



# ACHIEVING PROCESS ROBUSTNESS THROUGH PAT IMPLEMENTATION

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# Abbott Bioresearch Center

Worcester, Massachusetts

*Center of Excellence in Biologics*



- **Biologics Discovery & Development**

- Clinical & commercial manufacturing of Abbott and Third Party products

- Over 13 years experience handling more than 25 different biologics

- **Workforce of ~700 (~430 in operations)**

# Process Analytical Technology (PAT)

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- The goal of PAT is to
  - Understand and control the manufacturing process, which is consistent with our current drug quality system
  - *quality cannot be tested into products; it should be built-in or should be by design.*
- Process Analytical Technology is:
  - a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

# PAT Tools

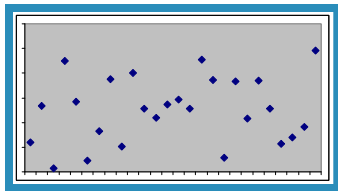
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It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

- Multivariate data acquisition and analysis tools
- Modern process analyzers or process analytical chemistry tools
- Process and endpoint monitoring and control tools
- Continuous improvement and knowledge management tools

# Better Control

Raw Materials  
Equipment  
Environment  
Operators

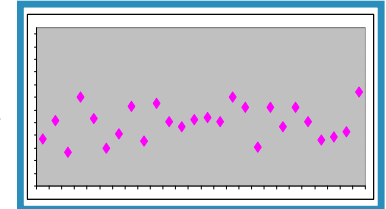


Variable  
Process Input

Without PAT

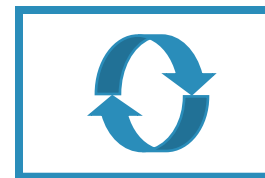


Fixed  
Process

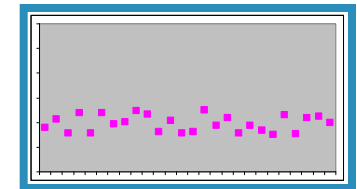


Variable  
Process Output

With PAT



Adaptive  
Process



Consistent  
Process Output

Design Space

# Reactive vs preventive system

“Quality cannot be tested into products; it has to be built in by design”

	<b>Traditional</b>	<b>Future</b>
Process	Static, recipe driven	Dynamic, Science and knowledge based Adjustable within design space
Control Strategy	Measure and reject Off-line analysis	Real time monitoring and response to variation Feedforward and feedback controls
Validation	validated process	validated controls; continuous process varification
Testing	End product testing	continuous quality assurance, real time release

# ACHIEVING PROCESS ROBUSTNESS THROUGH PAT IMPLEMENTATION

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- **Raw material variability**
- Using PAT to gain a better understanding of cell culture systems and titer challenges
- Controlling processes and reducing variability to achieve robust upstream systems
- Successfully implementing automation in cell culture systems

# Raw Material Variability in Cell Culture

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## Complex raw material

Refined hydrolysis of natural derived raw material

- Soy hydrolysate, Wheat hydrolysate
- Baker yeast extract or brewer yeast extract

## Control Strategy

## Evolving

Multi-pronged Approach

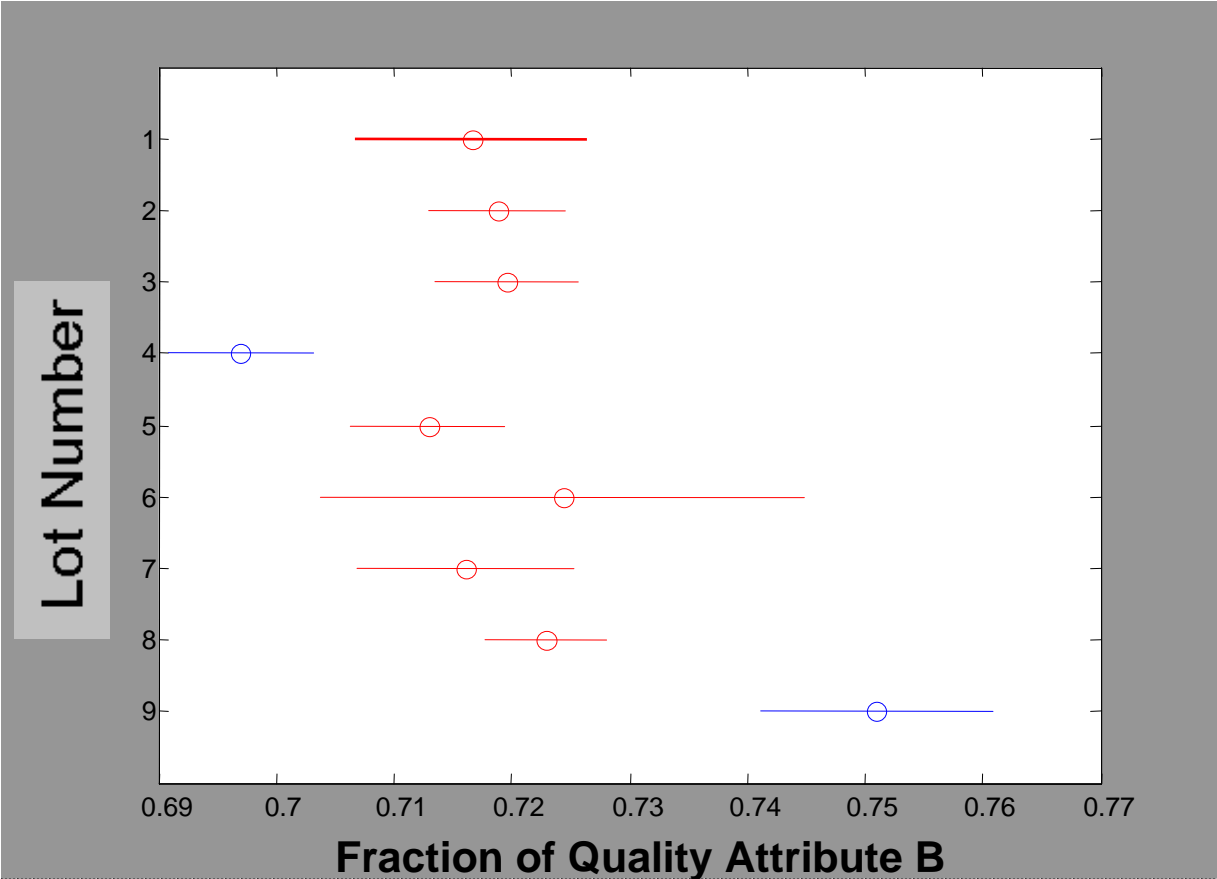
- Chemical analysis
- Growth promotion test
- Process adjustment
- On-line process control

# Hydrolysate Composition and Function

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- Hydrolysates improve mammalian cell culture performance
  - Digests of animals, plants or yeast
    - Enzymatic or chemical means
      - Degree of hydrolysis leads to varied results
    - Major components:
      - Proteins, peptides, amino acids, carbohydrates, lipids, vitamins, salts...
  - Numerous methods employed to analyze
    - many unknown components

# Correlation of Raw Material Lots to Product Quality

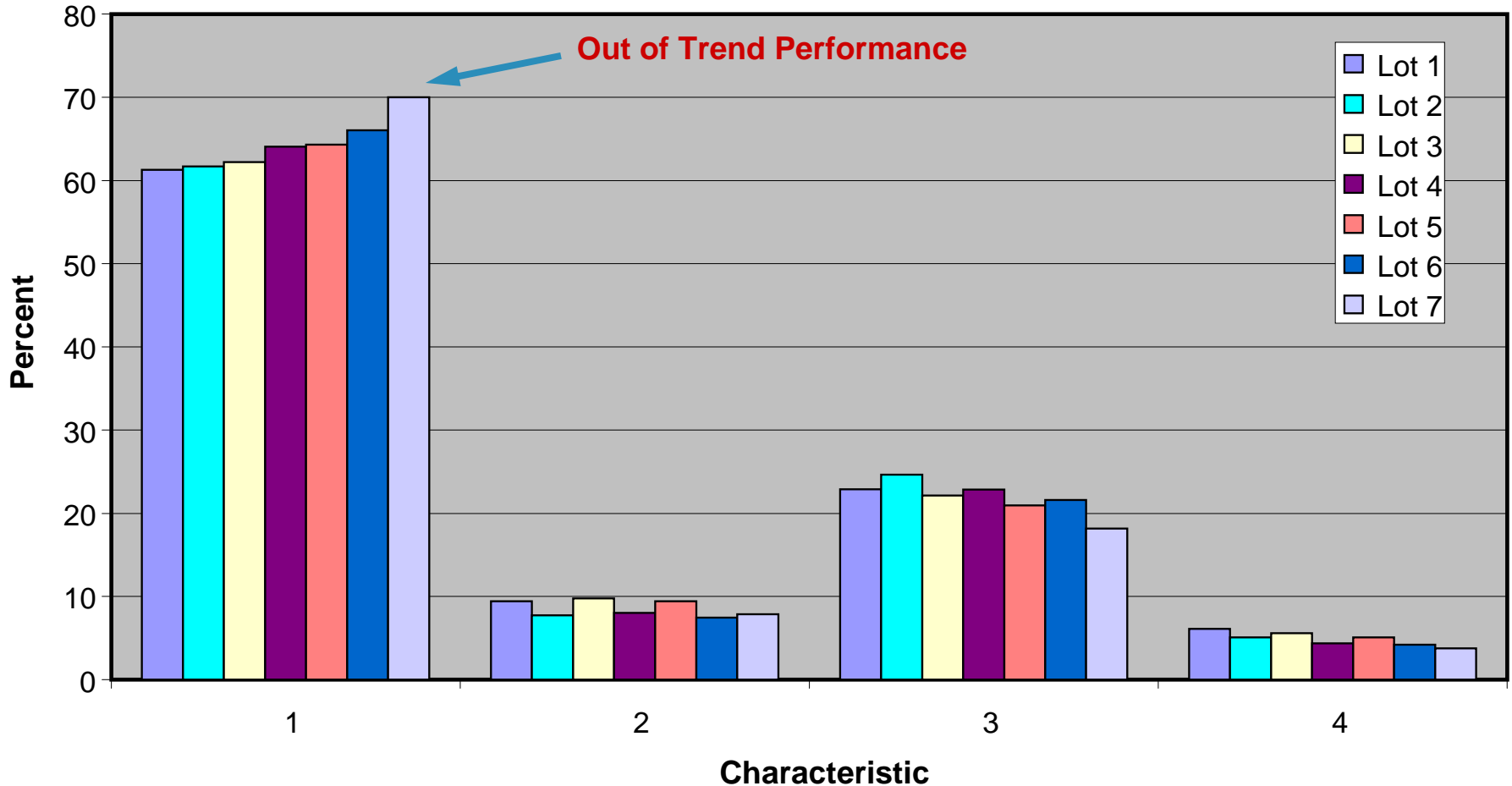


# Raw Material Analysis

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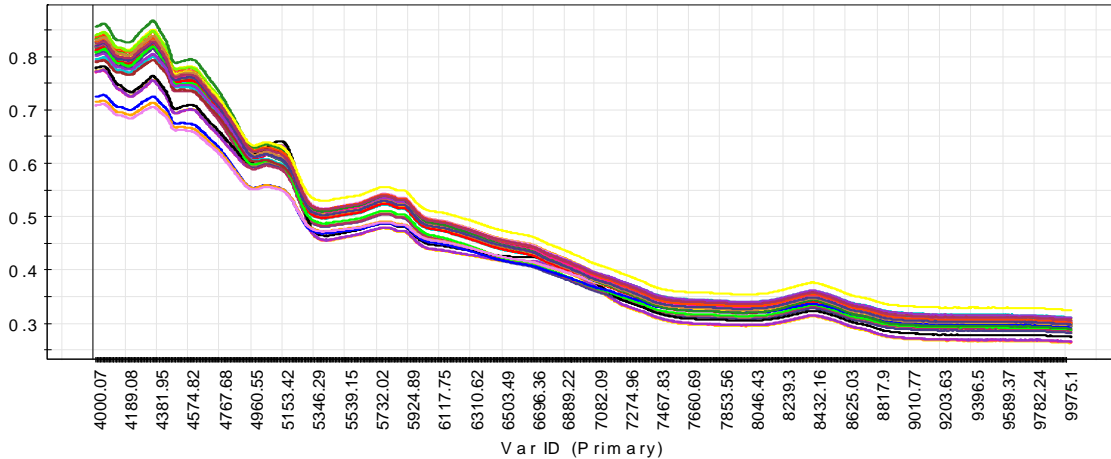
- Chemical Testing
  - Amino acids
  - Peptide molecular weight distribution
  - Carbohydrates
  - Lipids
  - Vitamins...
- Spectroscopic characterization
  - NIR Spectrum analysis

# Chemical Analysis for Hydrolysate Lots



Higher % Characteristic 1

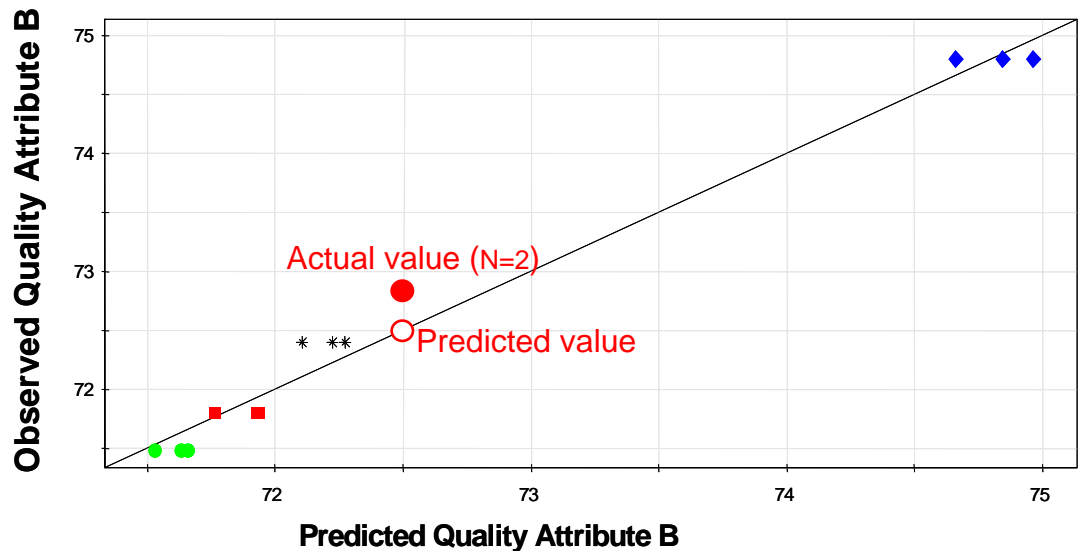
# NIR Spectrum Analysis



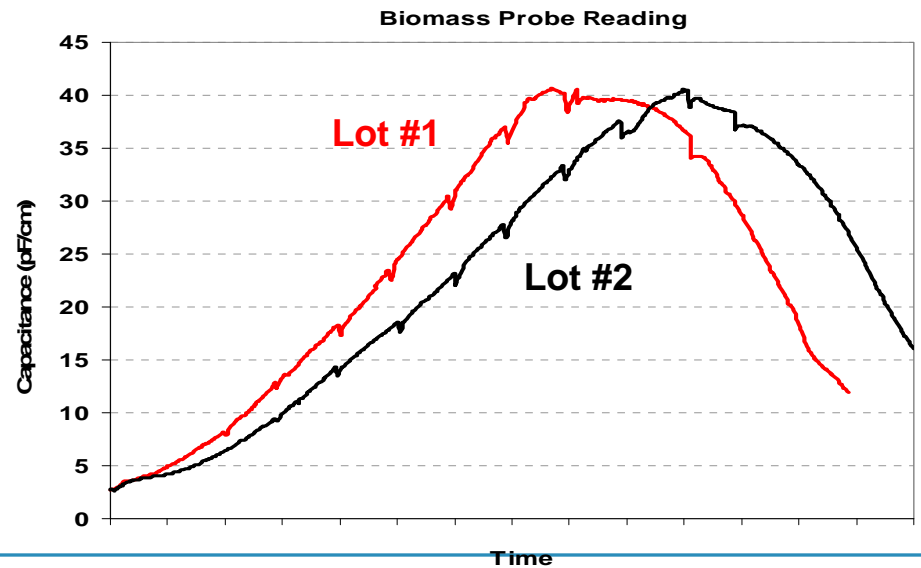
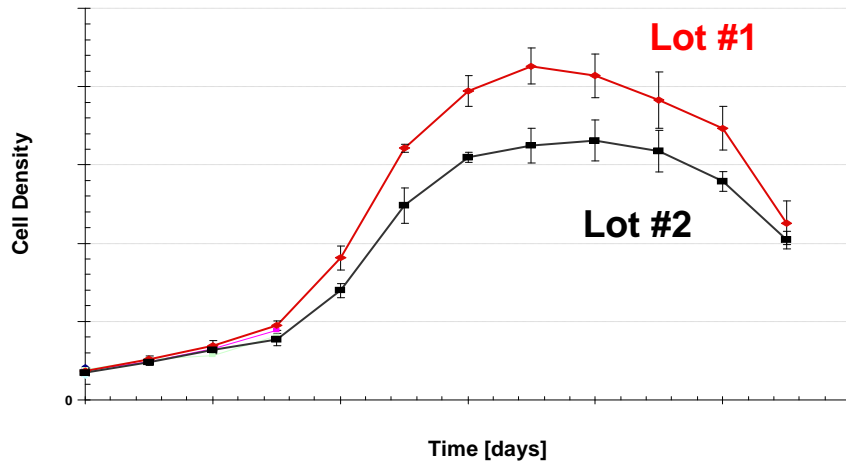
- Analysis of various hydrolysate lots through NIR spectrum

- Building Library based on quality data and NIR Spectrum
- Model prediction
- Principle Component Analysis (PCA)

SIMCA-P+ 11 - 9/5/2006 5:50:49 PM



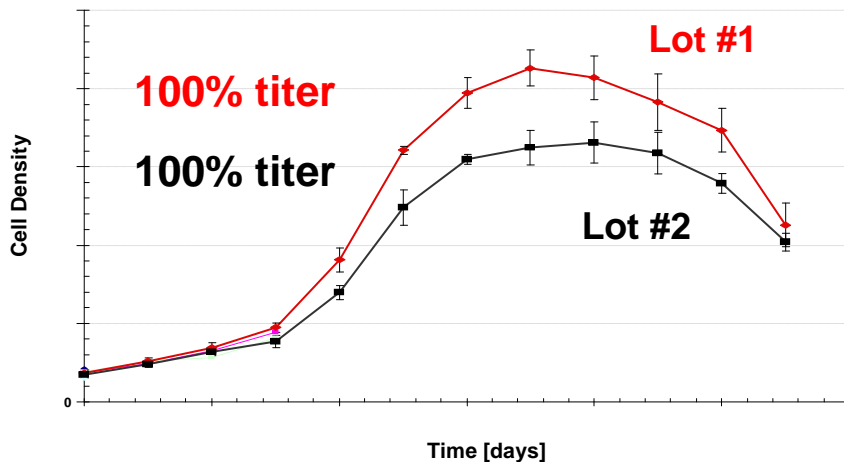
# Screening of Hydrolysate Lots



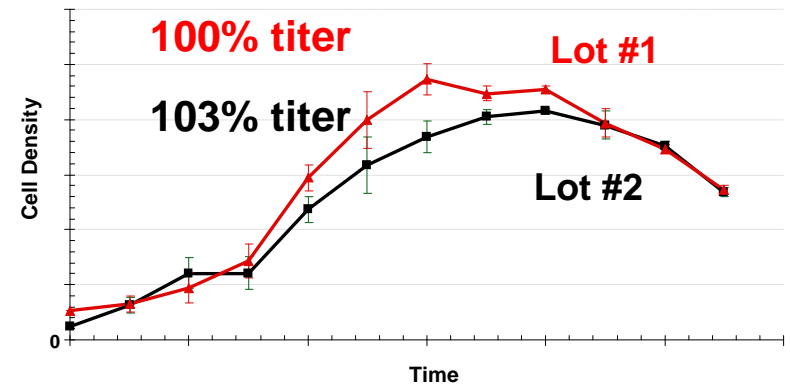
# Effect of Raw Material is Cell Line Dependent

- Cell line responds differently to raw material changes.
- Cell growth and titer

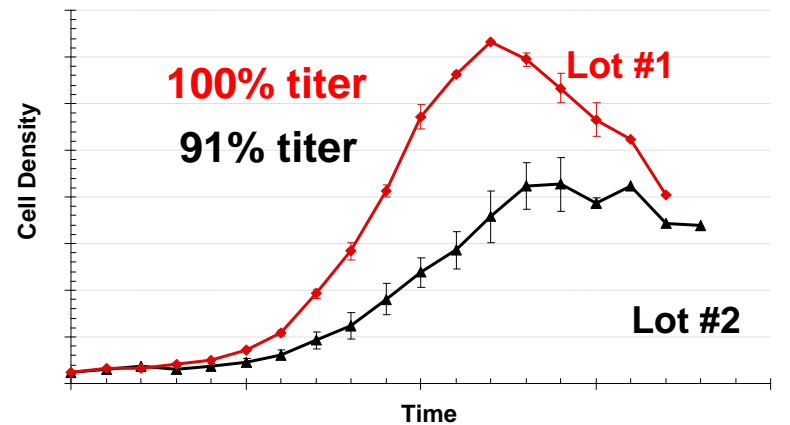
## Cell line #1



## Cell line #2



## Cell line #3



# Complex raw material

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- Leads to process variability
- Chemical testing and lot screening is imperative
- Challenges remain to determine appropriate tests and specifications
  - Many unidentified components
  - Need significant no. of lots to establish correlation
  - Lab screening may not be predictive
  - Cell line dependent

# Lessons Learned from Classical Fermentation

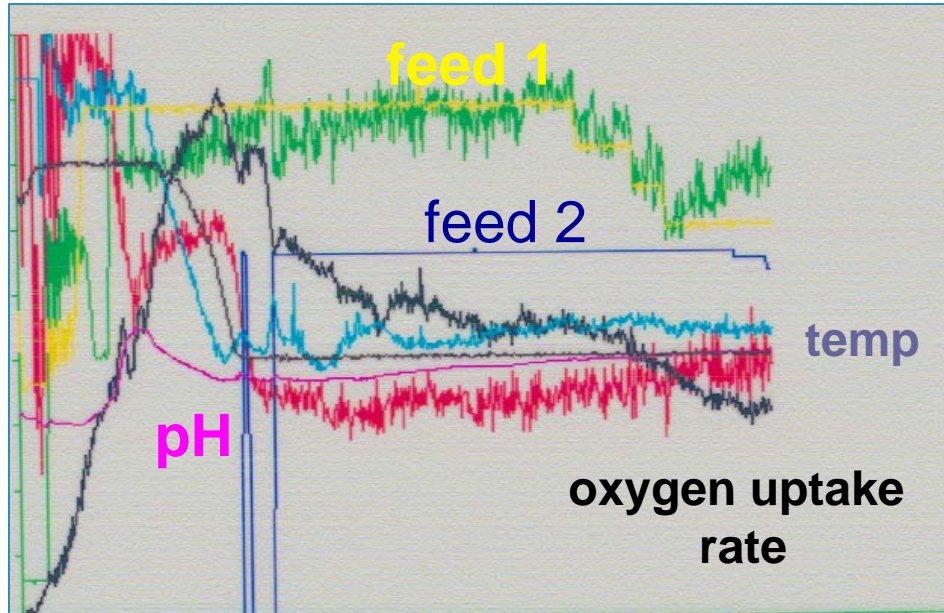
## Raw Material Variability

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- Brewery, production of industrial enzymes, amino acids, antibiotics (1950s-1990s)
- **Crude natural derived raw material (to reduce commodity COG)**
  - Corn Flour or corn steep liquor, molasses; soy bean oil
  - Whole brewer yeast or brewer yeast extract
  - Soy grits/flour, cotton seed flour
  - Fish meal
- **Productivity can vary significantly**

Control strategy and process tuning  
has evolved to **expert process control**  
based on **metabolic data**

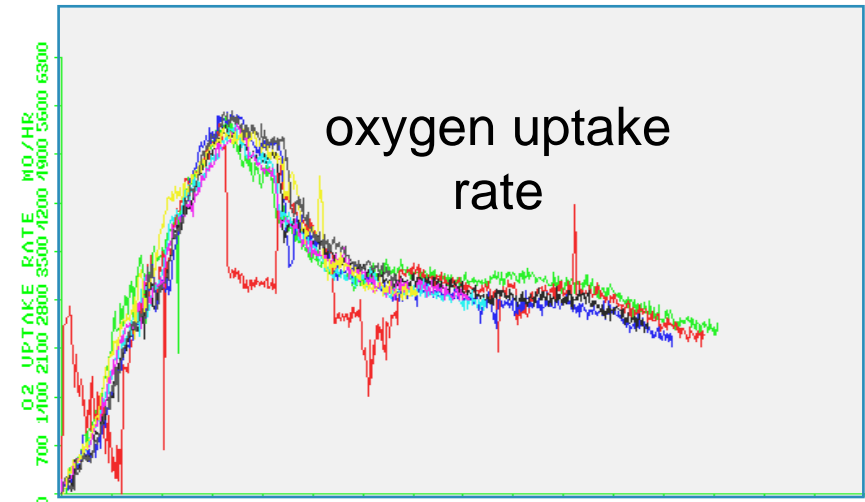
# Expert Process Control Microbial Fermentation



**Control temperature and nutrient feeds  
based on oxygen uptake rate and pH**



**Consistent performance**

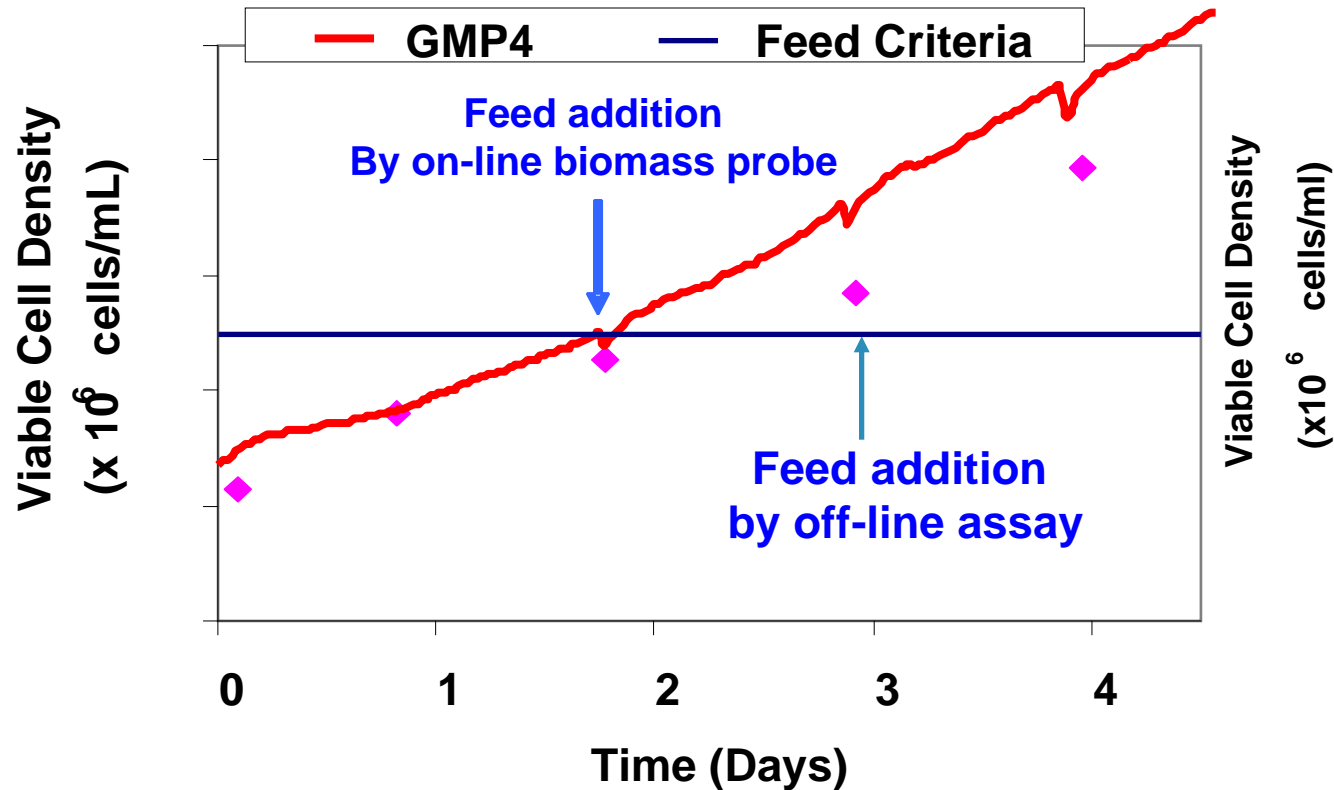


# Process Control and Automation

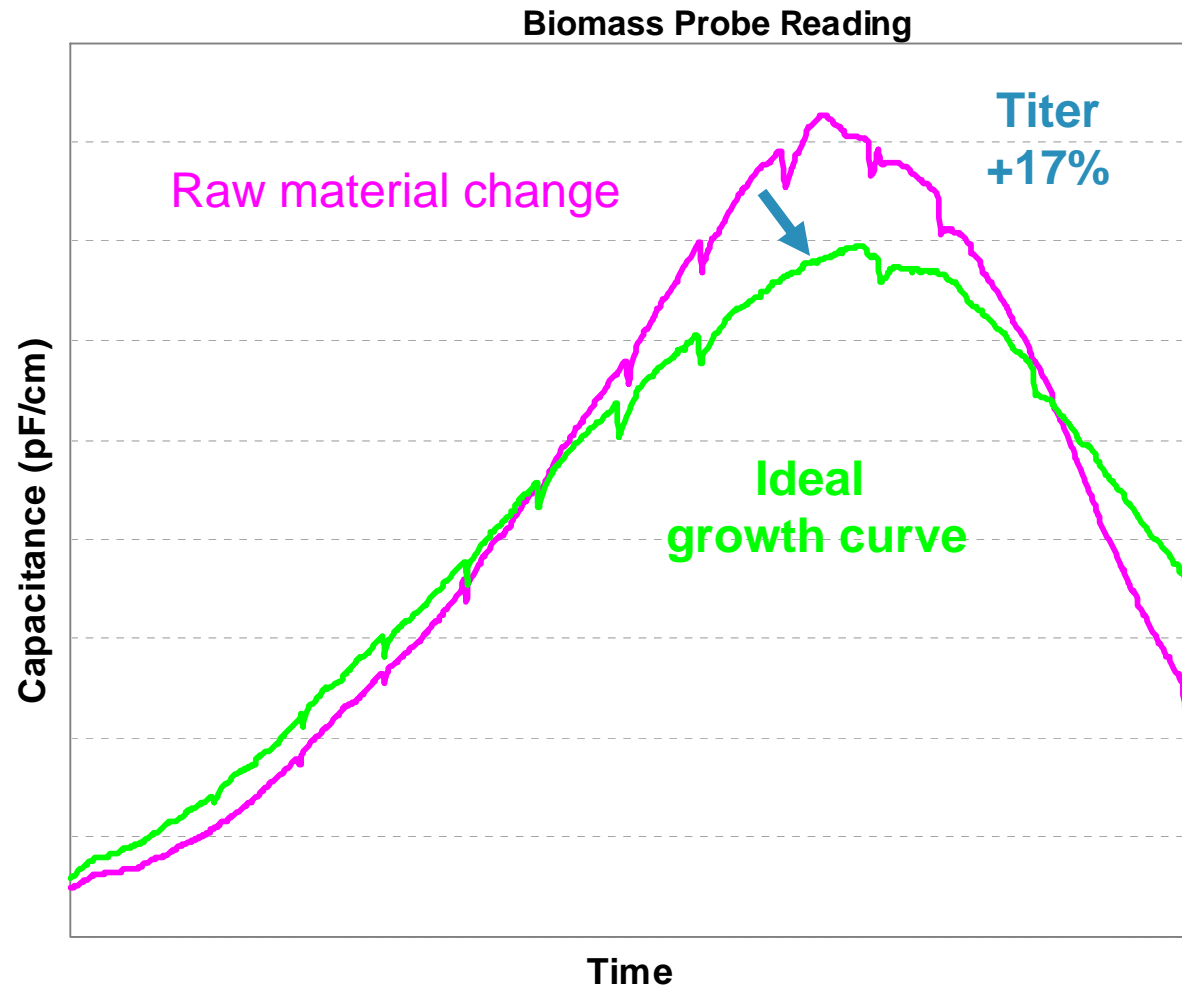
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- Process automation
  - Control cell growth and/or metabolic events
  - Improve consistency
- Expert controls
  - To maintain “ideal” state
  - Examples

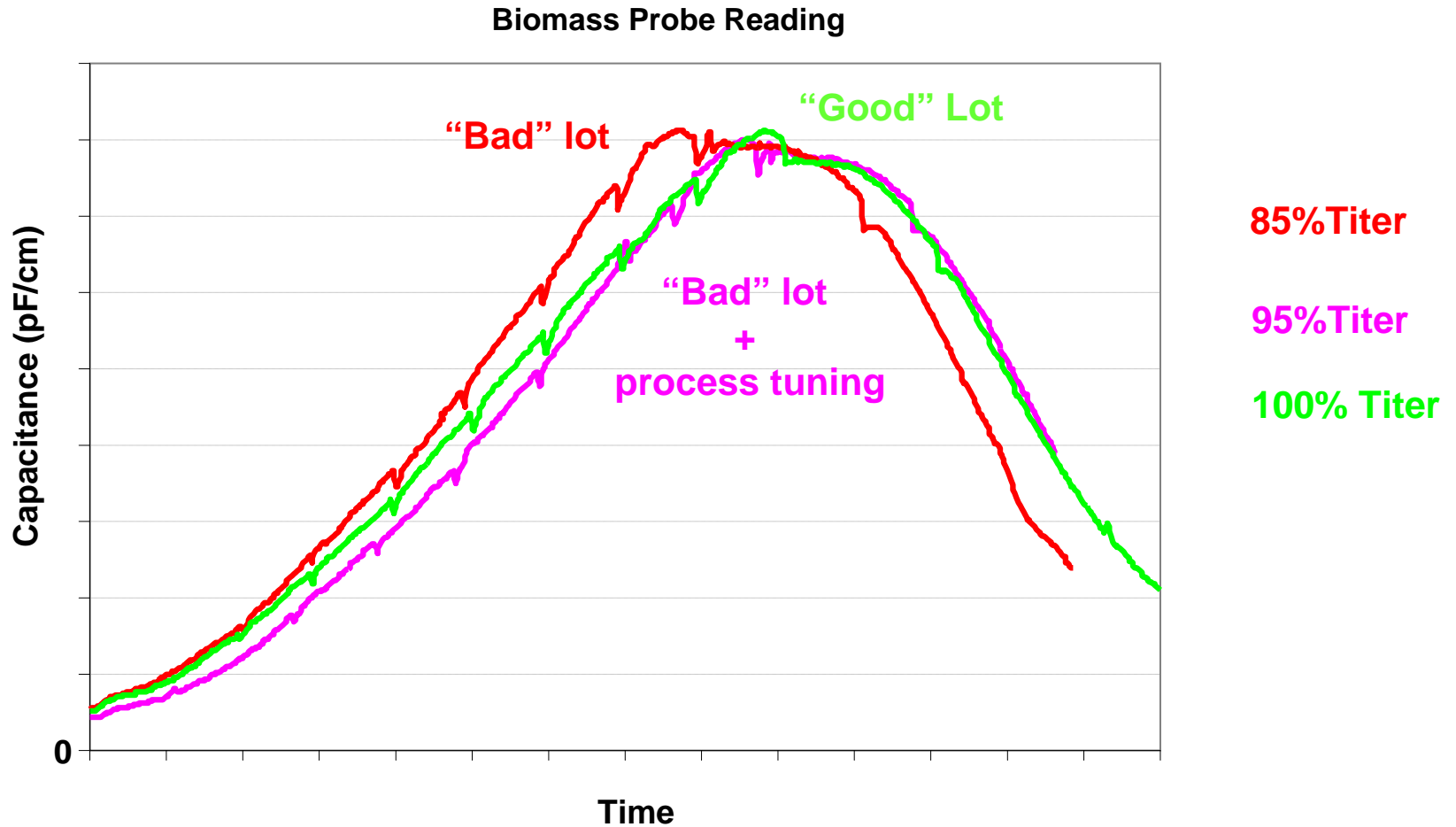
# Implementation of on-line biomass probe allows process automation and improves consistency



# Process control and tuning to reach “ideal” growth profile

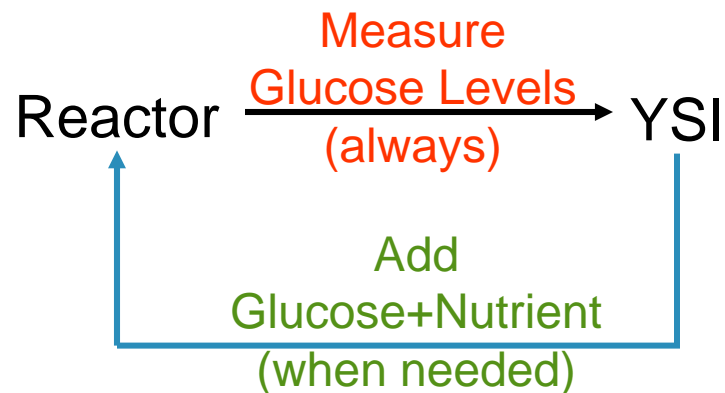


# Process Tuning in Response to Raw Material Change

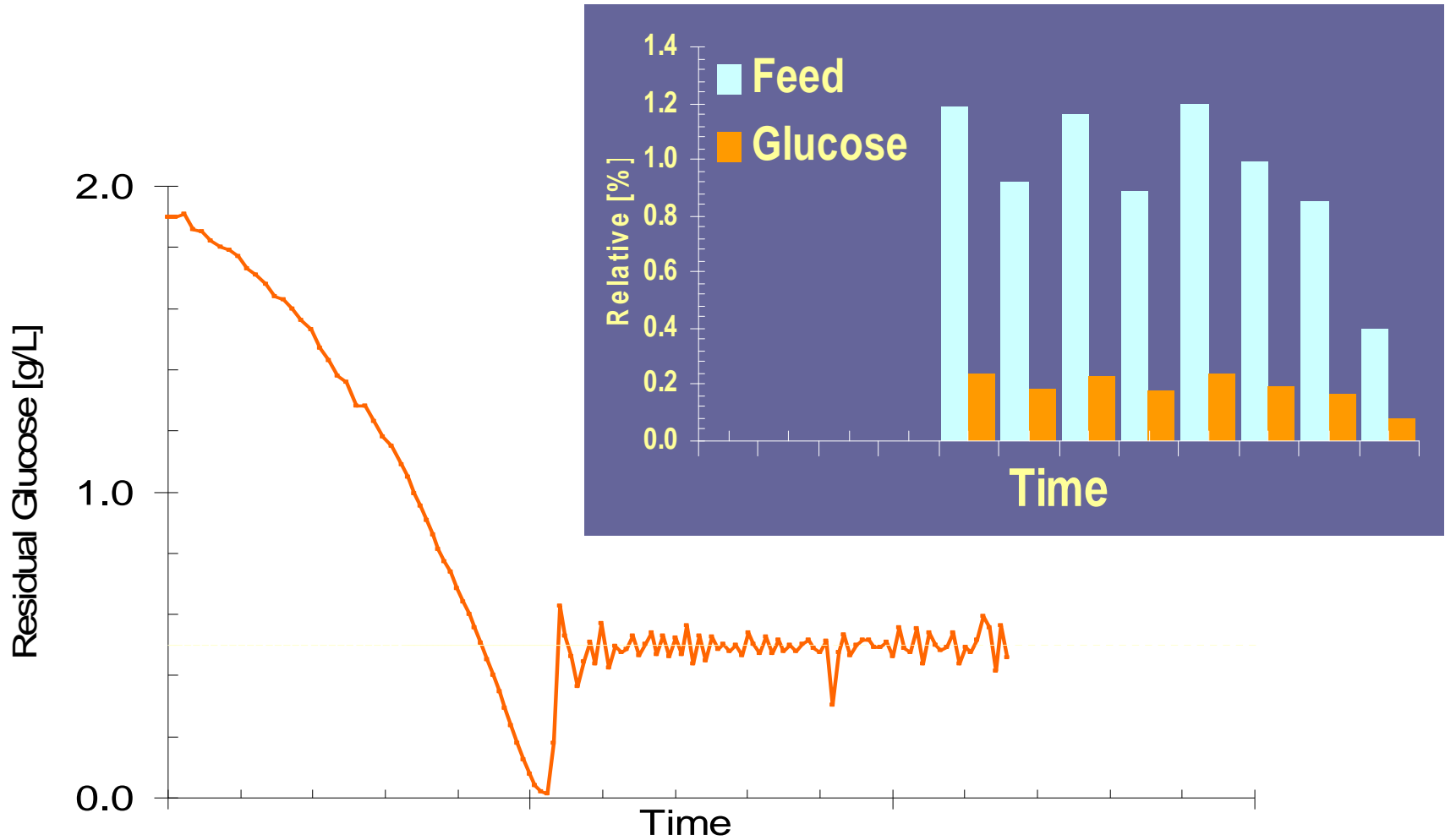


# Feed by Demand

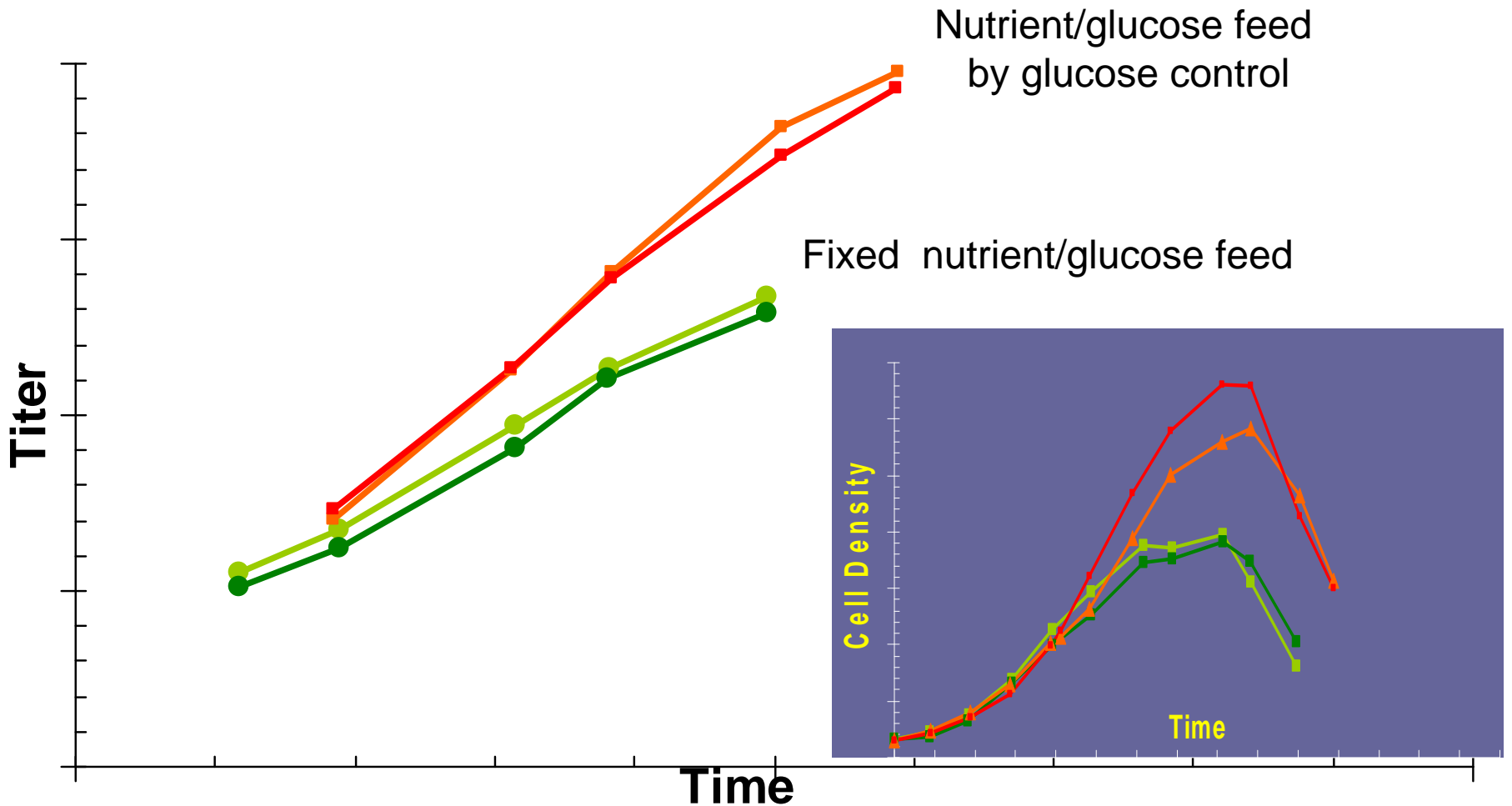
- Rational approach to optimizing hydrolysate nutrient feed strategy
  - Complex hydrolysate nutrient feed: many unknown nutrient components
  - Glucose consumption rate as a surrogate indicator for other nutrient metabolism
  - Add glucose/hydrolysate nutrient feed based on glucose consumption
- Automated monitoring and control to maintain constant residual glucose level



# Feed by Demand



# Feed by Demand



# Feed by Demand

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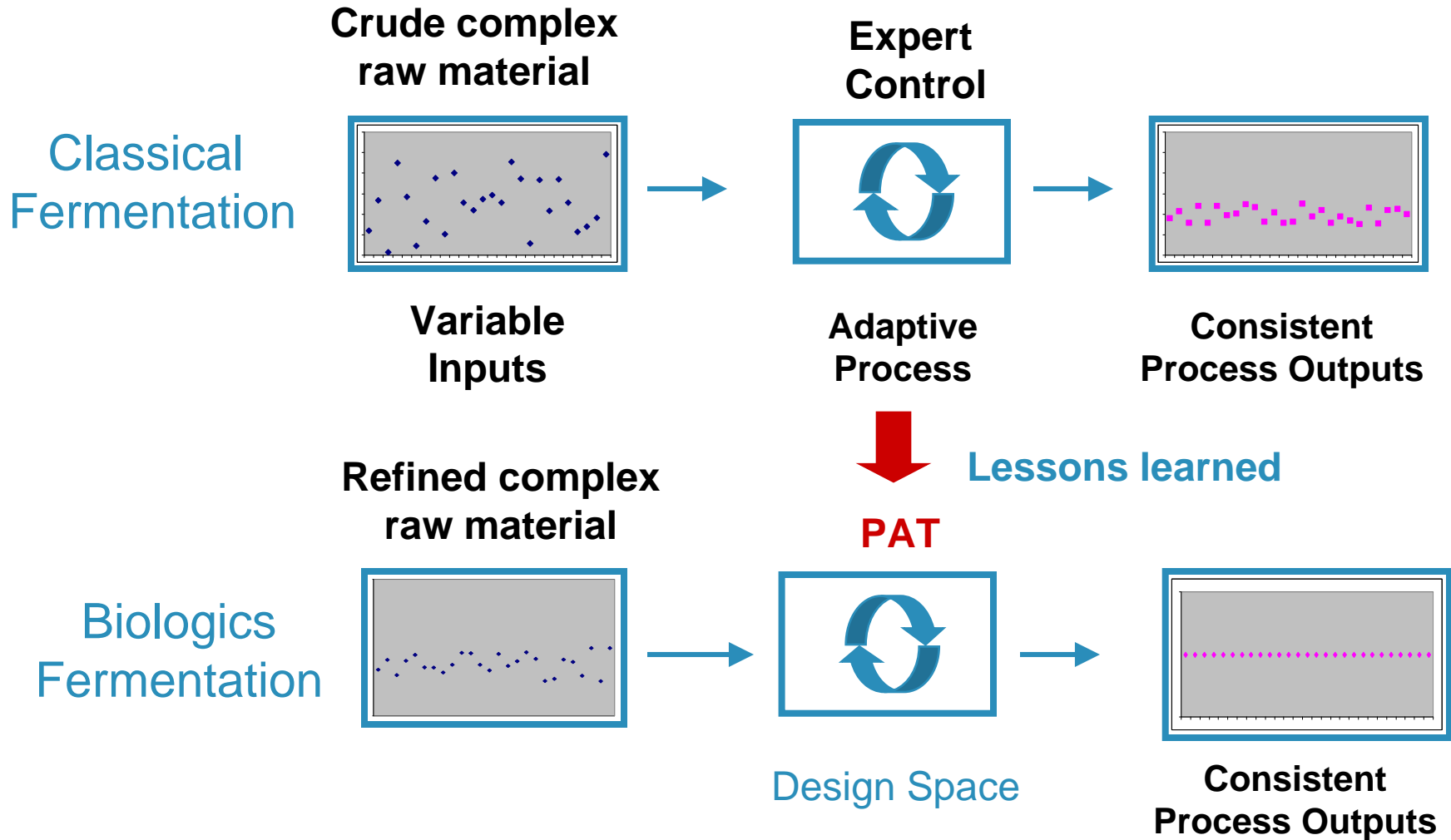
- Complex hydrolysate feed
  - Feeding strategy can be achieved based on the glucose consumption rate
  - Glucose-control nutrient feed
- Continuous optimization

# Expert Control Requires Advanced Sensors

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- Metabolic Indicators
  - Cell growth
  - Oxygen uptake rate
  - Glucose
  - glutamine/ammonia
  - Amino acids
  - Vitamins
- On-line sensors
  - Biomass probe
  - Mass spec off-gas analyzer
  - NIR Probe
  - Raman Probe
- At-line analyzers
  - HPLC
  - NOVA, YSI etc

# Achieving Dynamic Controls



# Summary

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- Process Analytical Technology is:
  - a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.
- PAT in response to complex raw material variation
  - Multi-pronged approach
    - Analyze raw material characteristics
    - Define better specifications
    - Screen lots in lab; predictive model
    - Process tuning and on-line control to reduce performance variation

# Acknowledgement

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- Cell Culture Groups
  - Process Sciences
  - Technical Operations
- Engineering
- Manufacturing
- API Fermentation at North Chicago site

