Raman spectroscopy applied to monitoring, modeling and control of biologics production

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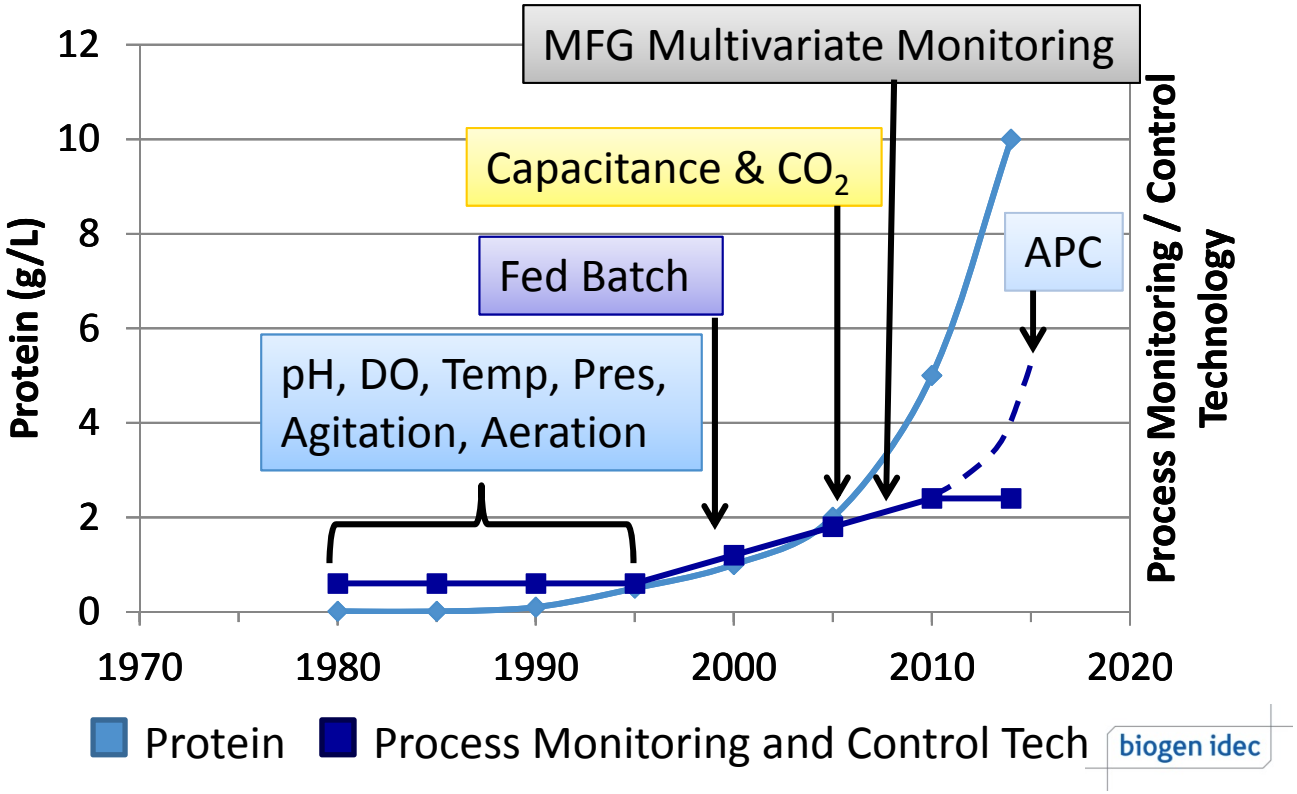
Outline

- Background
  - Current and future state of bioprocess control
  - Biogen's vision for APC
  - What is Raman Spectroscopy?
- Raman
  - *In Situ* Application
  - Model development
  - Case Study
- Feedback control strategies
- Technology rollout in manufacturing

Evolution of Cell Culture Processes

- From the 1980's to present, processes continue to evolve in order to:
  - Maximize protein production
  - Improve product quality
  - Accelerate development and commercialization

- **Productivity has increased 1000 fold in 30 years**
- **Real time monitoring and control has not grown nearly as fast!**
- **APC will reduce this deficit yielding better controlled processes**



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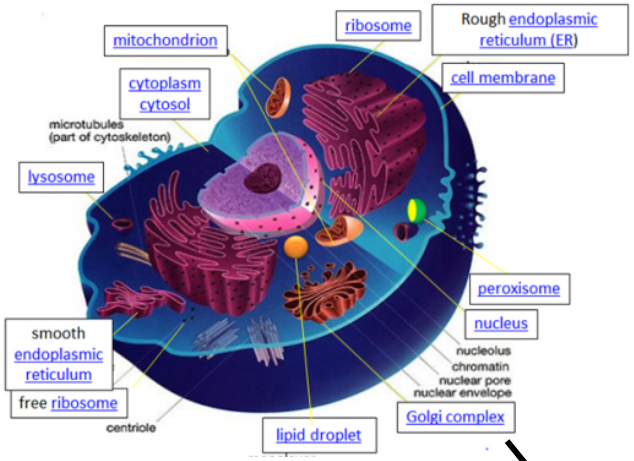
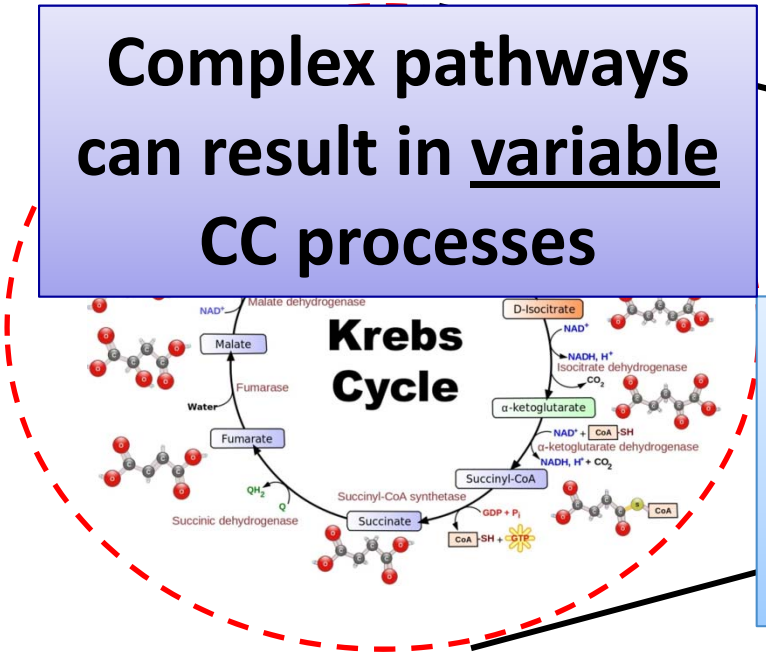
Biologics Today

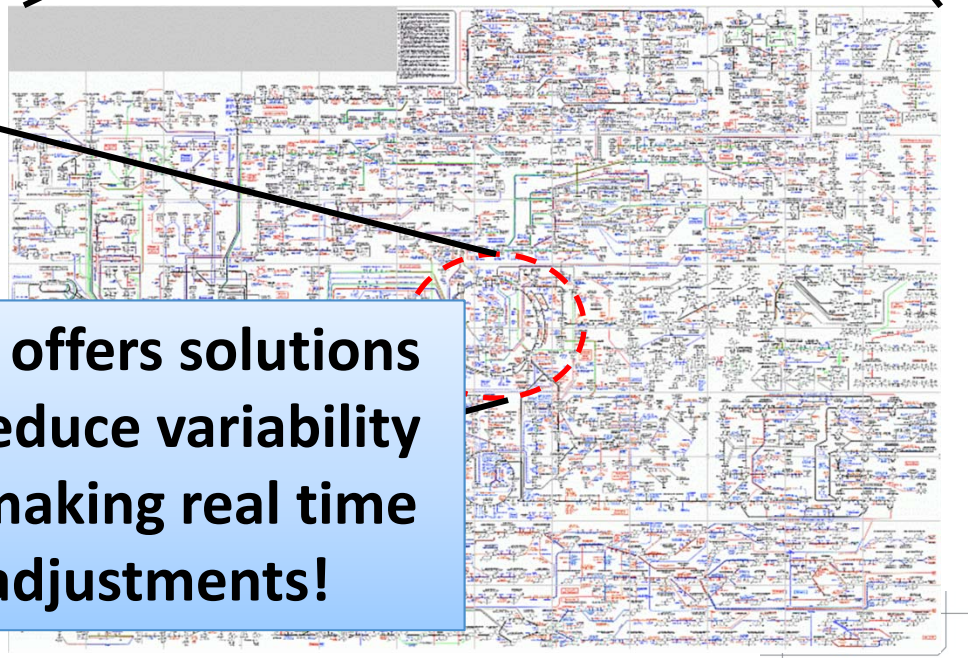
Discovered by
Theodore T. Puck

- CHO cell line generated in 1957
- Complex cellular pathways
  - Still not fully understood
  - Highly complex and interrelated
  - Sensitive to changes in environment



Complex pathways can result in variable CC processes





APC offers solutions to reduce variability by making real time adjustments!

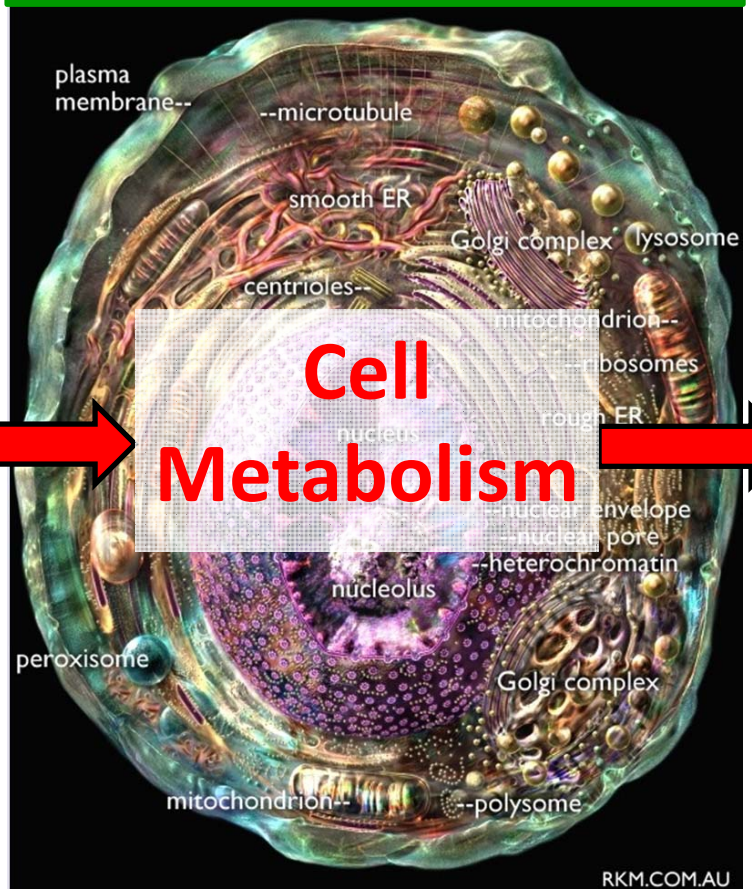
Monitor & Control of Cellular Pathways is Critical

Major Inputs

- Seed density
- Feed strategy
- Environment
  - pH
  - DO
  - Temp
  - Mixing
  - Aeration
- Glucose (APC)
- Nutrients (APC)
  - (total amino)

Current State Monitor/Control

Future State of Monitor/Control (APC)



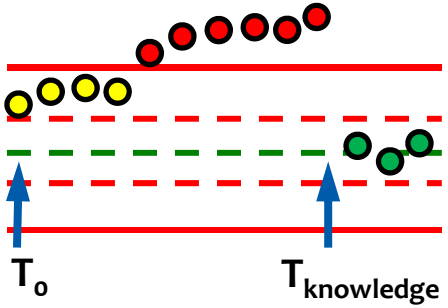
Cell Metabolism

Major Outputs

- Waste (APC)
  - Lactate
  - Ammonia
- Protein (APC)
  - Titer
  - PQ Attributes

Biogen's Overall Strategy

Consistent Cell Growth = Consistent titer and PQ



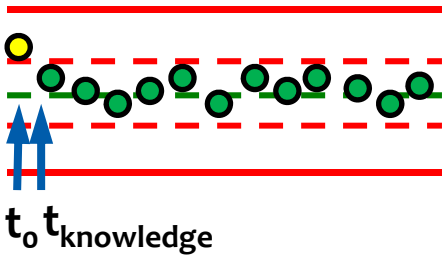
Event Occurred

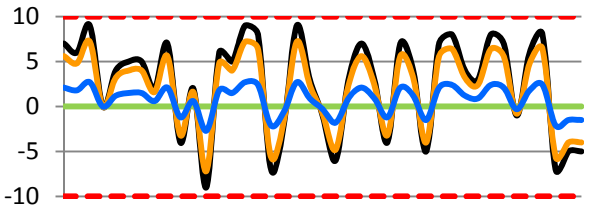
Transformed data into info and decision/action;

Shorten Reaction Time

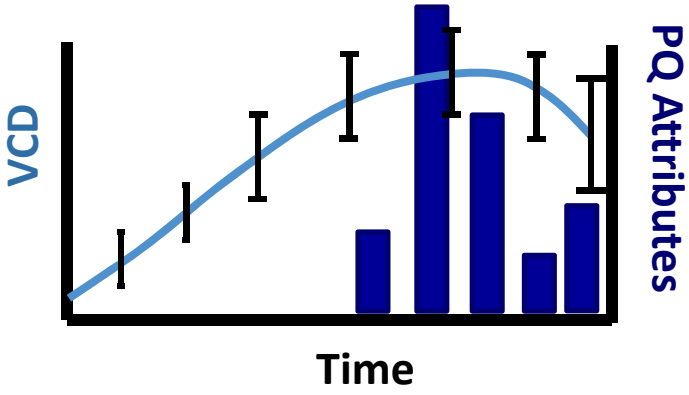
+

Tighter control





Without APC



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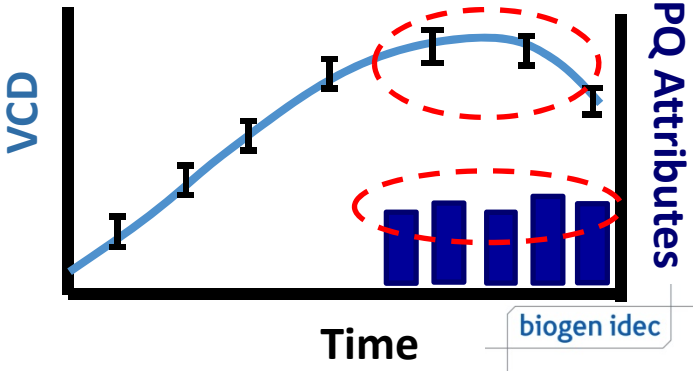
Increase Process Consistency

With APC

Under more control



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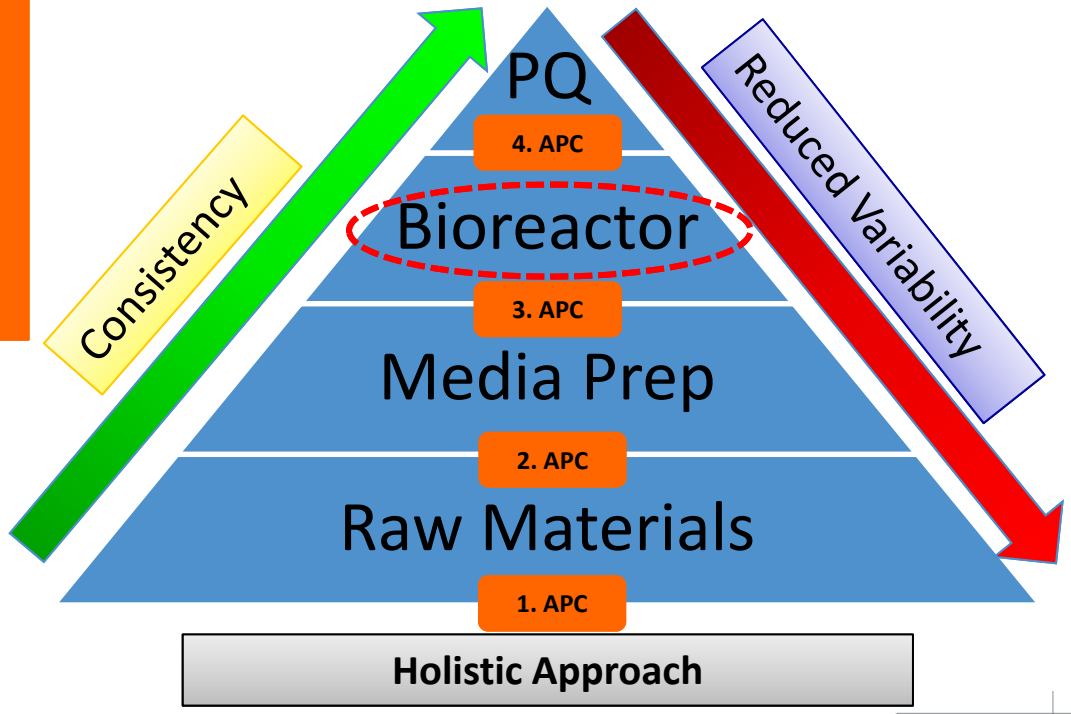
CCD APC Team

- **Core Objective:** Control cell culture variables in such a way to achieve **consistent** batch to batch performance

APC: Building the process of the future

1. Vendor raw material lot screening
2. Advanced BIIB QC raw material testing
3. Advanced monitoring during buffer prep (MFG)
4. Advanced monitoring and control of bioreactor (MFG & MS)

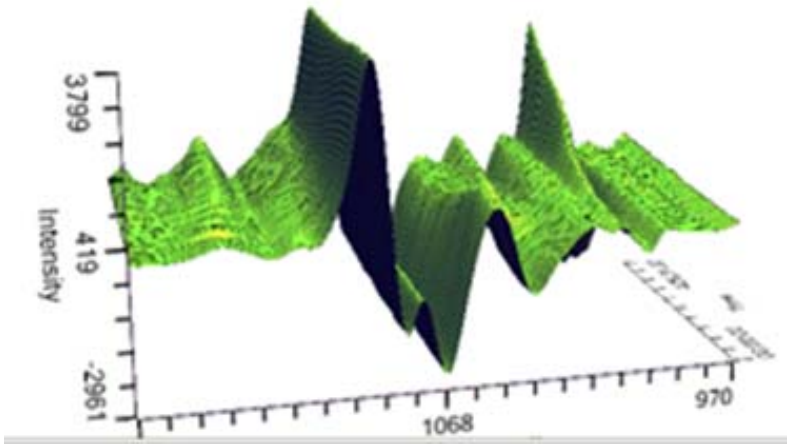
Goal: Reduce variability at each step…fine tune at bioreactor



Raman Spectroscopy

7Nov1888 – 21Nov1970

- Optical analytical technique based on inelastic scattering of monochromatic light
  - Discovered in 1928 by Sir C.V. Raman, FRS
  - Non-destructive
  - Advantage: High chemical specificity with little water interference
  - Disadvantage: Fluorescence
- Works well in industry
  - Used for analysis of solids, liquids or gases
  - Used *in situ* or bench top
  - Commercial grade equipment available
- Raman in Biotech
  - Multiple applications
  - Measure multiple constituents at once
  - CIP, SIP, autoclave tolerant
  - Low maintenance



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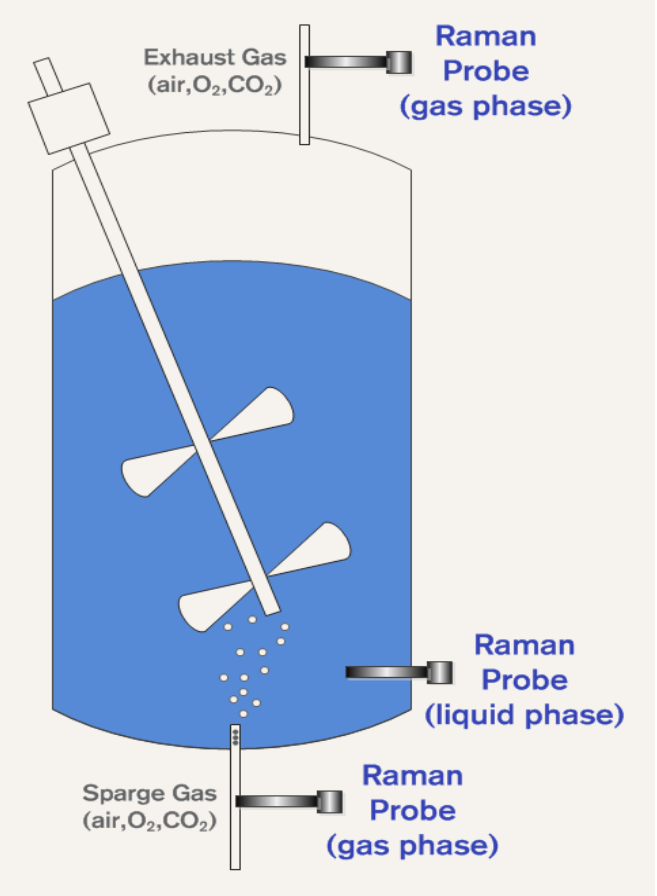
Applications of Raman

- Bioreactor – *in situ* — Presentation Focus
- Bioreactor – off gas — In development
- Media prep — PoC completed
- Downstream — Exploration phase



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Bioreactor (*In Situ)*

- Mammalian cell culture
  - Multiple literature publications in last 7 years
  - Multiple constituents monitored successfully
    - Glc, Lac, Gln, Glu, NH3, Titer, VCD, TCD, Viab.
  - General or product specific models
    - Depends on accuracy needed for control
  - Offline reference method
    - Nova Flex or Cedex Bio HT
  - Scalability of technology platform demonstrated

Bioreactor (*In Situ*) Biogen Experience

Process Metabolites & Electrolytes

- Glucose ★
- Lactate ★
- Glutamine
- Glutamate
- Ammonium ★
- Sodium
- Potassium
- pH

Cell Growth Profiles

- VCD ★
- Total Cell Density
- Viability

Batch Performance, Product Quality, & Assay Based Data

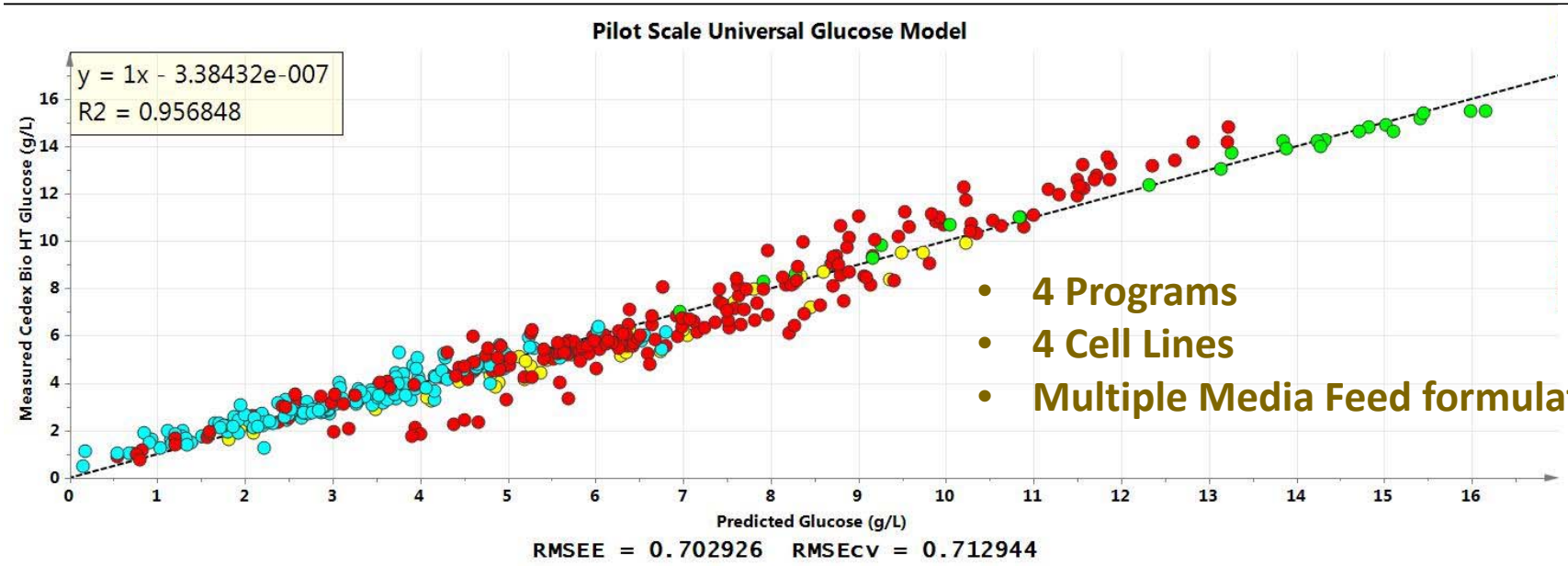
- Titer
- Amino Acids (Total Amino) ★
- Product Quality Attributes

Legend

- Established Models at BIIB
- In development at BIIB
- Potential Future Work
- Focus Areas ★

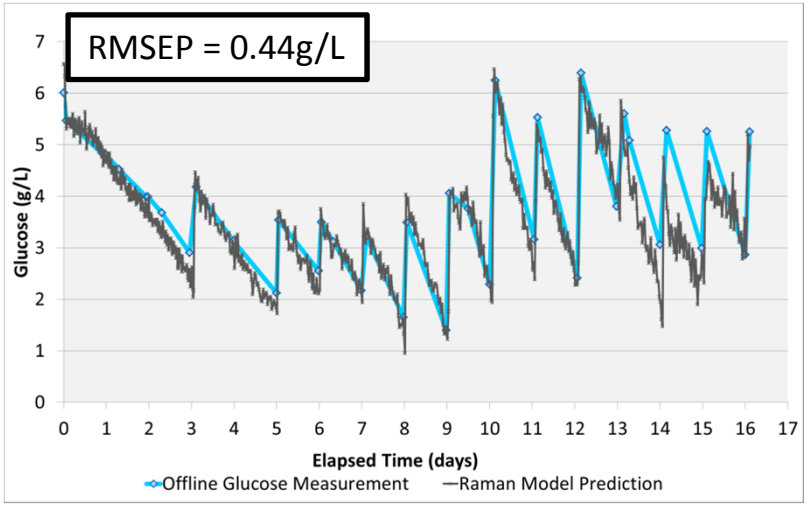
- Focusing resources on critical models that have immediate process impact that will justify further development of technology

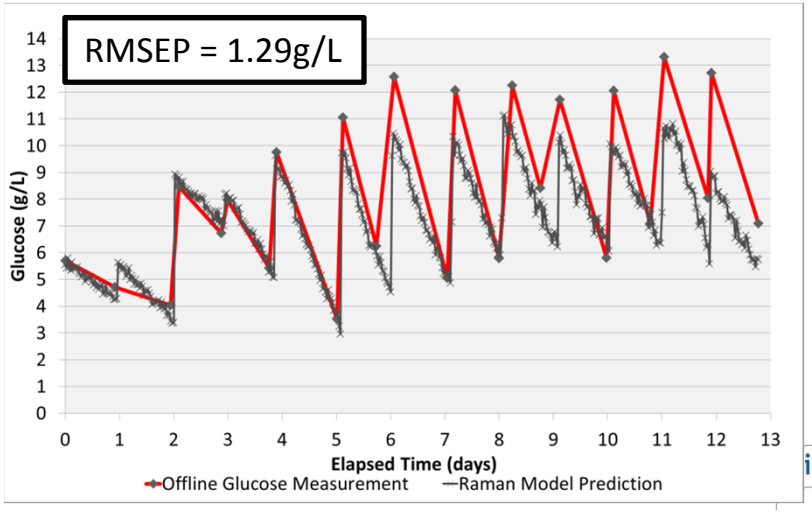
Universal Process Glucose Model



- 4 Programs
- 4 Cell Lines
- Multiple Media Feed formulations

Can we use a single model in many programs? (different medias, component ranges, cell densities, turbidities, etc.)





Universal vs. Program Specific Model Comparison

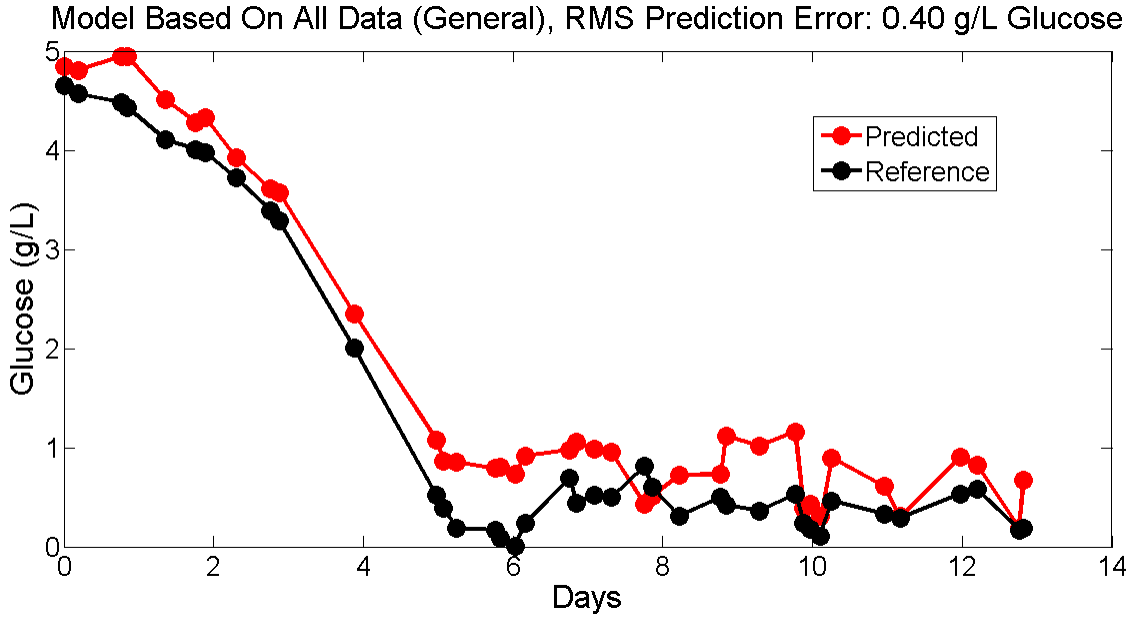
Universal Model

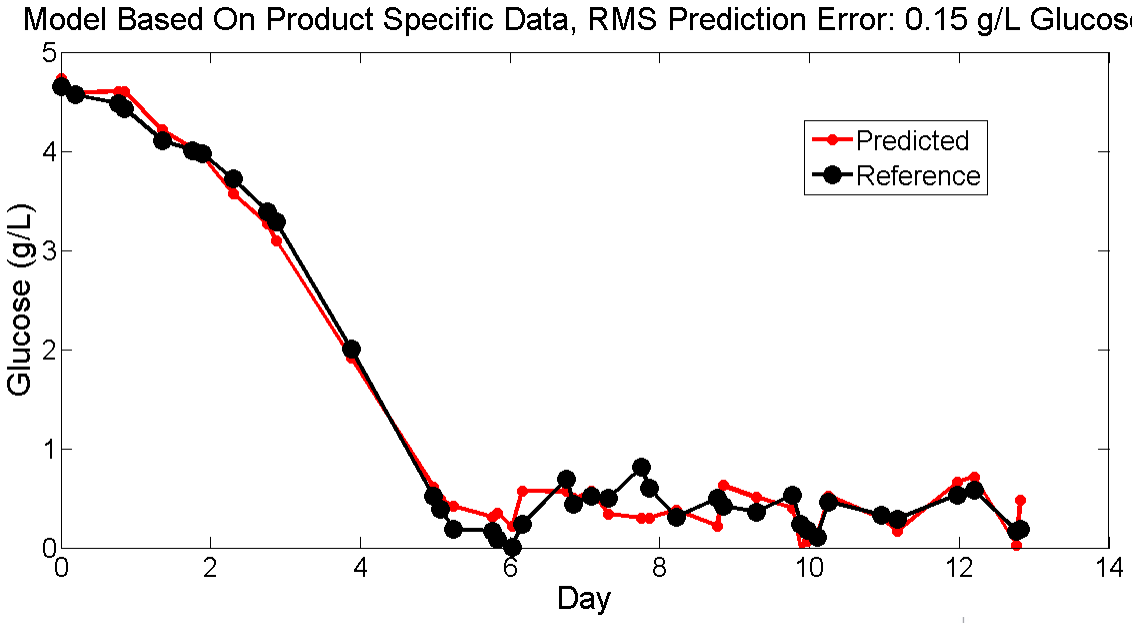
RMSEP 0.4g/L

To

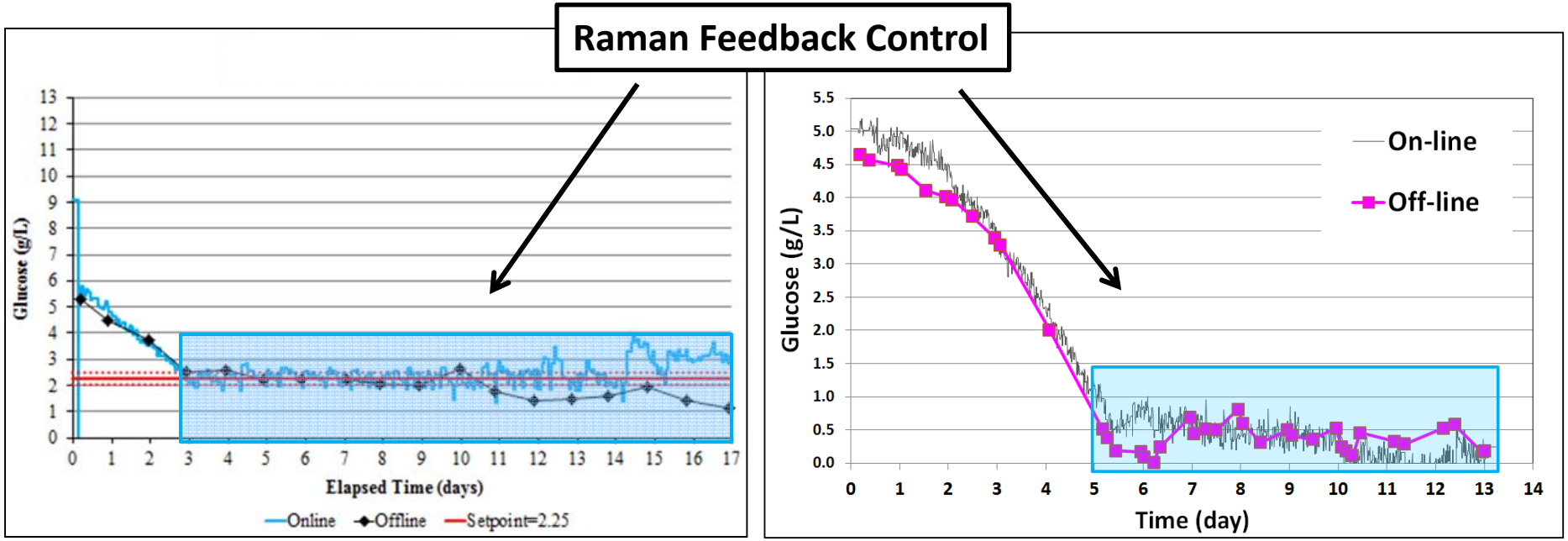
Program Specific Model

RMSEP 0.15g/L





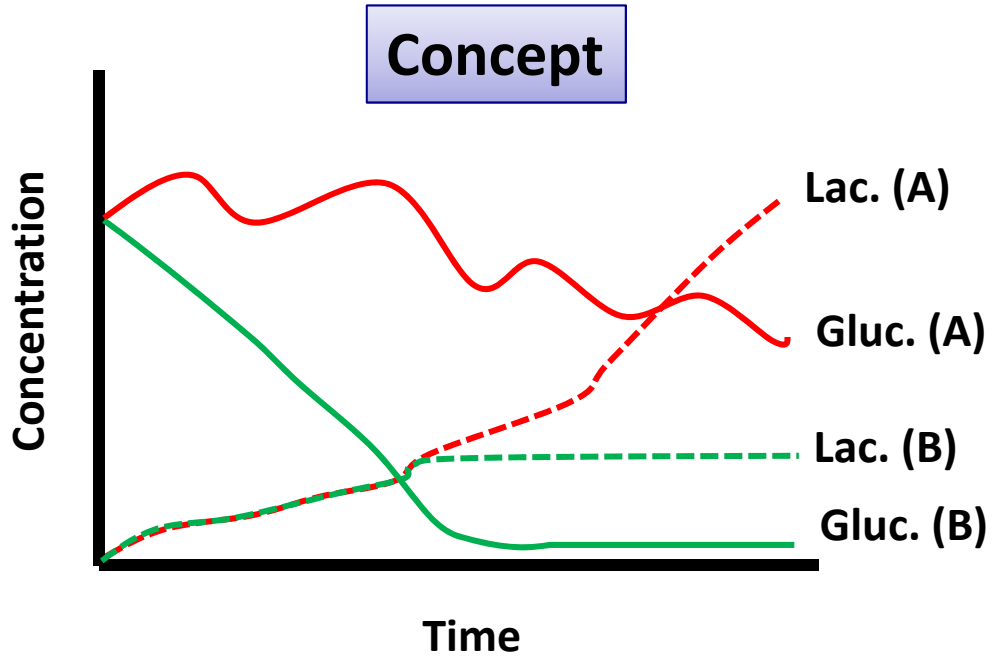
Examples of Glucose Control



- Traditional glucose set point control to improve process consistency

Glucose / Lactate Feedback Control

- Problem: High lactate process is impacting VCD, viability, duration and titer
- Strategy: Control glucose at low level to induce lactate consumption



Measurable: VCD ↑ Duration ↑ Titer ↑

Glucose / Lactate Feedback Control

- Problem: High lactate process is impacting VCD, viability, duration and titer
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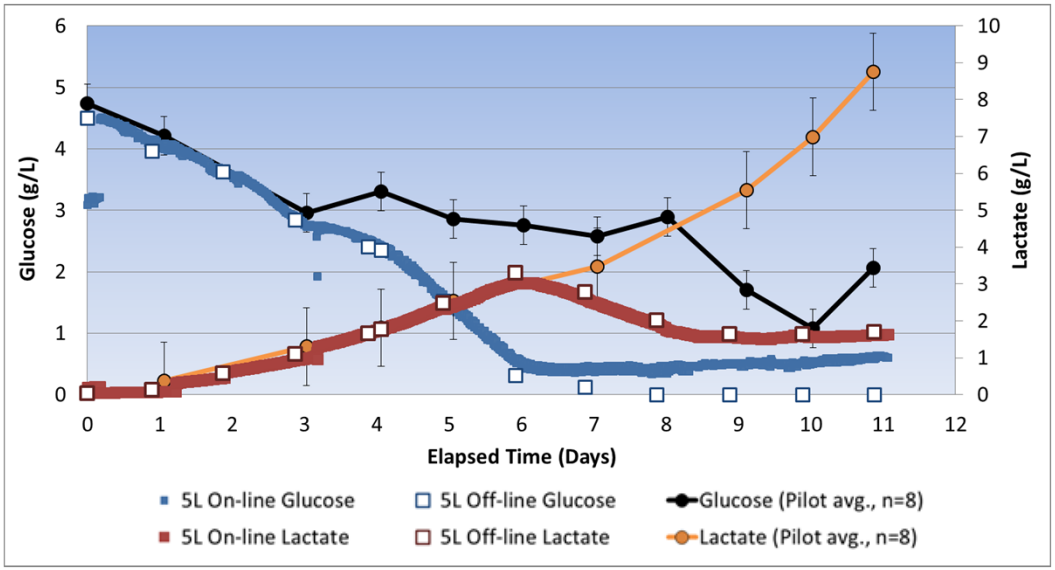
Small Scale PoC



Measurable: VCD 35% ↑ Duration 20% ↑ Titer 60% ↑

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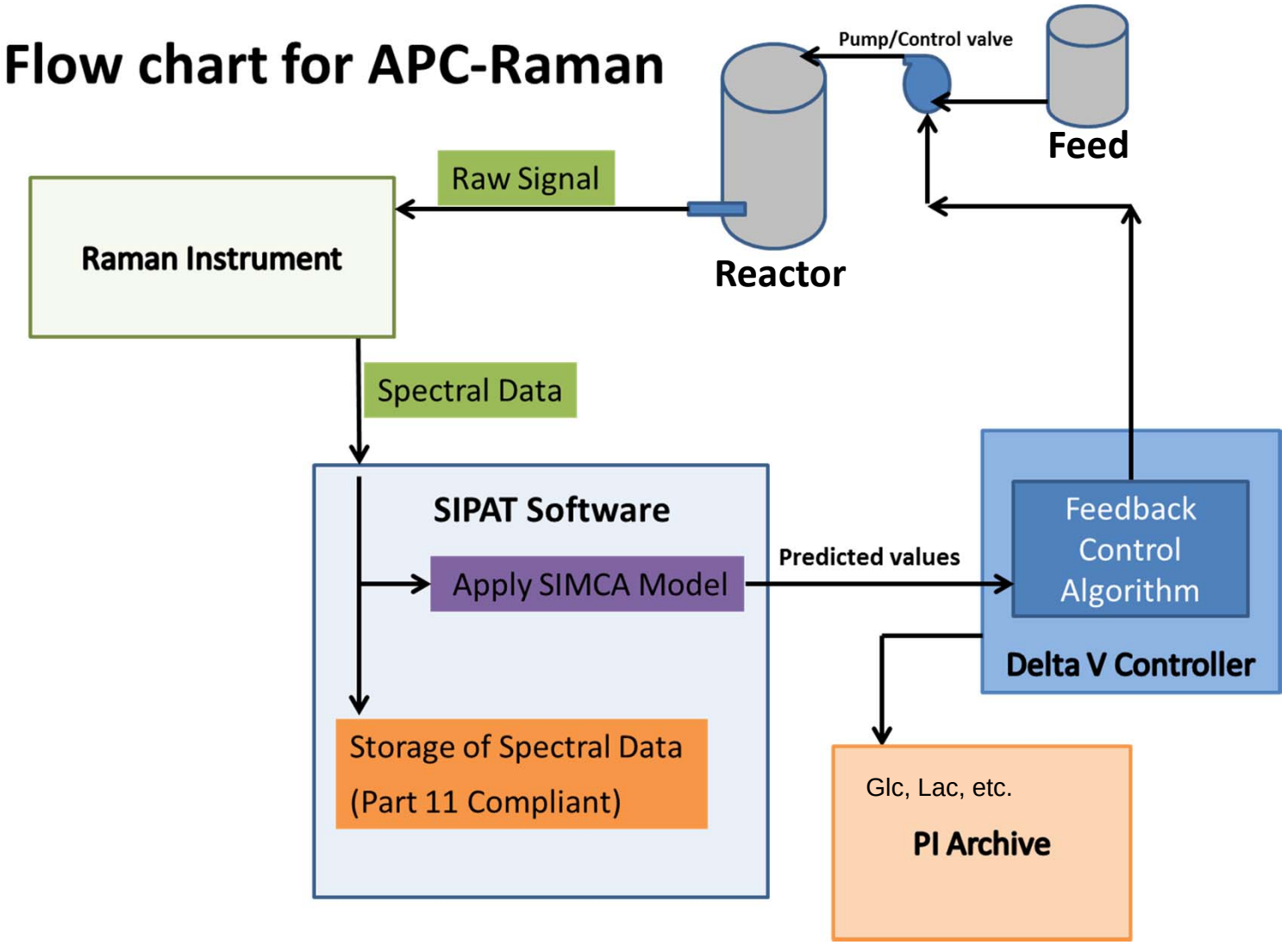
Raman / SIPAT Software



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MFG Implementation – Things to Consider

- Build Infrastructure
  - Add extra reactor ports if necessary
  - Integrate control valves / pumps to enable feedback control
  - Integrate new software platforms that can interpret spectral data
  - Create feedback automation code
  - Identify long term ownership of systems
- Identify the value proposition per process
- Align technology with company priorities/focus

Acknowledgements

- CCD APC Team
  - Raman Team
    - Justin Moretto
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Questions