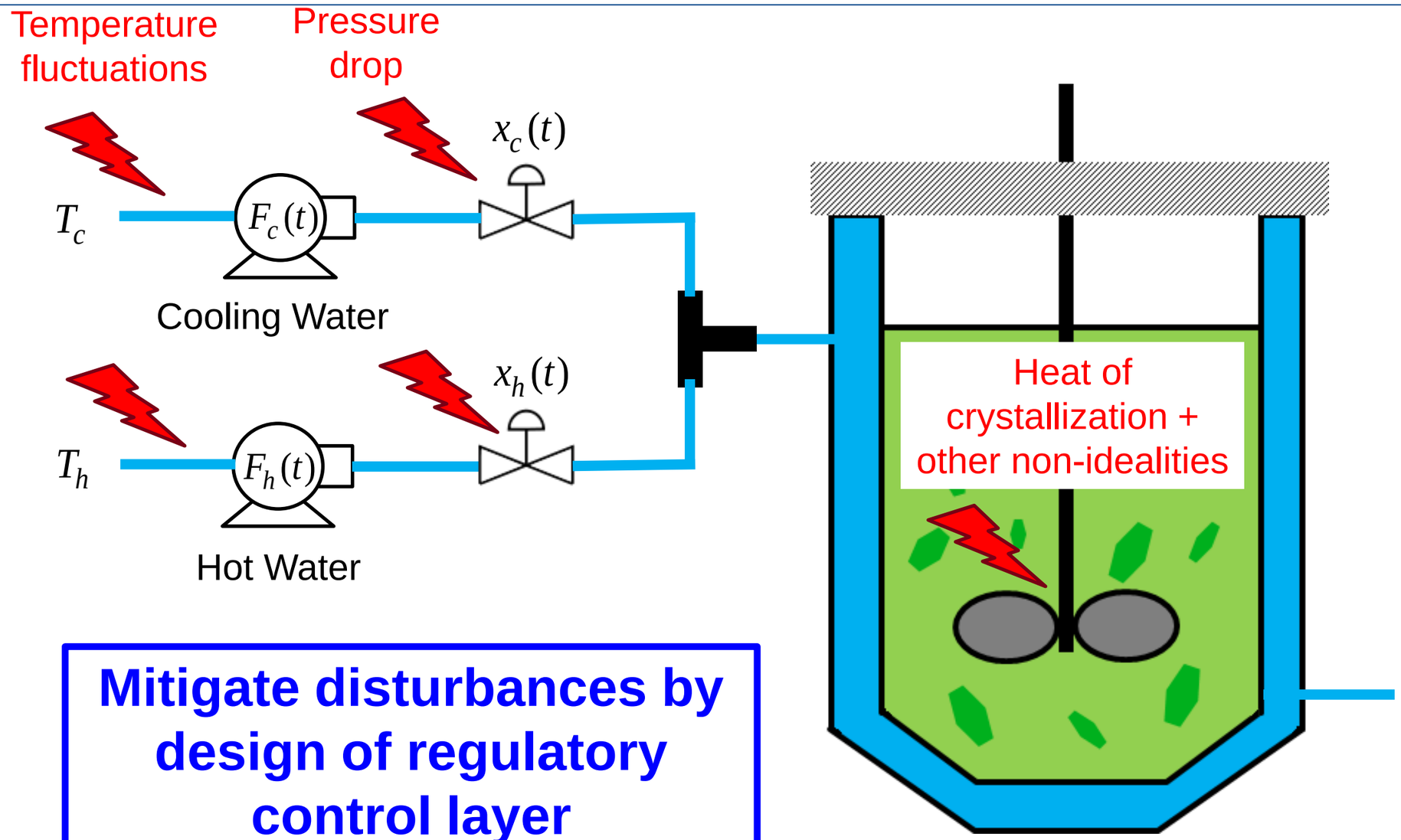
“Basic” PID Control Has to Work



- Temperature profile, T(t), is main design variable for cooling crystallization
  - Cannot set T(t) directly; T(t) specified from valve positions of cold and hot water streams

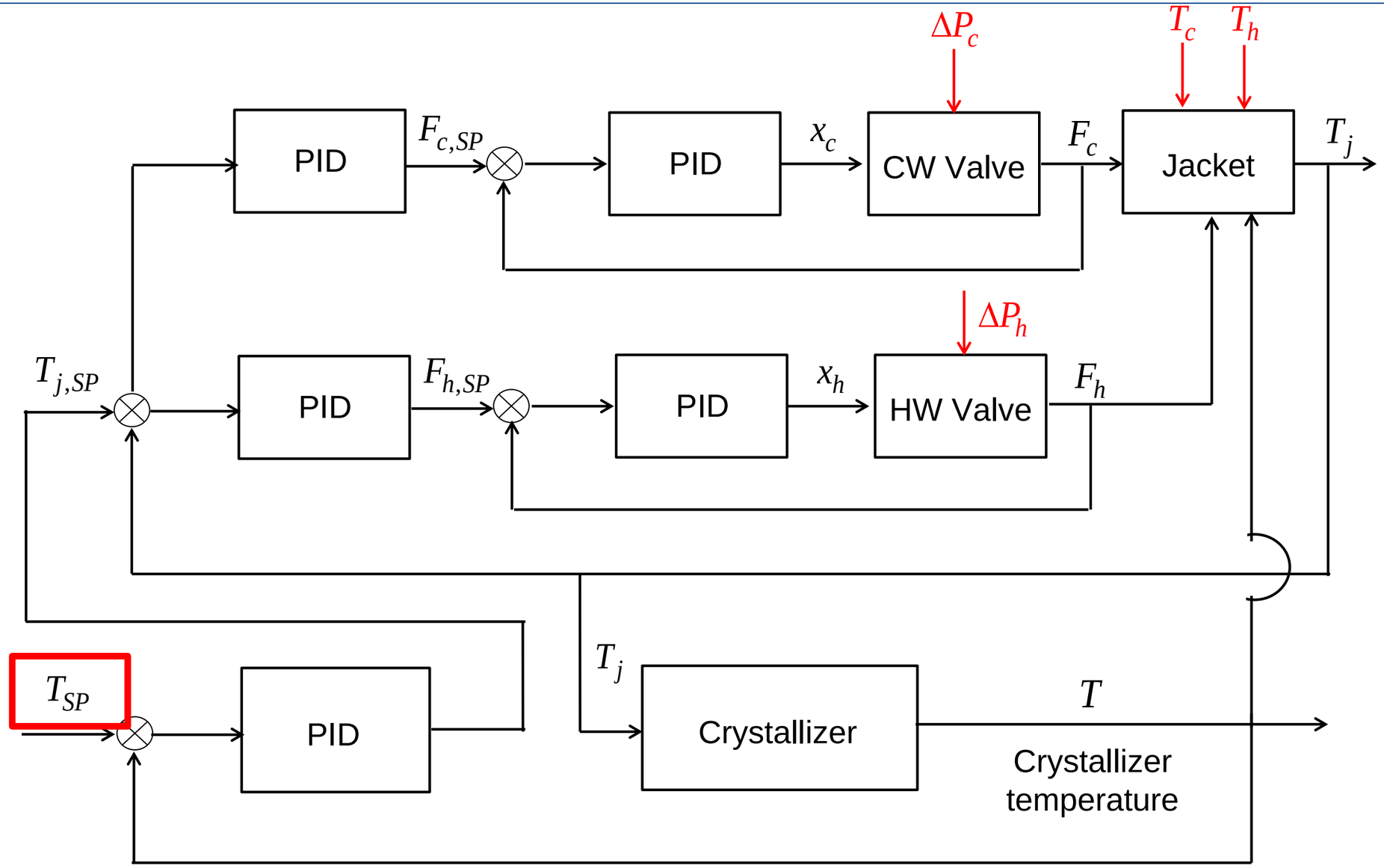


Account for Likely Sources of Disturbances

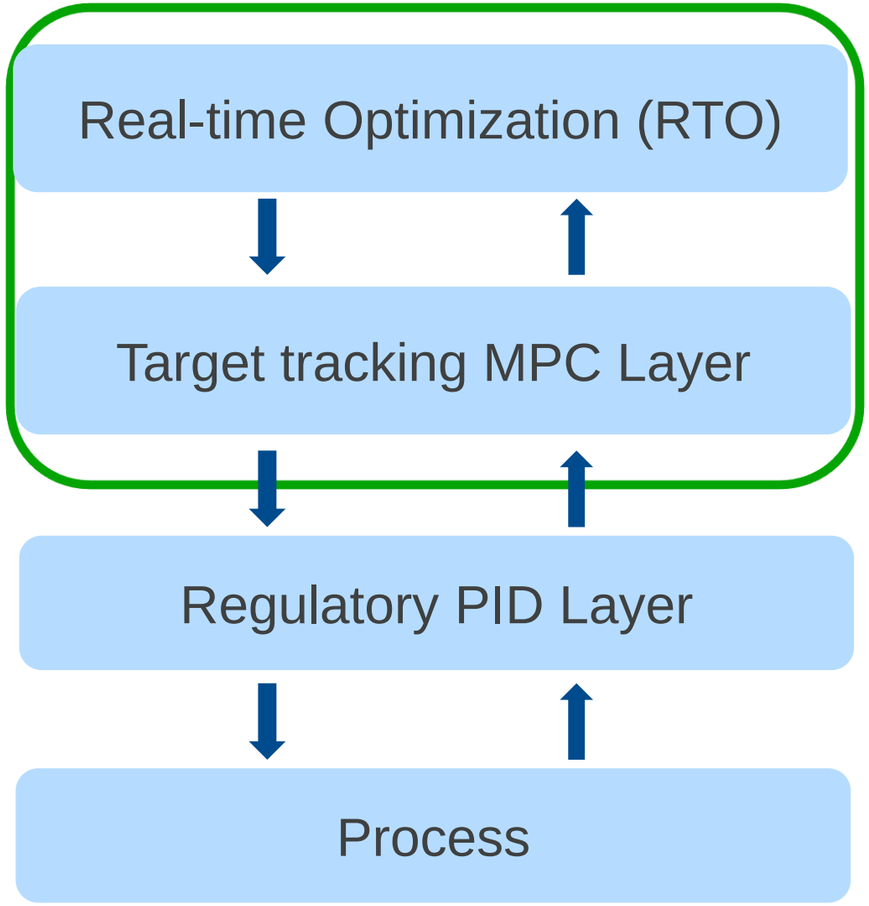


Mitigate disturbances by design of regulatory control layer

Design of Regulatory Layer: Cascade Control



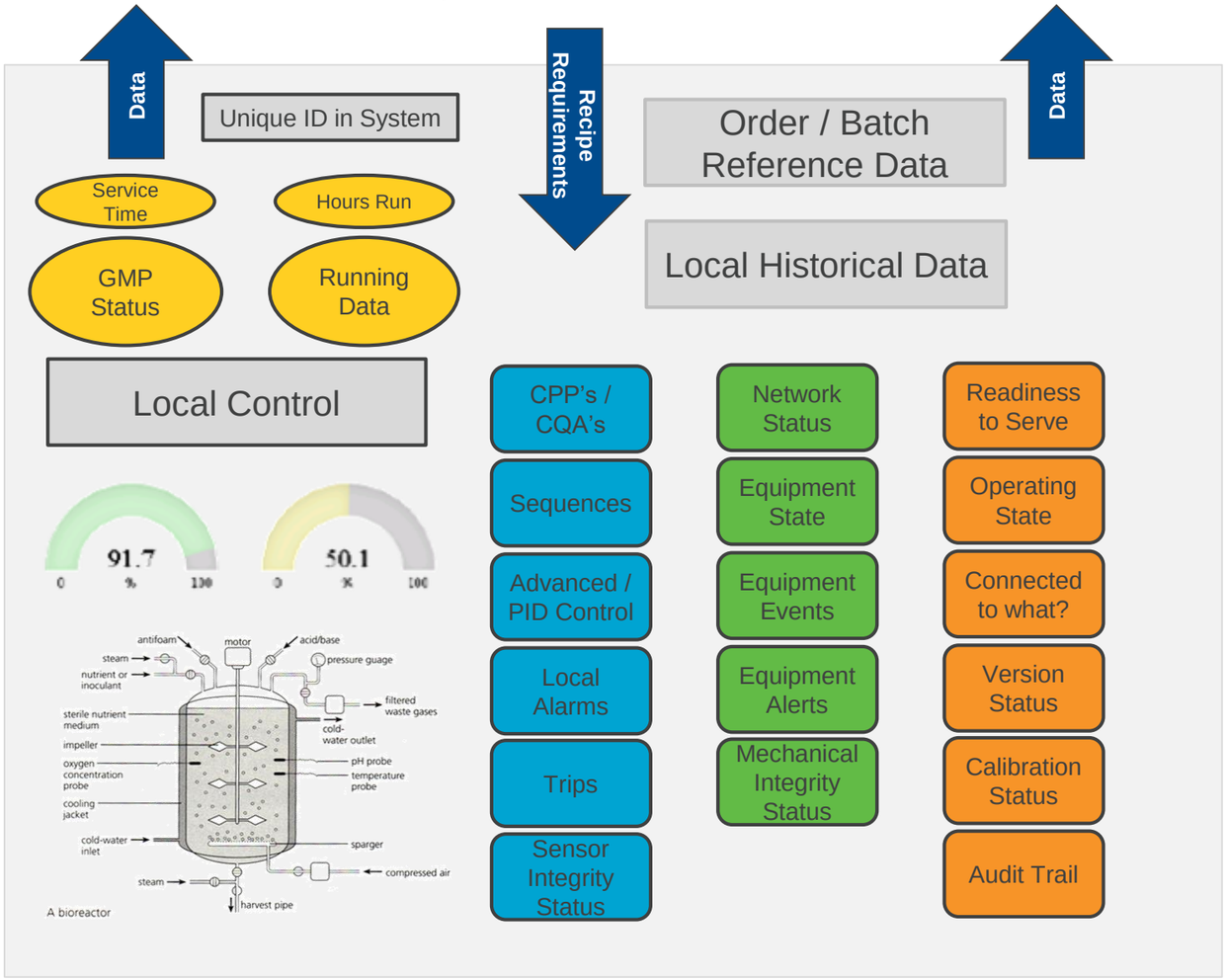
Now You Can Add Modeling to Characterize / Optimize, But….



- Studies in other industries show control loops in “manual”, much less auto or cascade >50% of the time
- When models are used to optimize a unit, the first thing done is “tune the control loops”
  - >75% of optimization benefits come from getting loops properly tuned, valves working properly
- Is a heat exchanger, motor or pump working per spec for the model or has it’s performance degraded over time?
- Am I running the correct version of the configuration for this product for this model?
- Is the devices or sensor sending out a good value?

Context to Consider for Modular Automation Needed to Support Modular Unit Operations

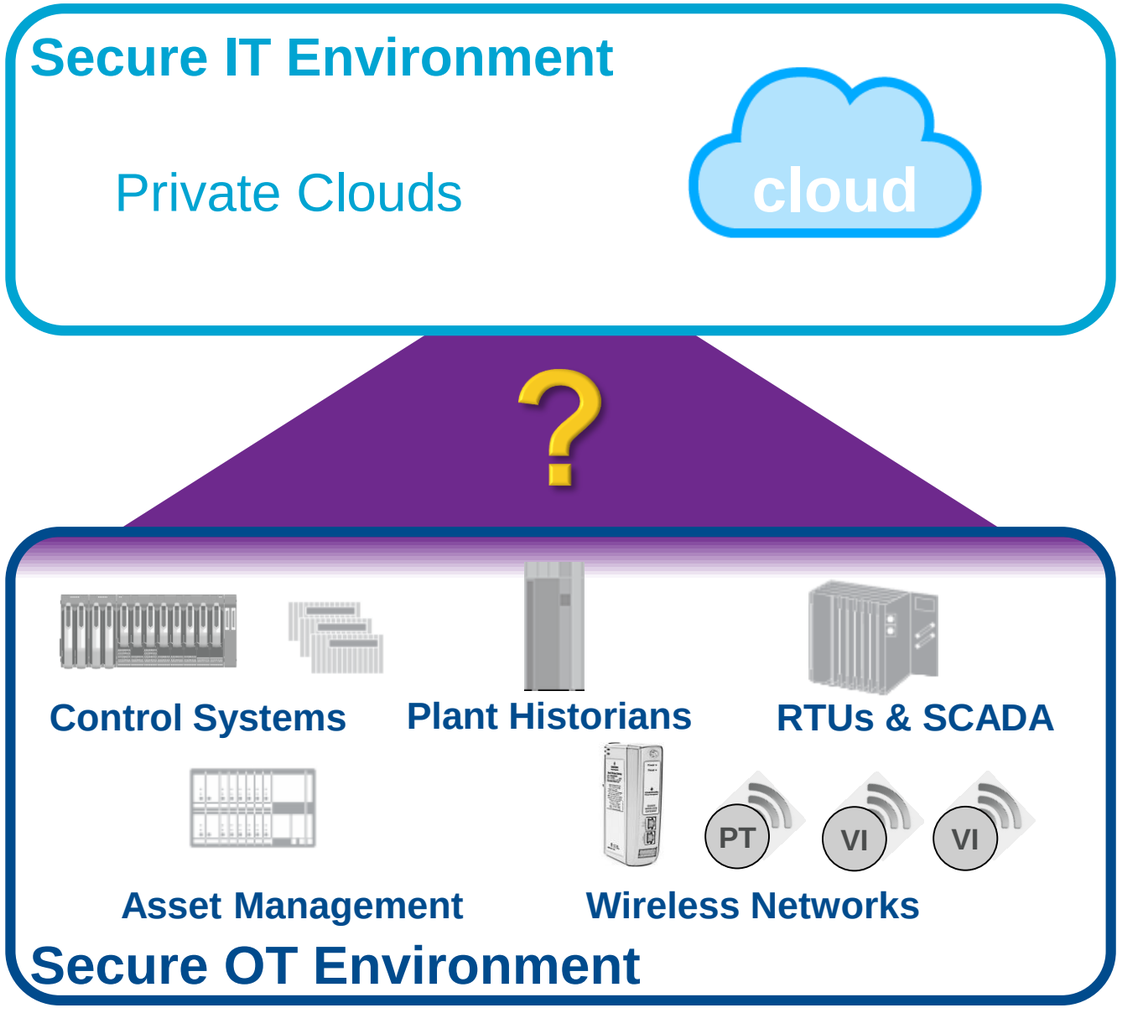
- Standardized, modular automation



- Units need to be autonomous
- Support a complete scope of solutions for optimized unit production
  - Measurements with measurement integrity
  - Equipment status with equipment integrity
  - Unit / unit control system status
  - Local control
  - Alarm management
  - Process history
  - Start-up / shutdown / product change-over sequencing for on-the-fly transitions
  - Order / batch context
- Retention of set-up when powered off
- Auto-sensing when connected to a control network

Great! Now How Does Data Get Out for Broader Optimization?

Plant to Cloud! Securely?



Sensor data powers cloud applications and services that can improve operations,

But….

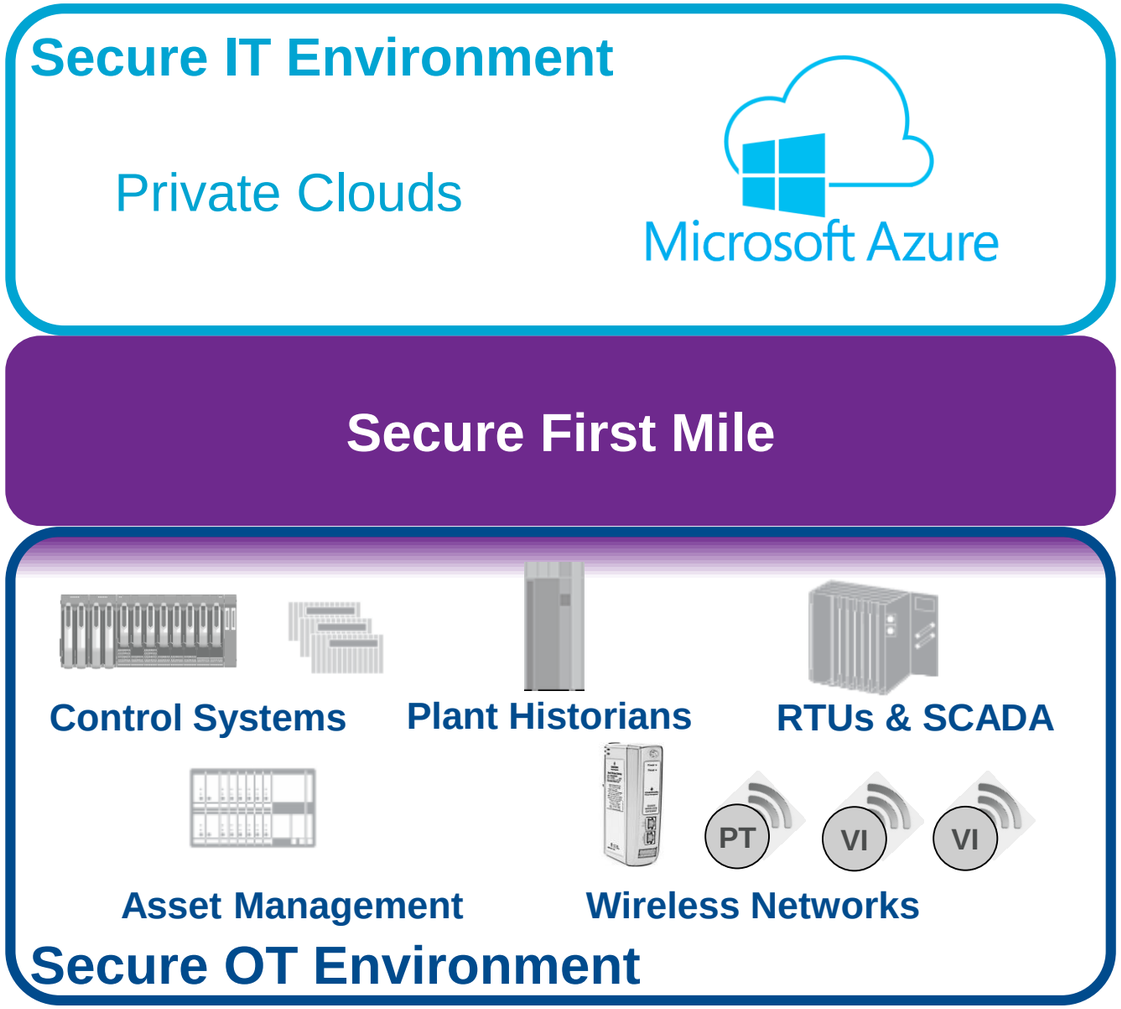
How do we connect the secure OT Environment to the Secure It Environment?

How do I translate the OT protocols to the IoT protocols?

How do we control who gets what data?

How do we prevent intruders from getting into the critical plant OT systems?

Secure First Mile™



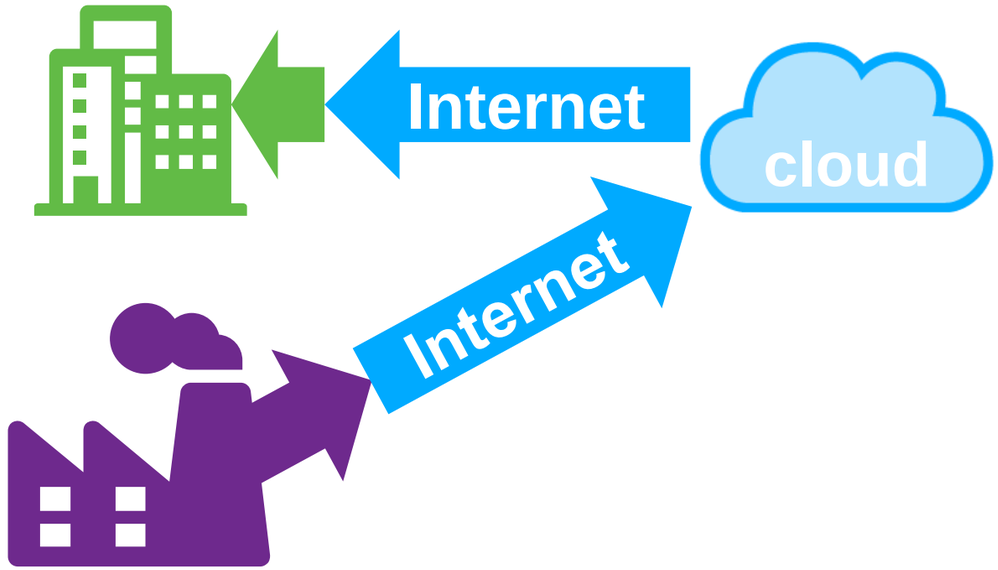
- Architectural designs to connect data from operation systems (OT) to IT environments, such as cloud applications
- A portfolio of technologies and services to implement those designs
  - Servers, Firewalls, Gateways, Data Diodes
  - User management, data encryption, key management, code signing
  - Data flow control for enhanced security
  - Enhancements on our OT portfolio of products and systems
- Optimizes the plant to cloud communications

Securely Connects and Transforms OT Data into IT!

Why First Mile?

Last Mile

Refers to the portion of the telecommunications network chain that physically reaches the end-user's premises

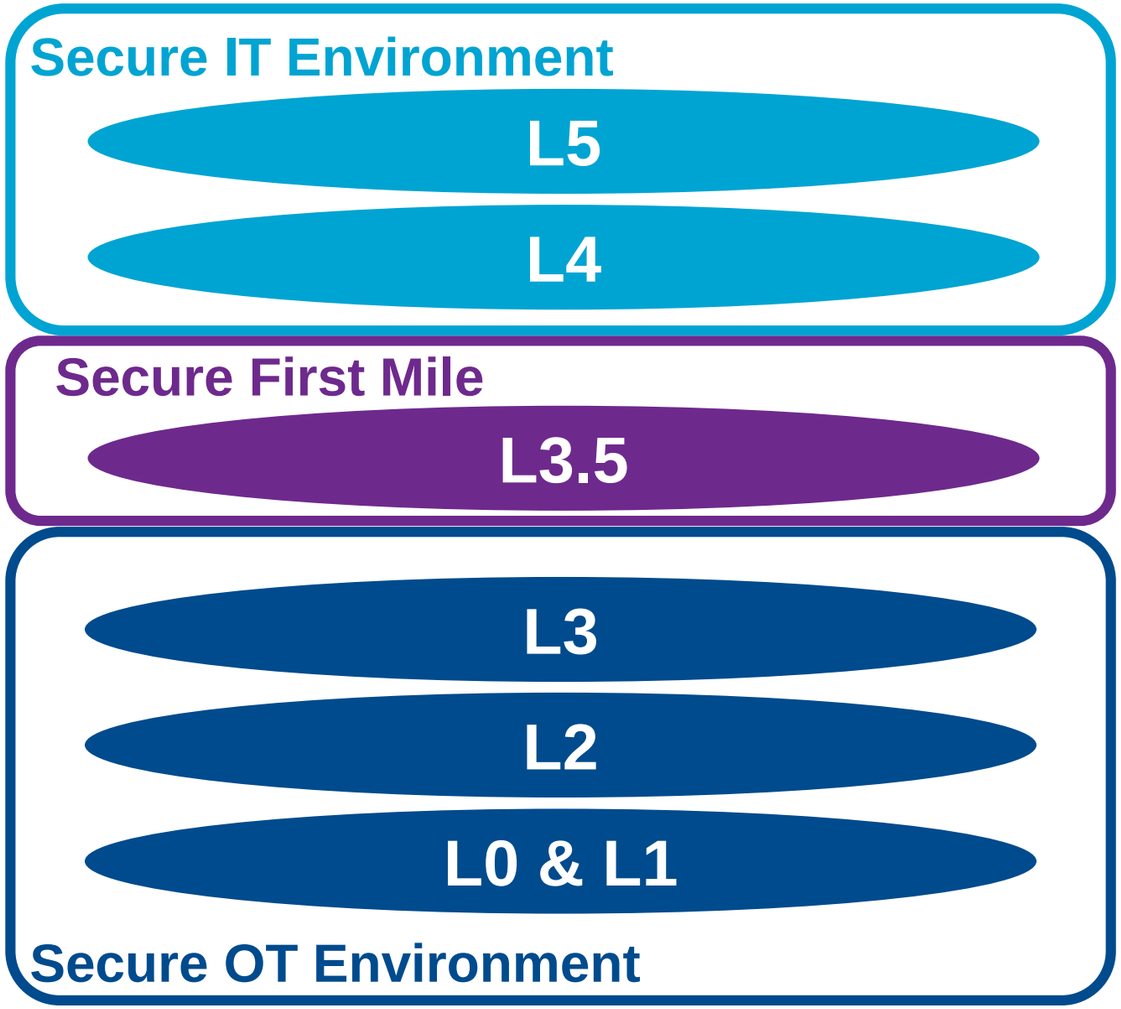


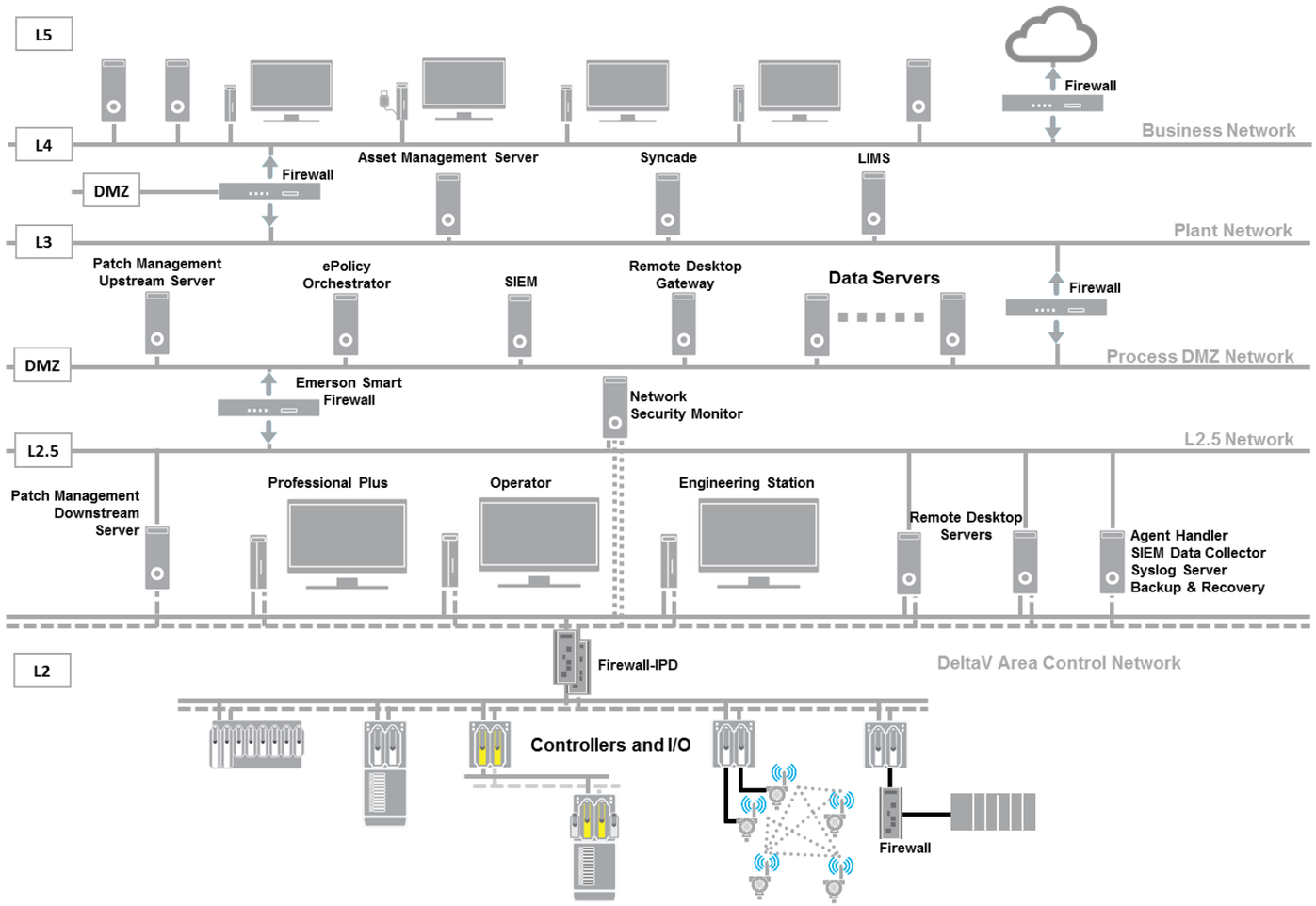
First Mile

An analogy to the last mile, indicating where the data is been generated

The First Mile Represents the Portion of the Network Where Data is Generated

Purdue Model is the Current Solution

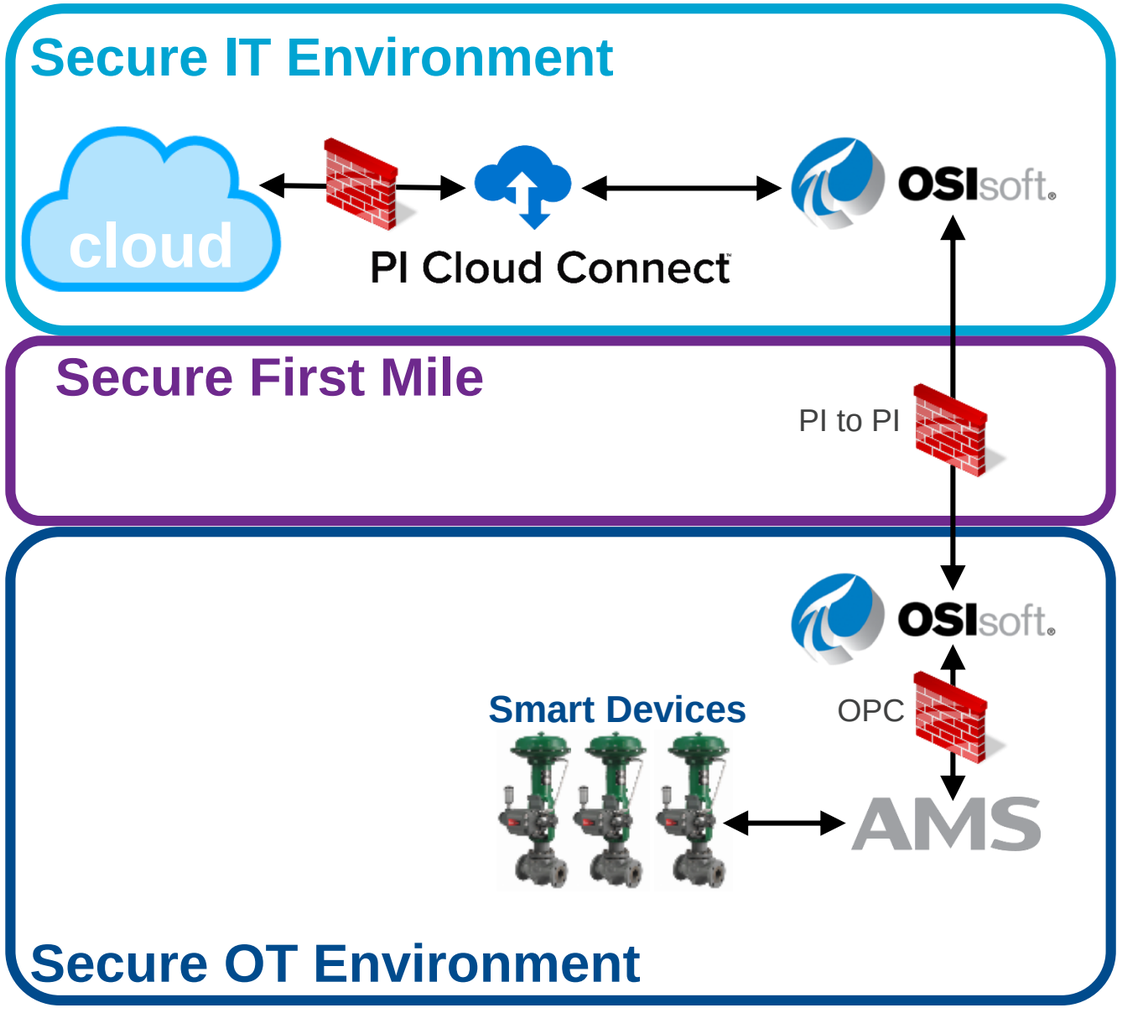




Purdue Model Solutions Already Exist in Many Installations

They are Complex due to Multiple Security Layers to be Properly Configured and Maintained

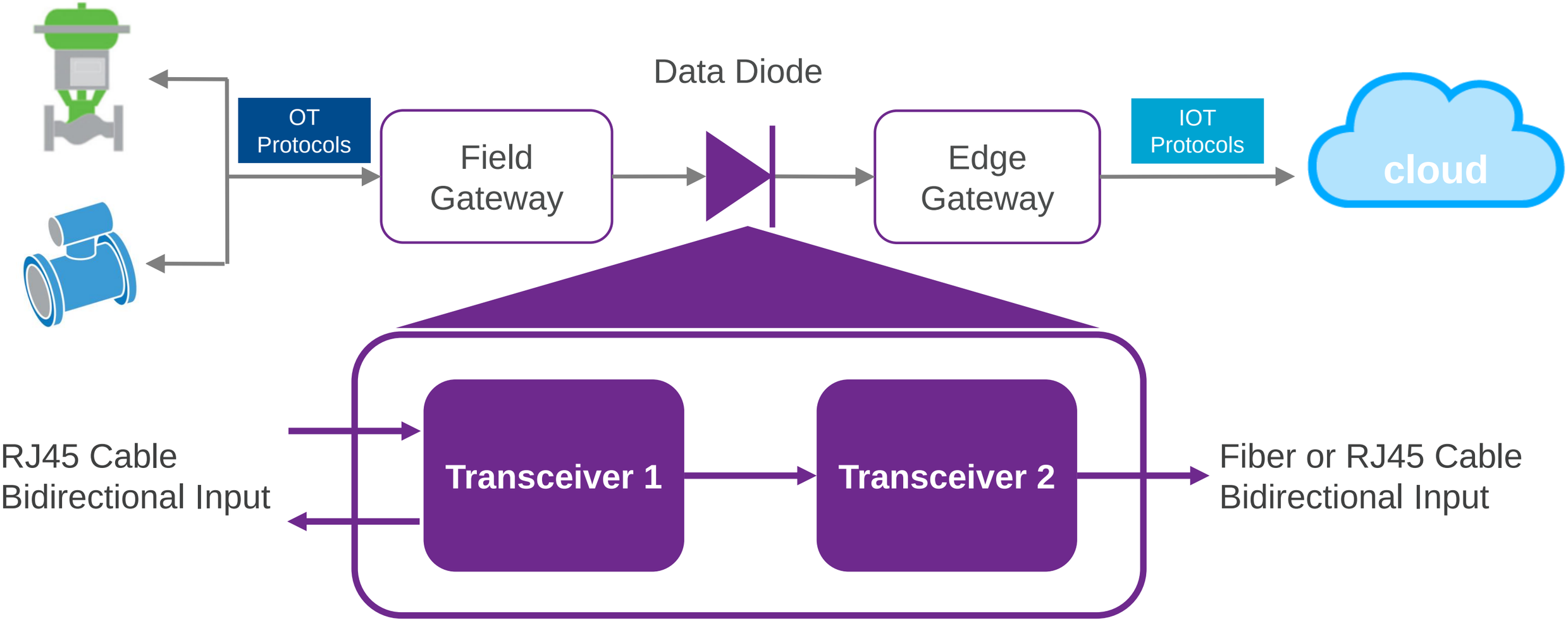
Purdue Model Example:
IIoT Asset Management using AMS and OSIsoft



- Uses conventional layered security through firewalls and user management
- Requires multiple levels of software to move data from one layer to the other.
- Involves multiple stakeholders
- Network penetration difficult but not impossible
- Effective but complex to maintain

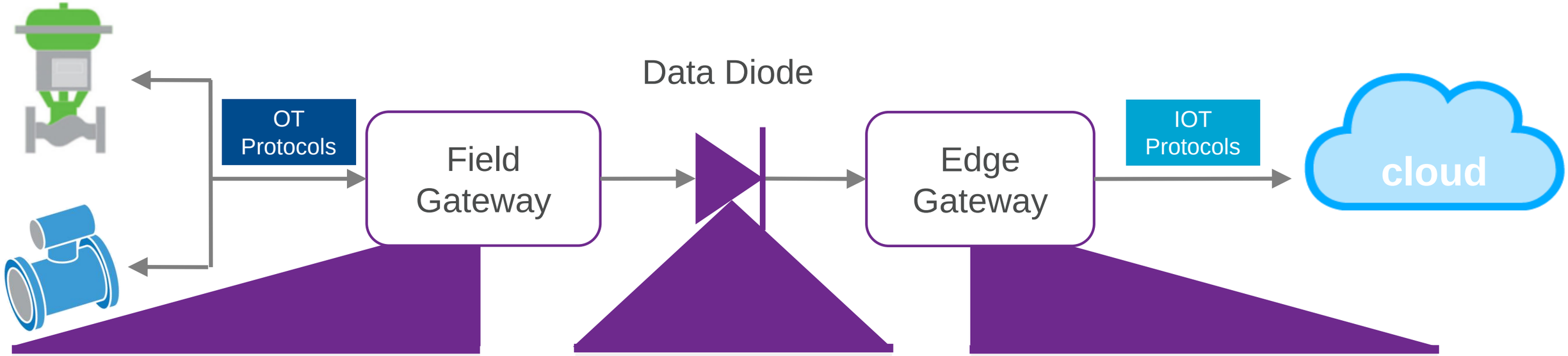
Connecting Smart Device Data to Cloud Services!

The Data Diode
A Simpler Way to Protect from Inbound Communications



Extra Security by Creating a Physically Unidirectional Network!

A New First Mile: Simpler Security Architecture Based on Data Diodes



Field Gateway

Collects Data from OT systems

Convert OT Protocols into protocols that support unidirectional data flow. (e.g. User Datagram Protocol - UDP)

Data Diode

Physically disables the inbound path

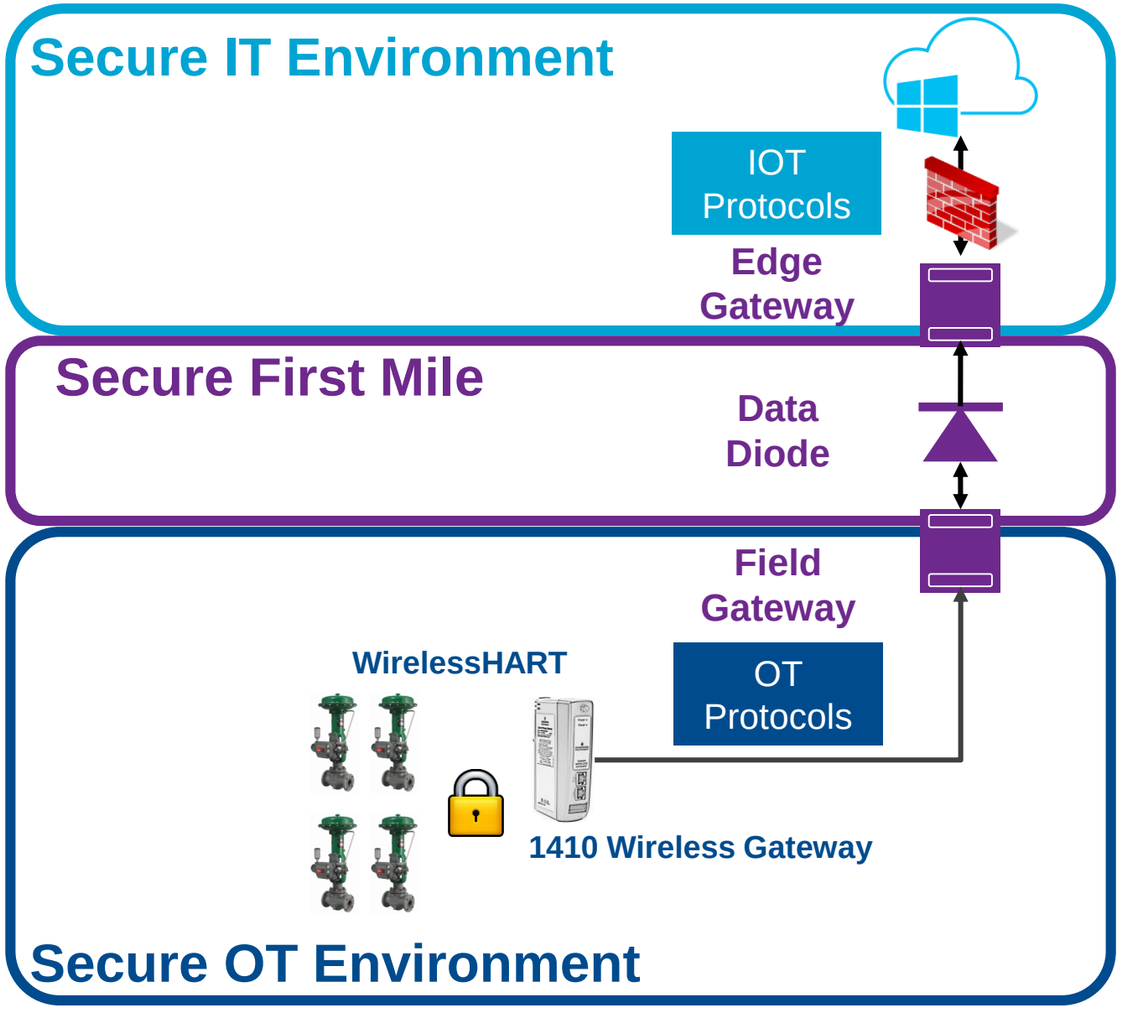
Create an air gap for inbound communication

Edge Gateway

Converts incoming protocols into IoT Procotols

Provide secure data transfer to the IT Systems (External or Private Clouds)

Example:
Applying Data Diodes for Valve Monitoring Connected Service



- 1410 Gateways supply WirelessHART valve information to Field Gateways
- Data Diode prevents outside access to the OT environment
- Windows 10 IoT Edge Gateway converts data to IoT protocols (AMQP), sends it to cloud services powered by Azure
- End to end encrypted communication

Simple & Secure: Inbound Connections Not Possible!

Change Required for Modular / Continuous Life Science Manufacturing

Continuous Manufacturing in Life Science is progressing. Assess **people, processes and technologies** within your organization to determine how to get the benefits

Continuous / modular manufacturing requires a new approach to automation and data

The technology barriers are being addressed

Requires re-thinking your manufacturing approach and how technology is then applied

Requires people with a combination of process and automation / data technology skills

Requires re-thinking approach to data integrity compliance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