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Enabling Manufacturing Summary Statistics Analysis Using the PI System

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Genentech, Inc *(A Member of the Roche Group)*

Introduction/Agenda

- Background (My Company and Role)
- Summary Statistics System Overview
- Defining and Coding Individual Summary Statistics
- Summary Statistic Examples:
  - 1.) Filter Fouling Issue
  - 2.) Shifts in Process Step Performance
- System Economic Benefits
- Next Steps for Summary Statistics System/OSIsoft Product Line
- Acknowledgements
- Discussion

Genentech

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Founded more than 30 years ago, Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes medicines to treat patients with serious or life-threatening medical conditions.

Marketed Products for BioOncology, Immunology & Opthalmology, Metabolism & Primary Care, Virology & Specialty Care

The company became a member of the Roche Group in March 2009.

Craig Taylor's Experience/Role

- Over 14 years of experience implementing and using the PI System in the Biopharmaceutical, Power Transmission/Distribution and Oil/Petrochemical industries
- Focus has been on monitoring, analyzing and troubleshooting large scale manufacturing processes
- My role evolved from PI System user to admin back to user; leveraging the toolset for improved analysis

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Summary Statistics System Overview

Purpose: The purpose of the system is to provide a repository of post process execution summary statistics to be used for process monitoring and analysis.

Scope: All products/lots since 1999 for site

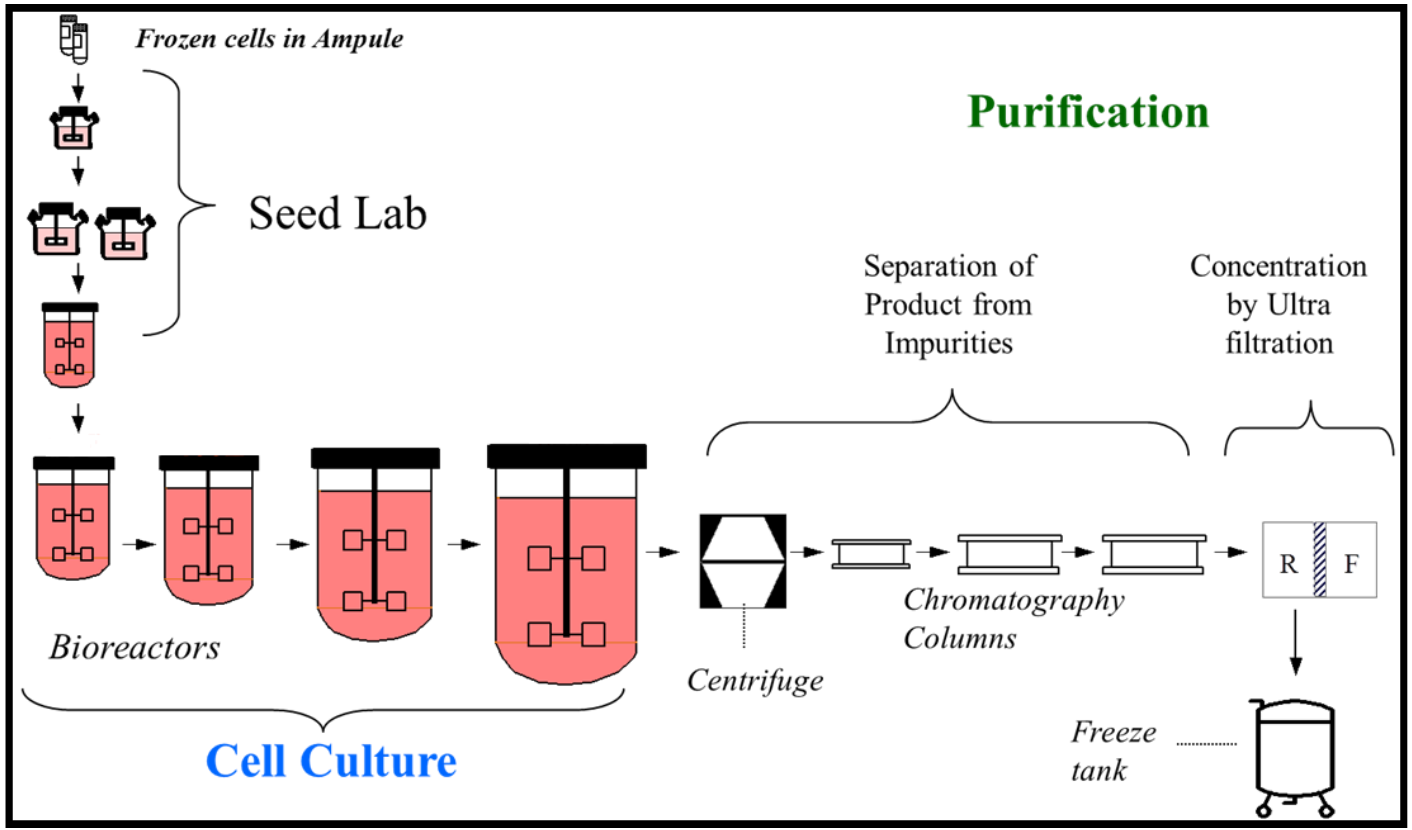
(focus areas: Cell Culture, Purification & Clean In Place)

Guiding Principles:

- 'Analysis Ready' Data - Data organization begets analysis efficiency
- Enhanced process understanding (multivariate analysis)
- Standardized complex calculations
- Enable flagging and commenting of significant operational excursions or anomalies

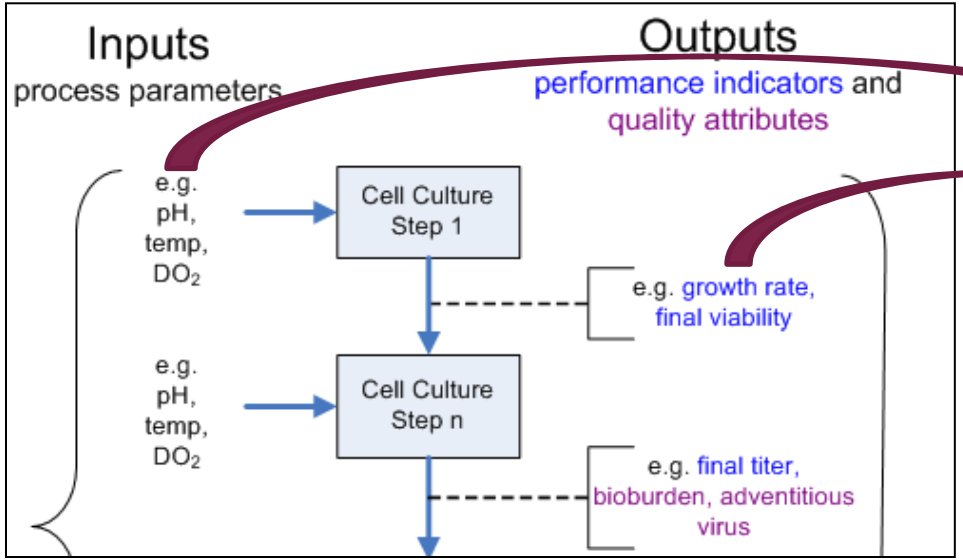
Implementation & Testing

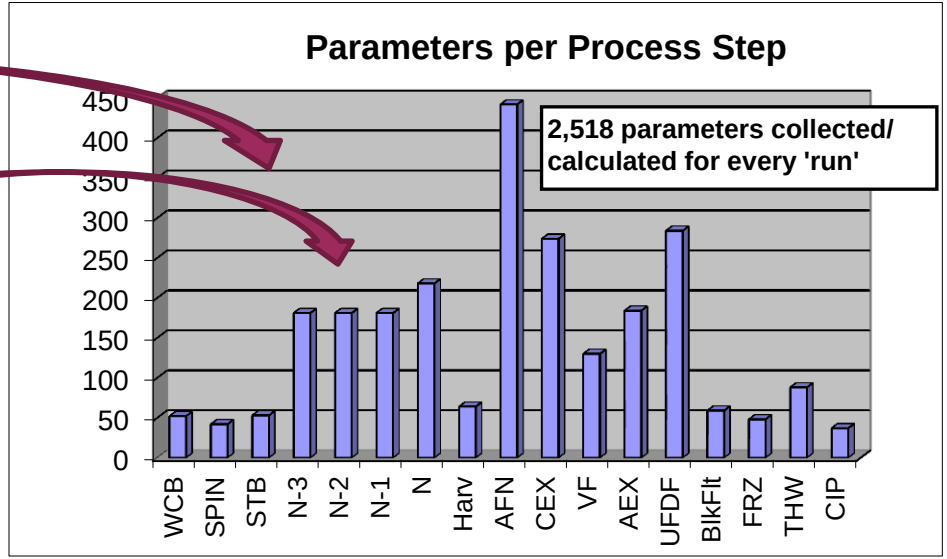
- System built in stages:
  - Organization Infrastructure
  - Purification
  - Cell Culture
  - Seed Lab
- Subject matter expert reviewed and correct results for each process step as they were deployed



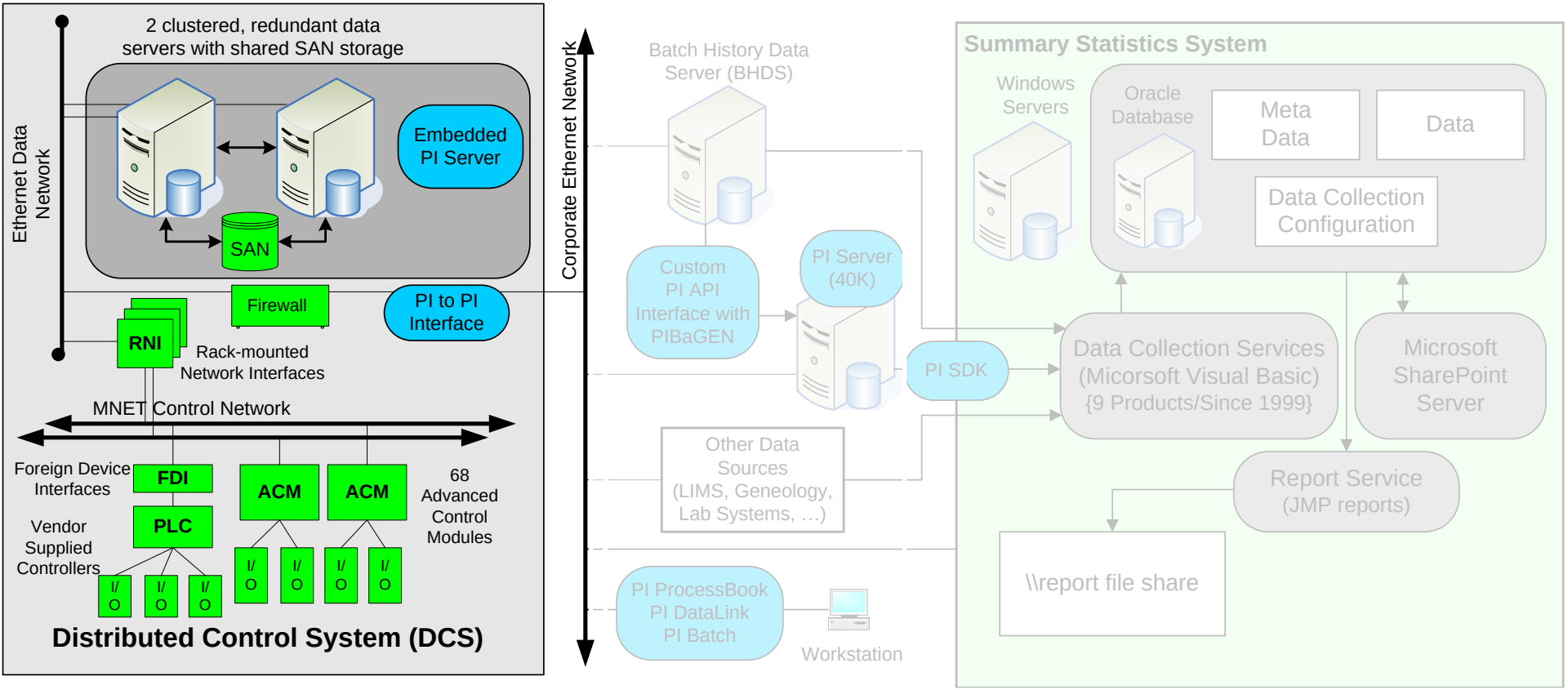
Requirements Collection

- Overall System Requirements: Included server and client software functionality (databases, interfaces and visualization)
- Summary Statistic Requirements: Defined by staff members responsible for monitoring each process step
  - Include: process parameters, performance indicators and quality attributes



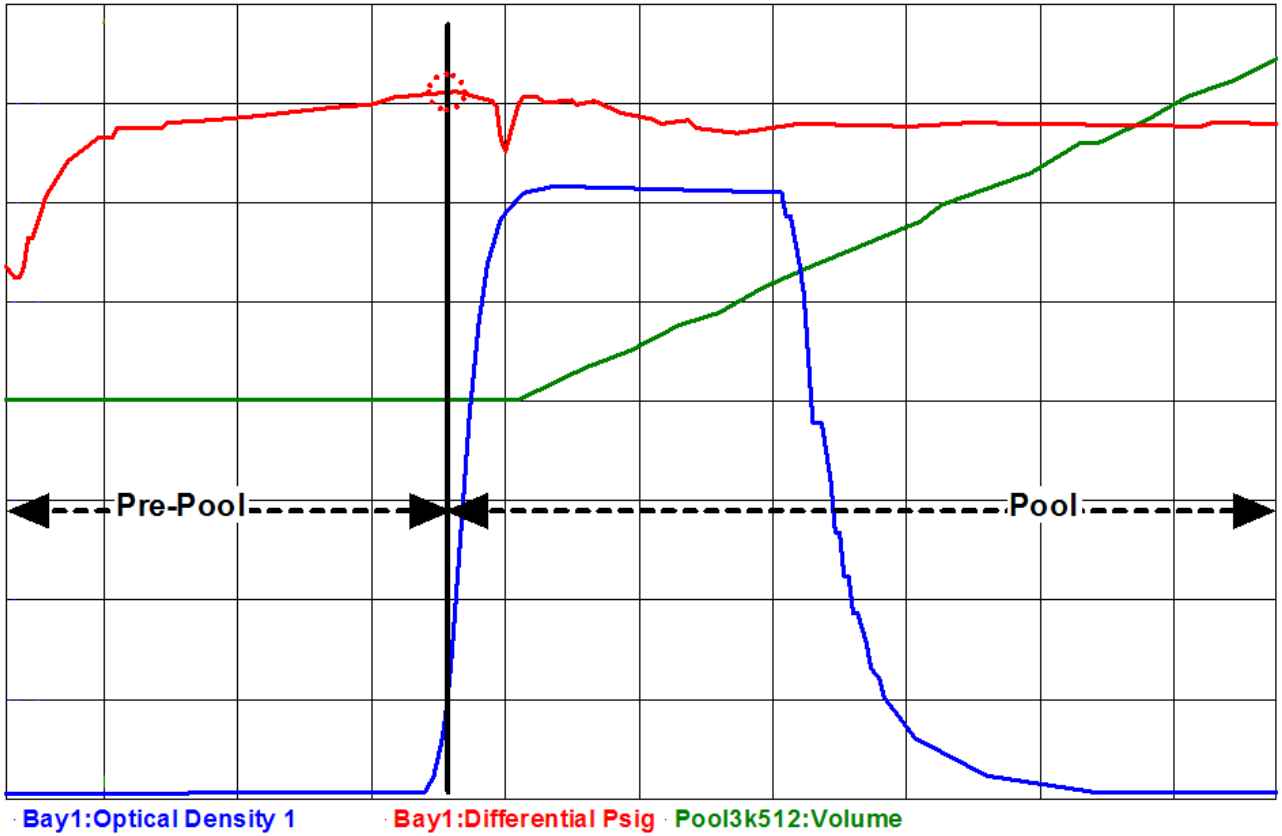


PI System Architecture & Data Flow



Defining Individual Summary Statistics

- Staff use PI ProcessBook, PI DataLink and PI BatchView to fully understand data and design code to collect and calculate summary statistics
- PI ProcessBook used to visualize Optical Density (OD), Differential Pressure (dP) and Tank Volume
- Summary value of dP collected when OD>=0.5
- This is an example of a difficult result to obtain only stored in the PI System



Coding Individual Summary Statistics

- Previous example translates into code using the PI Software Developers Kit (SDK):
  - Find time when optical density >= 0.5
  - Use that time to retrieve value from delta pressure tag
- Results are checked from the PI SDK calls using PI DataLink

Visual Basic Code

```
sFilter = "(NOT(BADVAL('" & piTag.Name & "')) AND " & _
  "('" & piTag.Name & "'>=" & sPIFilterValue & "))"
iNoOfVals = piEndTime_LDELT.UTCSeconds - piStartTime_LDELT.UTCSeconds
piVals = piTag.Data.InterpolatedValues(piStartTime_LDELT,
  piEndTime_LDELT, iNoOfVals, sFilter,
  PISDK.FilteredViewConstants.fvRemoveFiltered)
If piVals.Count > 0 Then
  'Get the Timestamp
  piStartTime = piVals(1).TimeStamp
End If

piVal = piTag.Data.ArcValue(piStartTime,
  PISDK.RetrievalTypeConstants.rtAuto)
If (piVal Is Nothing) = False Then
  dbValue = dbFactor * piVal.Value
End If
```

Summary Statistic Example 1: Filter Fouling Issue

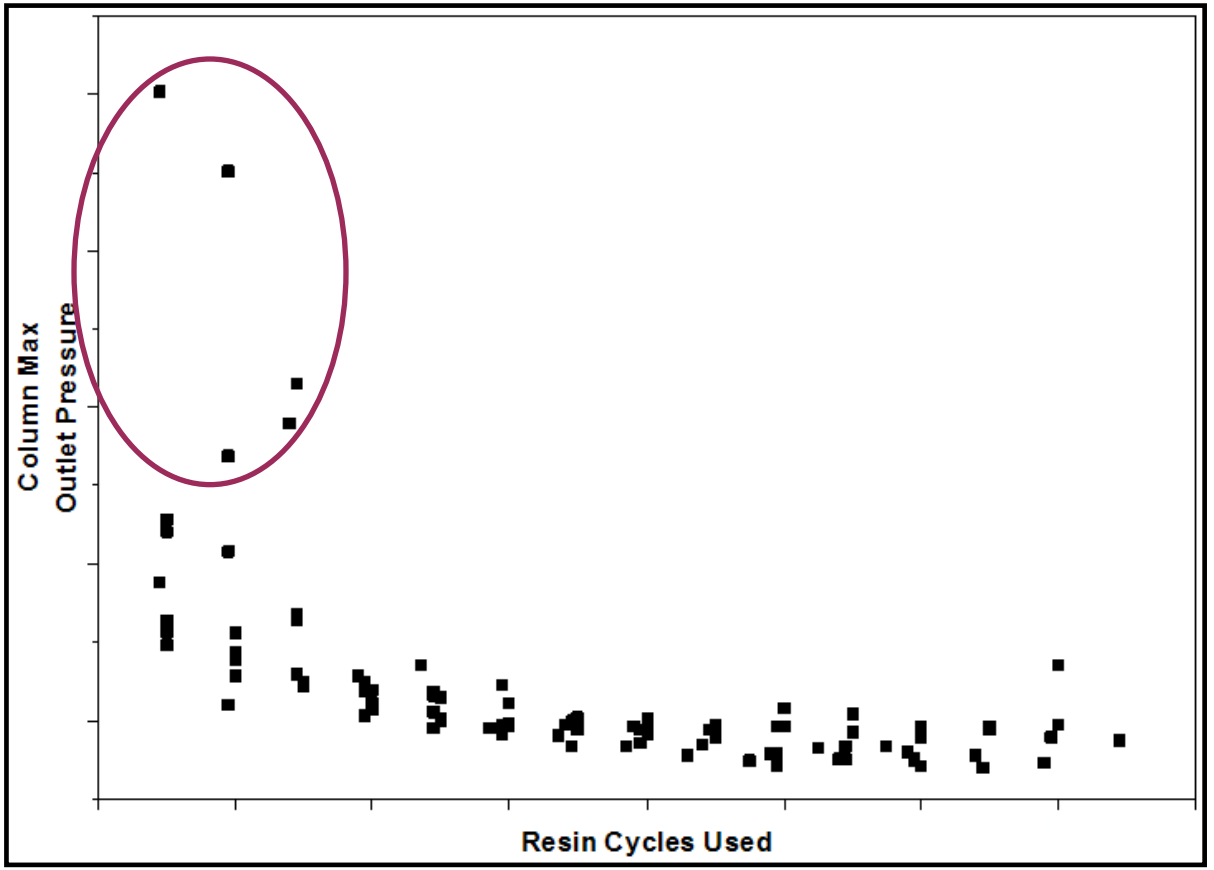
- The summary statistics database is organized to easily complete a multivariate analysis by aligning the data for each process step in one row

	Cell Culture				Purification						
1	N-3	N-2	N-1	N	Harvest	Chrom1	Chrom2	…	Chrom3	…	Bulk
2	N-3	N-2	N-1	N	Harvest	Chrom1	Chrom2	…	Chrom3	…	Bulk
3	N-3	N-2	N-1	N	Harvest	Chrom1	Chrom2	…	Chrom3	…	Bulk
4	N-3	N-2	N-1	N	Harvest	Chrom1	Chrom2	…	Chrom3	…	Bulk

- This organization allows for comparing the output of a process step to the input/output of another process step
- We observed a filter fouling downstream from our first Chromatography column, we needed to determine the cause

Summary Statistic Example 1: Filter Fouling Issue

- Investigated 2 summary statistics tracked for a Chromatography process step: Resin Cycles Used vs. Column Max Outlet Pressure for last 2 campaigns (~100 runs)
- Observed the pressure issue only occurred when Resin Cycles Used less than threshold
- Using this information performed a multivariate analysis to find variables that had an effect on Column Max Outlet Pressure

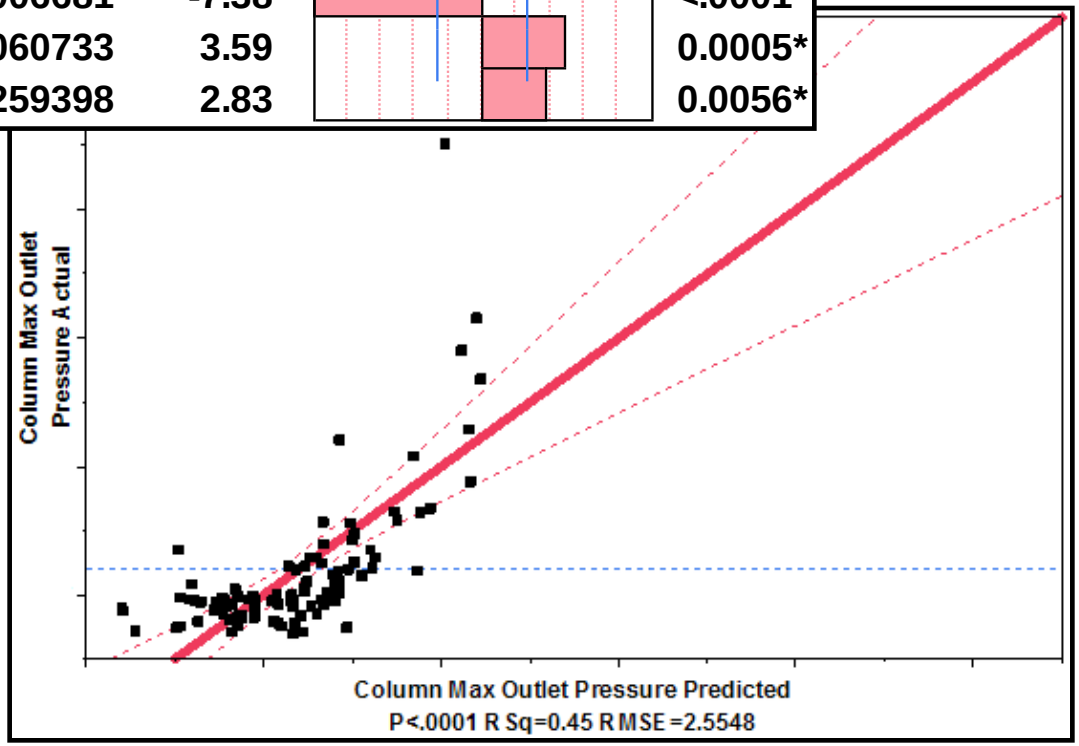


Summary Statistic Example 1: Filter Fouling Issue

Table 1: Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Resin Cycles Used	-0.049276	0.006681	-7.38	<.0001*
Lactate Concentration	0.2178576	0.060733	3.59	0.0005*
Harv Unit[U_CENT_X474]	0.7351531	0.259398	2.83	0.0056*

- The multivariate analysis explored for changes in the response variable (Column Max Outlet Pressure) in response to 3 input variables:
  - Resin Cycles Used
  - Lactate Concentration (byproduct of cells)
  - Harvest Unit
- The input variables account for around 45% of the variation observed in the Max Outlet Pressure



Summary Statistic Example 1: Filter Fouling Issue

Centrifuge Unit Effect:

- An investigation into the differences observed between our 2 different centrifuges revealed equipment was piped slightly differently
- The piping difference allowed increased water to enter the system diluting the centrate, contributing to filter fouling in both the centrifuge and chromatography process steps
- This understanding allows engineers to correct the process and reduce filter fouling

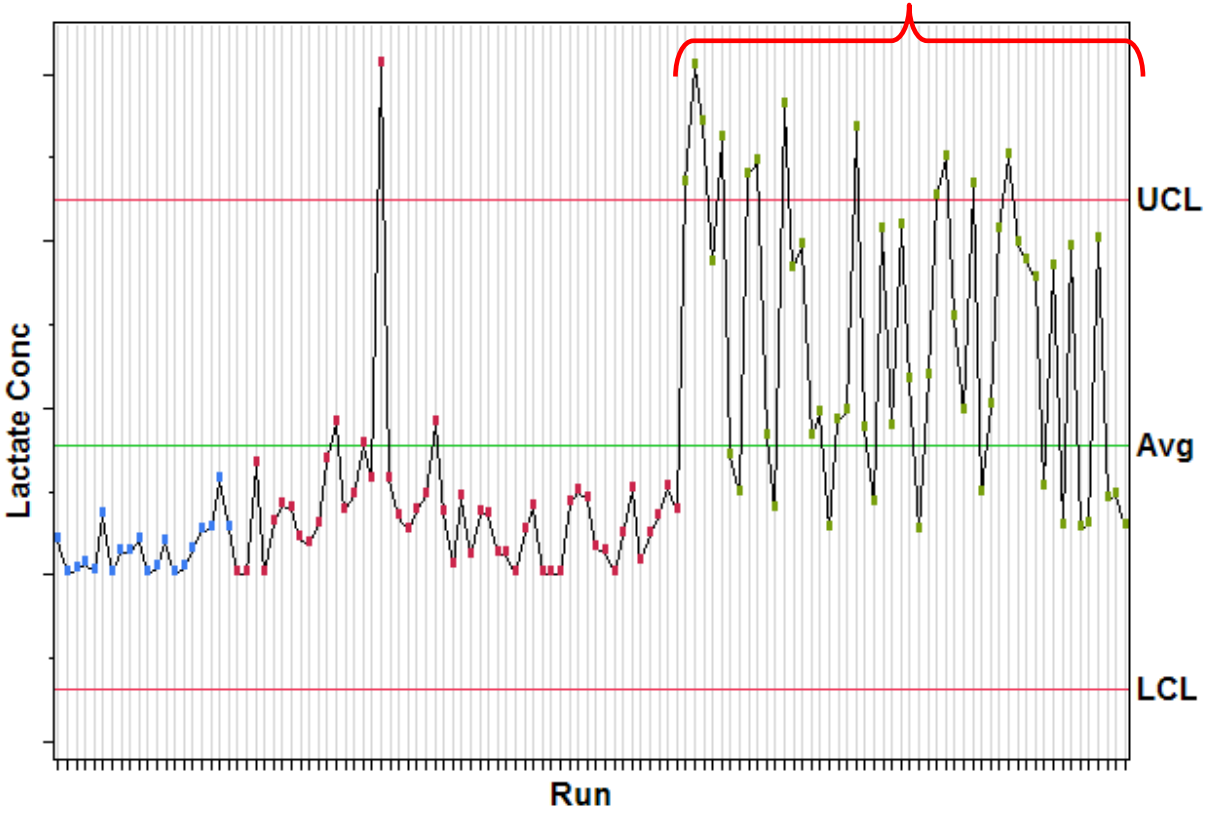
Summary Statistic Example 1: Filter Fouling Issue

Resin Cycles Used Effect:

- The observation of high dP with low resin cycles used might indicate a change to the resin
- We are following up by exploring resin impact by running small scale studies in our laboratory
- We are also exploring the interaction between Column Max Delta Pressure and Lactate Concentration

Summary Statistic Example 2: Shifts in Process Step Performance

- Certain processes have increased variability around lactate generation at the production stage
- Although Lactate does not impact product quality; it appears to impact protein production so it is an important parameter to monitor
- OSIsoft tools have helped collected and monitor lactate results; they allow for better process understanding
- This is a good visual example of increase process variability



System Economic Benefits

Intangible Benefits

- Our solution is used to gain better process understanding and help define causes for abnormal process unit behavior
- The system saves engineering time and allows for efficient process monitoring for each process step

Tangible Benefits

- We explored quantifying a ROI based on [Capital, Labor] vs. [Monitoring, Investigations], but decided for our industry the system is better described as increasing our staffs depth of knowledge
- Without the PI System our staff would not be reviewing these detailed summary statistics during normal process monitoring

Next Steps for Summary Statistics System Customer Input to OSIsoft Products *(wish list)*

- Allow for PI Batch/*Event Frames – PI AF* to track variables on any level of the S88 model:
  - Enterprise/Site
    - Area/Campaign/Run
      - Unit/Batch
        - Procedure/Unit Procedure/Operation/Phase/Sub-Batch
- Report/Aggregate these summary statistics on any of the levels:
  - Example: Sub-batch variables reported with Batch, Run, Campaign or Site
  - Example: Batch information reported for each Run in the Campaign (Campaign Summary Report)
- 1,000 + column report generated quickly across many batch/runs/campaigns
- Allow for tracking between batch (idle time/equipment)
- Potential impact to: PI Server, PI Batch/*Event Frames*, PI AF, Reporting & Statistical Tools

Acknowledgements

Roche/Genentech

- Dan Stark
- Shishir Gadam
- Jesse Bergevin
- David Peers
- Mark Smith
- Lisa Day
- Jason Gu
- Richard Parapar
- Arthi Narayanan
- Keri Mills
- Luke Pease

OSIsoft

- Rob Eisele
- Jack Aude
- Kumar Bangalore
- Marc Gallant
- Janelle (Loe) Minich
- Glenn Sharp

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Thank you

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