Strategic Developing Process Analytical Technologies for Real Time Quality Attribute Analysis in Bioprocess Development

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Biologics Development

Bristol Myers Squibb™

BMS Biologics Development Network

PROCESS/ANALYTICAL DEVELOPMENT & CLINICAL MANUFACTURING

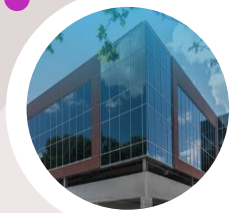
Devens, MA

- US Biologics COE
- Biologic Development
- MS&T, Quality AS&T
- Clinical Manufacturing
- Commercial Manufacturing

New Brunswick, NJ

US Biologic Development-Early Phase

Bioassay COE; GMP Testing



Summit, NJ

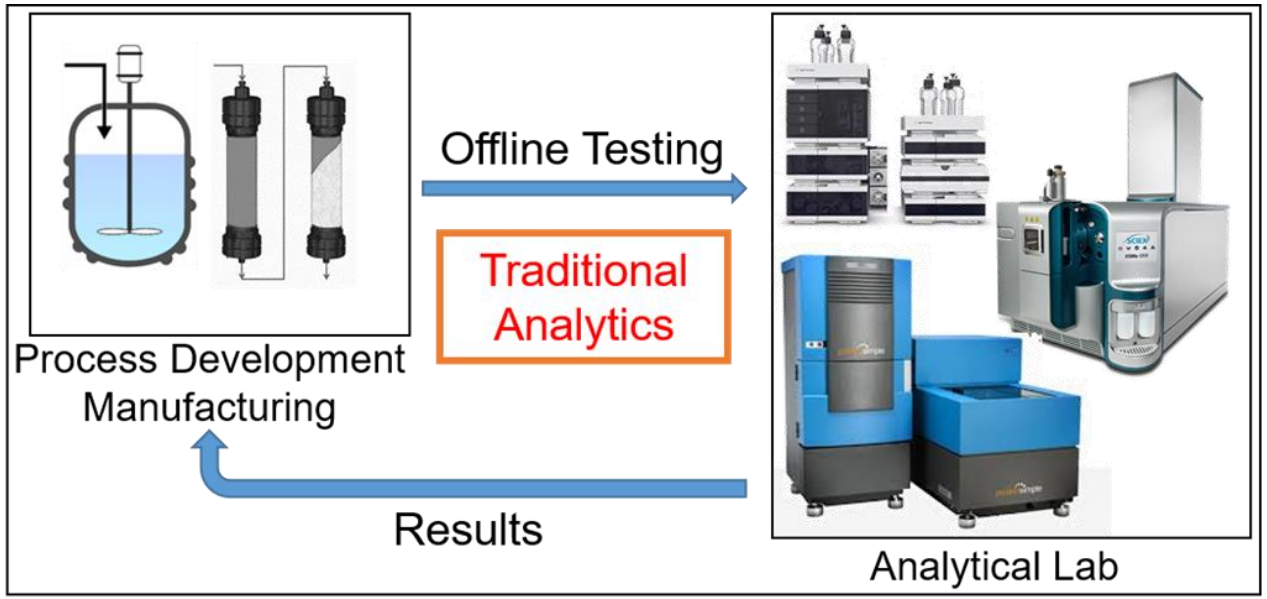
US Biologic Development-Early Phase

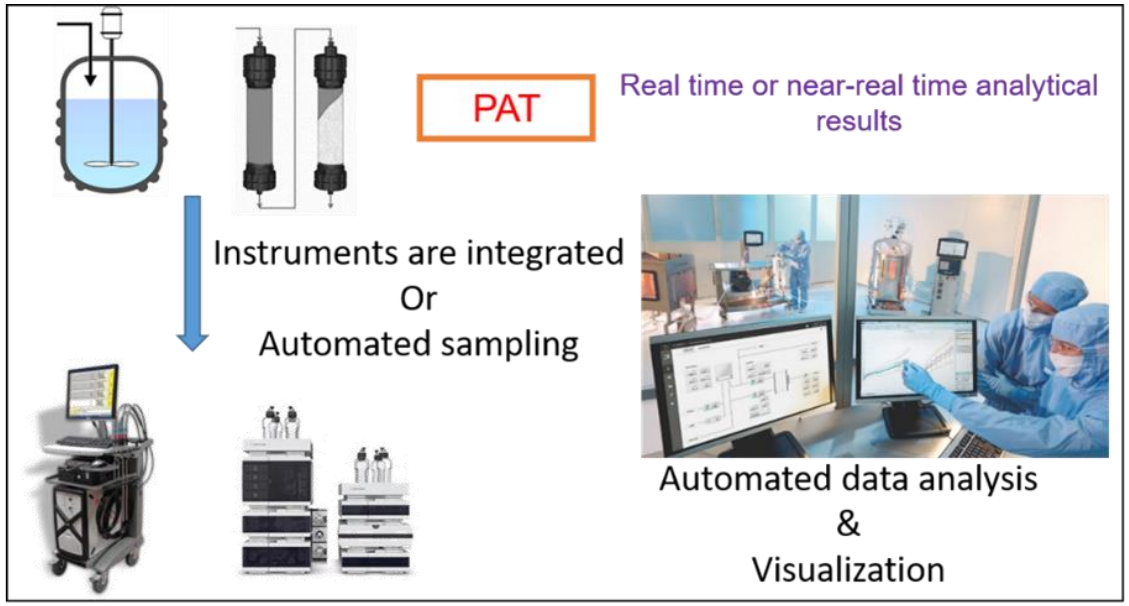
Clinical Manufacturing

Outline

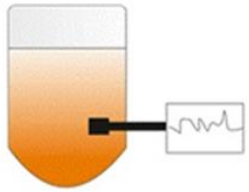
- Strategic Developing our Technology Roadmap Towards Real Time Product Quality and Bioprocess Monitoring
- PAT Vision and Technology Landscape at BMS with Case Studies
- What will this lead us into the future? – Future Outlook

Traditional Process-Analytical Integration vs. PAT



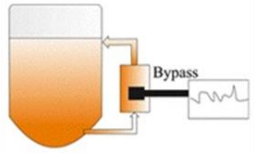


Modes of Integration



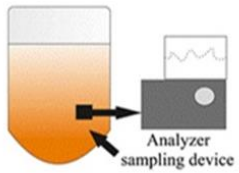
In-line

Samples are analyzed within the process stream



On-line

Samples are analyzed by taking out from the process stream in automated-fashion may or may not go back into the process stream



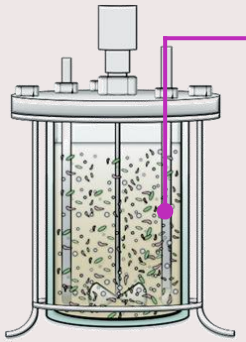
At-line

Samples are analyzed by taking out from the process stream

Strategy in Building Real Time Product Quality and Process Monitoring

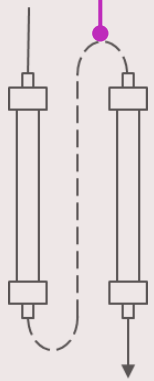
"Monitoring As It Happens"

Unit Operation | Attribute/ Process Parameter | Choice of Analytical Technology



- Charge Variant Profile
- Glycan Profile
- Product Titer
- Nutrient and Metabolites

On-line & In-Line

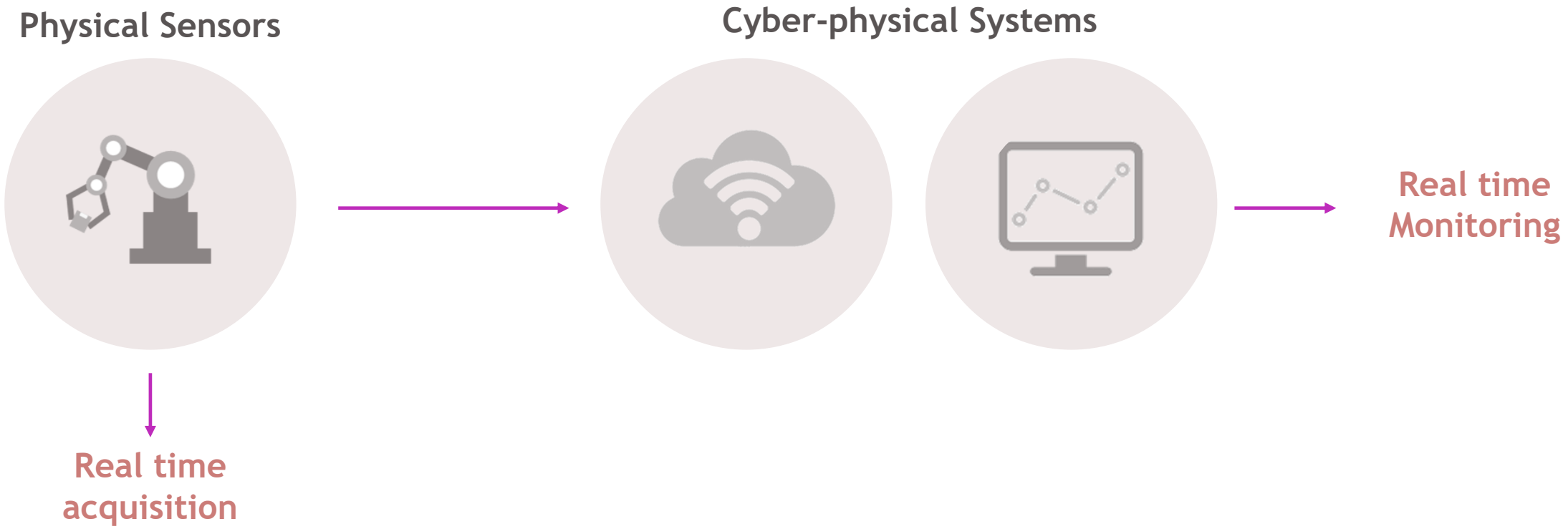


- Product Concentration
- Impurity Clearance

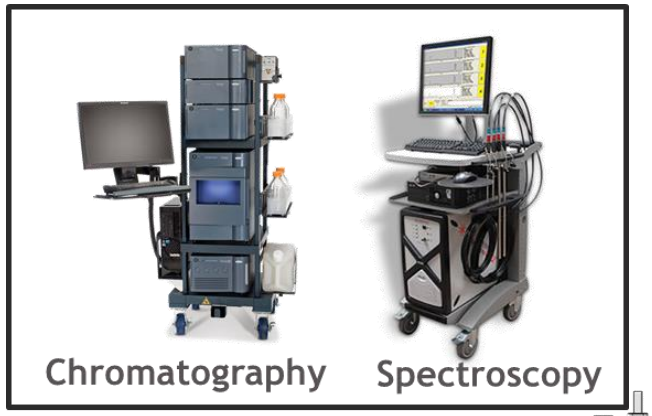
At-line & In-Line

Strategy in Building Real Time Product Quality and Process Monitoring

“Real Time Acquisition vs. Monitoring”



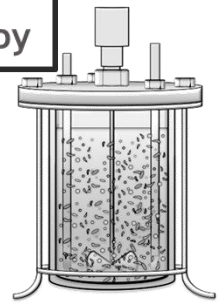
Our PAT Vision



Feedback/Feedforward Control

DCS

Sensors



Unit Operation

Analyzers & Visualization

Repository

Automation

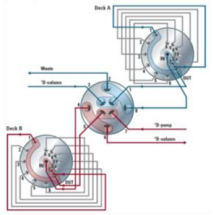
Samplers

Cell-free Samplers

Samplers/Distributors

Preparers

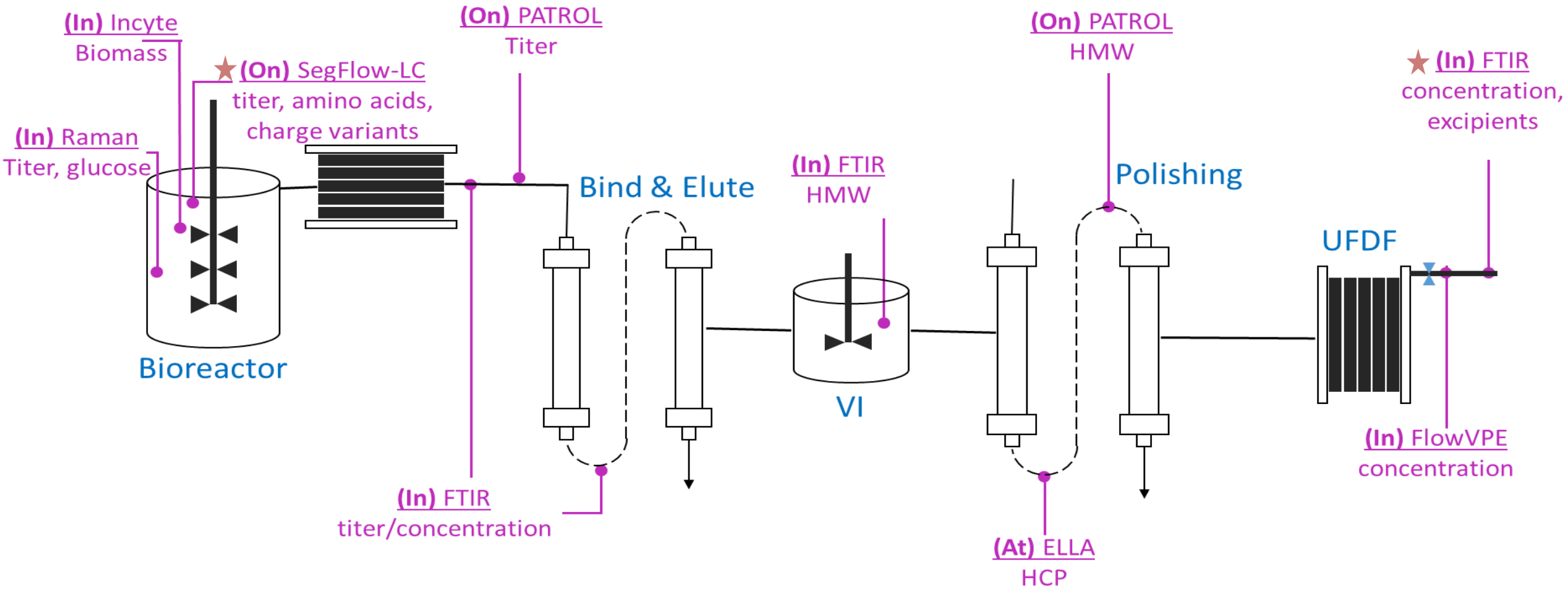
Sample Preparation



Onboard Preparation

Wasalathanthri, D.P.; Ding, J.; Li, Z. *American Pharmaceutical Reviews*, **2020**, 23,3, 72-75.

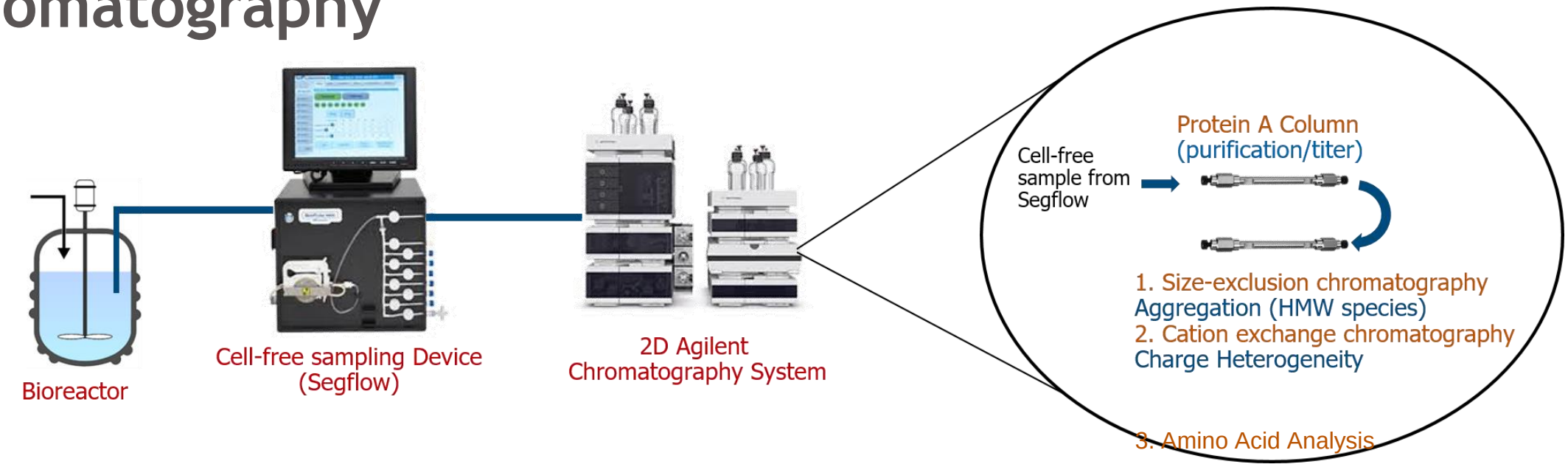
PAT Technology Landscape in BMS

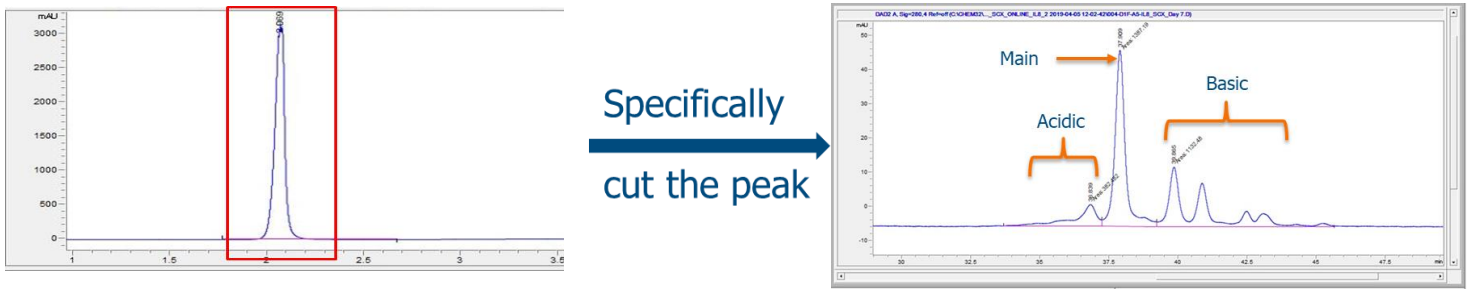


★ Case Studies to be presented

Wasalathanthri, D. P., Rehmann, M. S., Song, Y., Gu, Y., Mi, L., Shao, C., Chemmalil, L., Lee, J., Ghose, S., Borys, M. C., Ding, J., Li, Z. J. *Biotechnology and Bioengineering*, **2020** *117*, *3182-3198*.

On-line Product Quality Monitoring by Multi - Attribute Chromatography

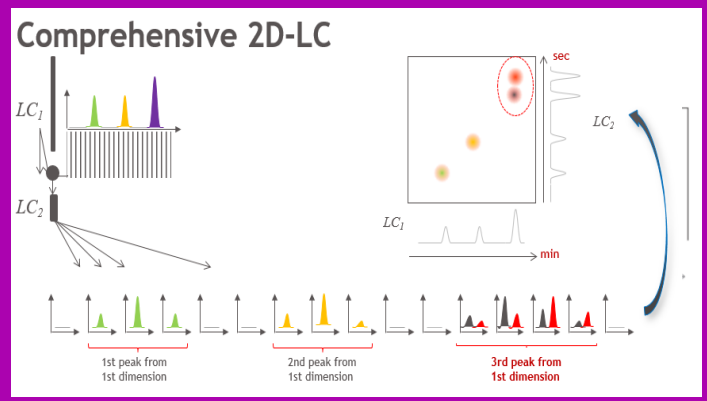




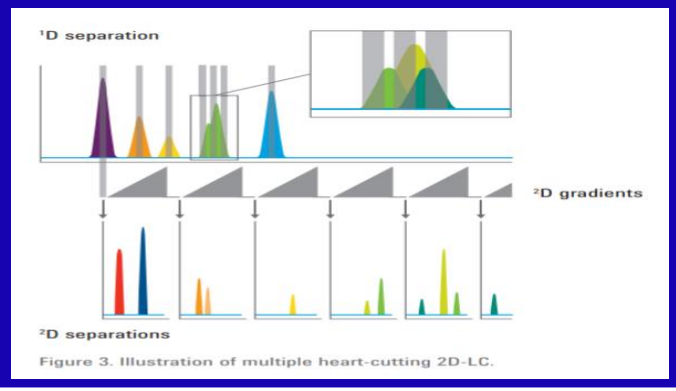
Strong Cation Exchange Chromatography

Agilent 2D-LC w/ High Resolution Peak-Cutting & Peak Parking: A Viable Option to Deal with Large 1st Dimension Peak Volume

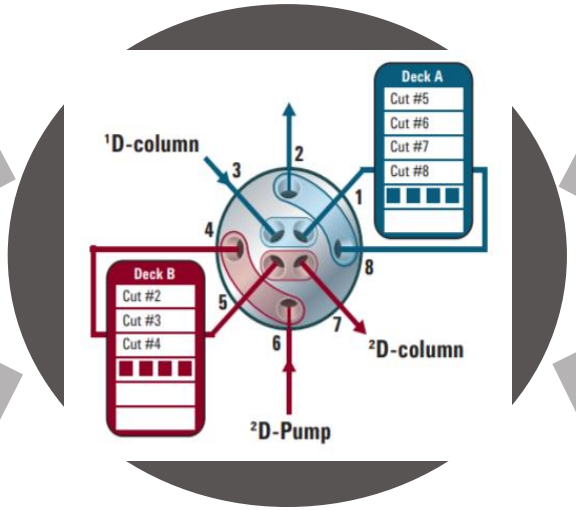
Comprehensive Transfer



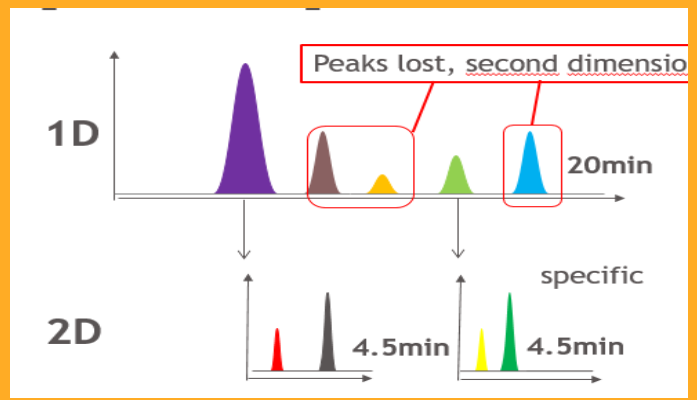
Heart Cutting & Peak Parking



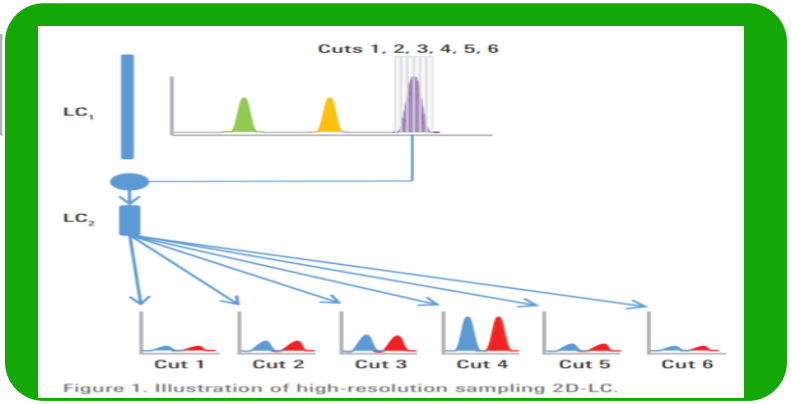
Peak Cutting Capabilities for Agilent 2D-LC



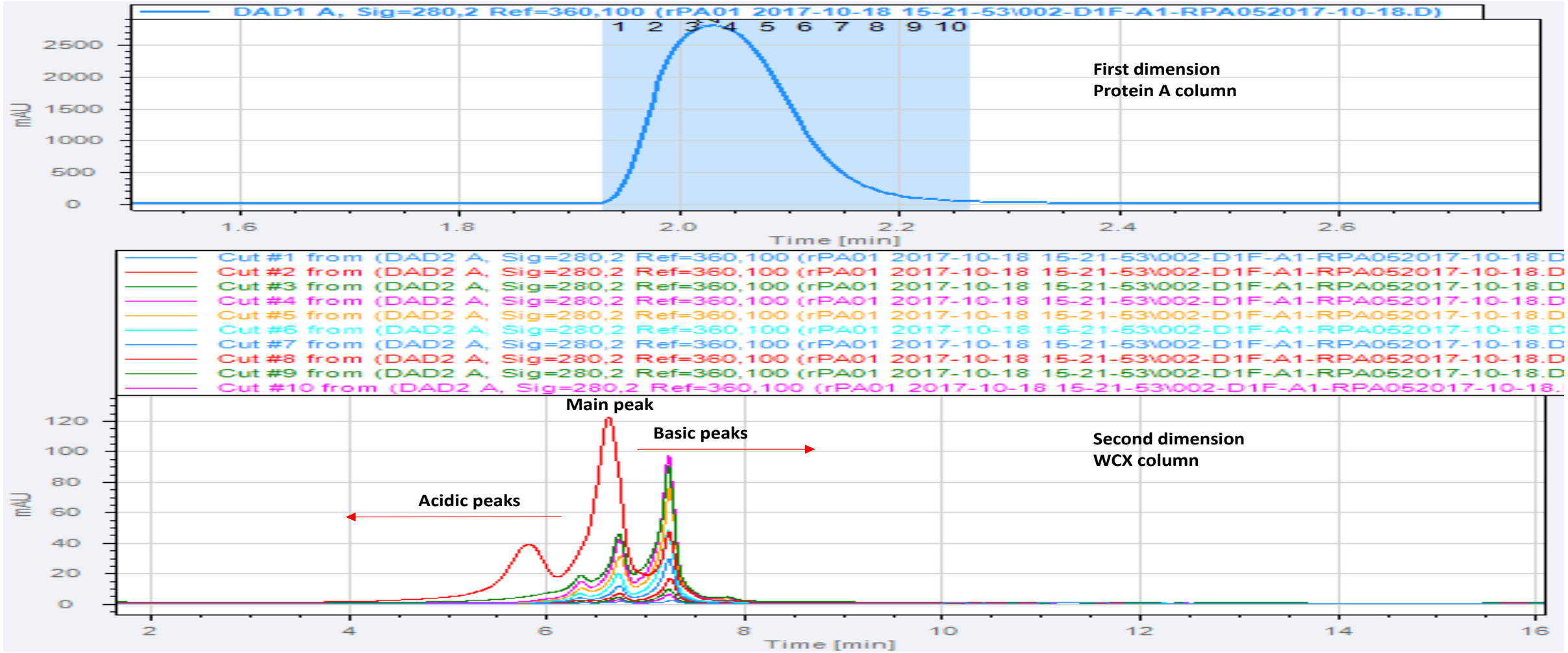
Conventional Heart Cutting



High Resolution Sampling



A representative IEX profiles of High Resolution peak cutting of 1st dimension Protein-A & a 2nd dimension IEX Chromatography



An Alternate Approach to High Resolution Peak Cutting & Peak Parking to Enable Near Real-time Analysis

High Resolution Peak-cutting & Peak Parking

Advantages:

- Agilent 2D-LC provides the option to collect multiple fractions of 1st dimension Protein-A peak in multiple sample loops and inject one fraction at a time
- Agilent OpenLab CDS Chemstation software is capable to integrate the data from multiple fractions to integrated final results

Disadvantages:

- Long analysis time for analyzing multiple peak cuts, which is not in alignment with the rapid analysis required for of PAT

Alternative Approach with Flow Splitting

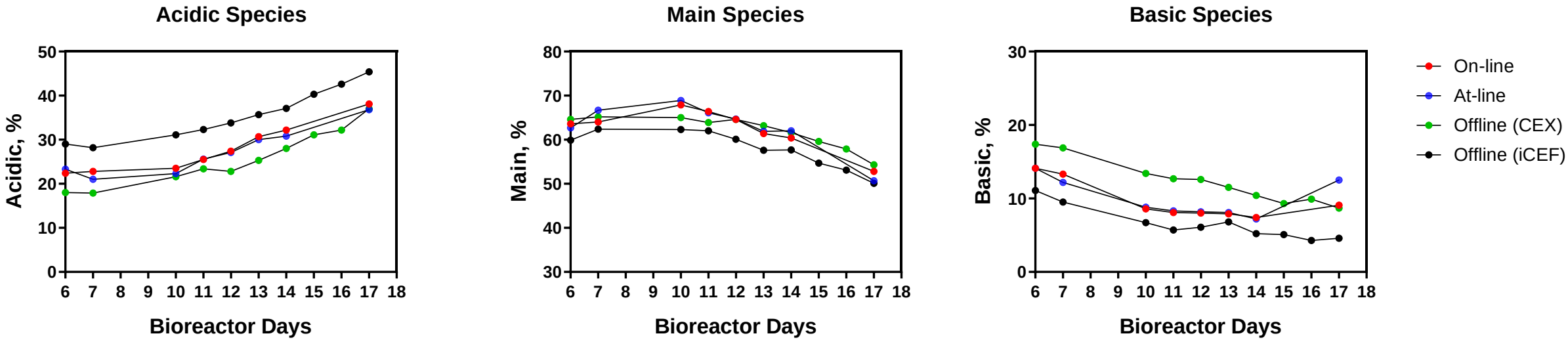
Advantages:

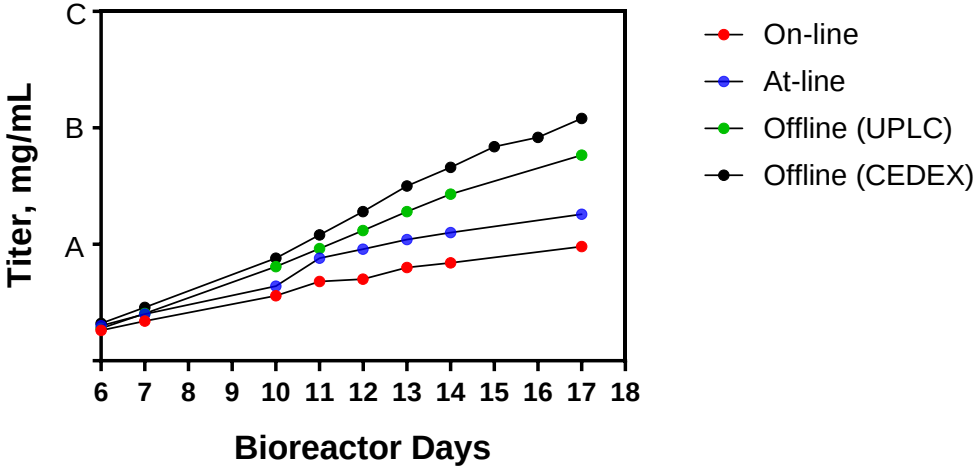
- Post flow-splitting of 1st dimension protein-A effluent can be achieved effortlessly with commercially available MS flow splitters
- Based on the peak volume of the 1st dimension protein-A chromatography, flow-splitters with different flow splitting ratios can be utilized
- With 1:10 flow-splitter, analysis time can be reduced by 10-fold

Disadvantages:

- No disadvantages

On-line Product Quality Analysis by 2D-LC CEX Multi - Attribute Chromatography



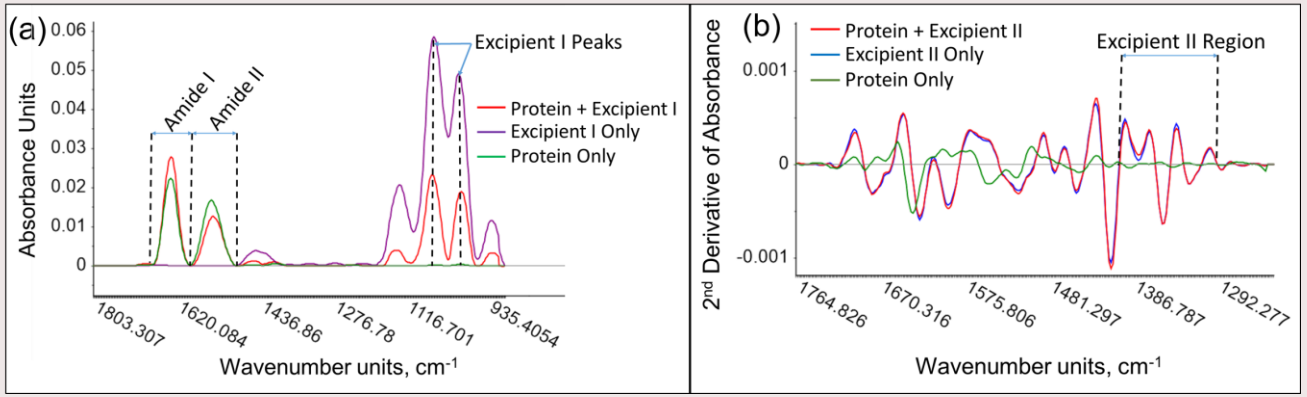


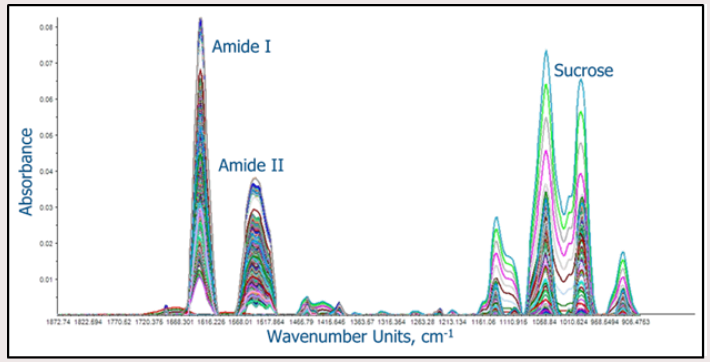
- Bioreactor titer obtained from 1D-LC acquisition
- A platform CEX method is applied at 2D-LC
- Multiple attributes, such as titer, charge profiles (acidic, main and basic groups) are measured near real-time by on-line 2D-LC technology

FT-IR & Chemometric Sensors at UFDF for Protein and Excipient Monitoring

Fourier-transform infrared spectroscopy (FT-IR)

- Vibrational Spectroscopy Technique
- Unique spectral bands for chemical bonds
- Measurement frequency – As fast as 10 sec.



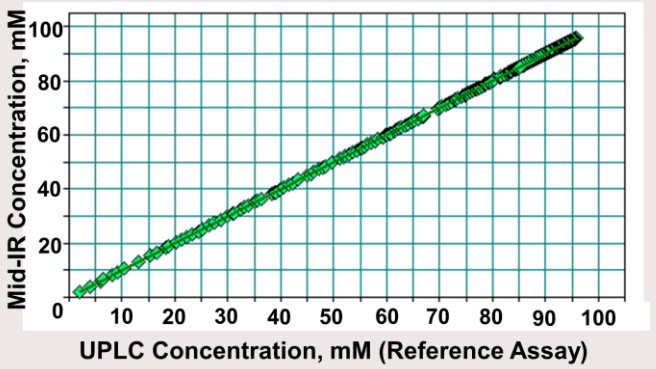


FT-IR Spectra

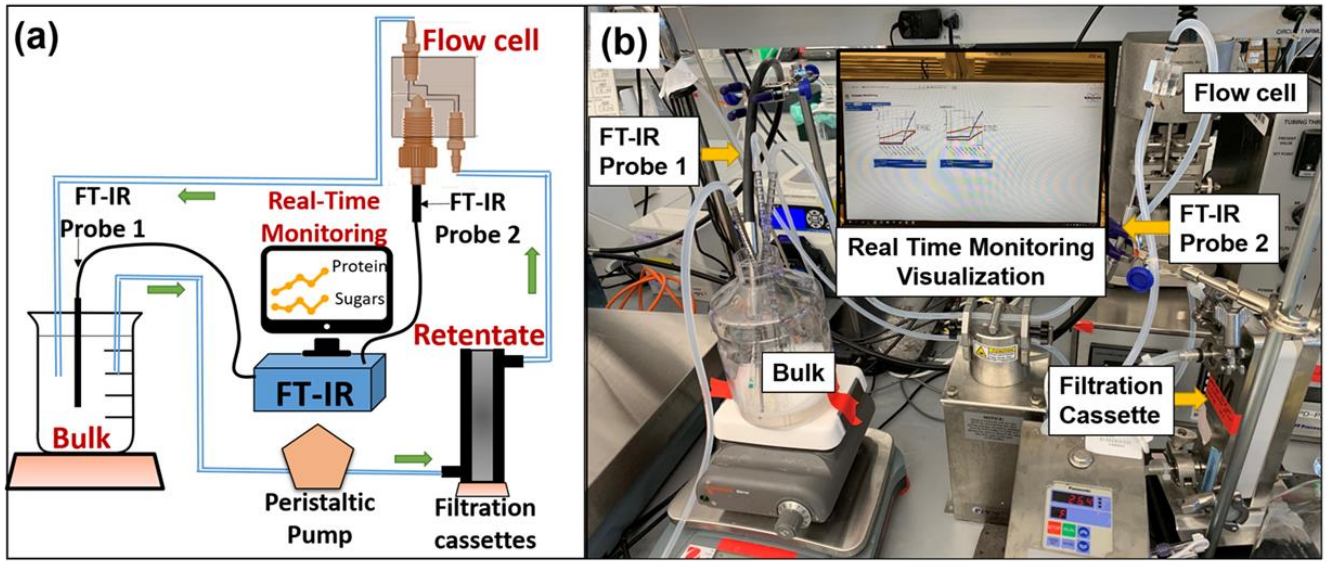
Pre-processing
- Baseline correction
- Smoothing
- Derivatives

PLS

Modeling



Real Time Process Monitoring - Downstream

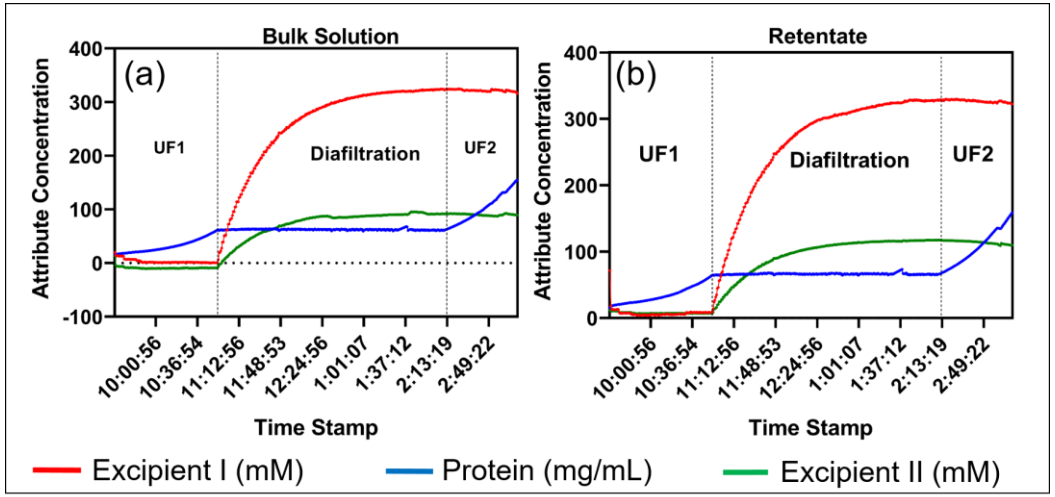


In-line FTIR

Real Time Monitoring of Proteins & Excipients in UF/DF

Automated,

1. Data Piping
2. Data Analysis
3. Visualization



Modeling software

CAMO
Bring data to life

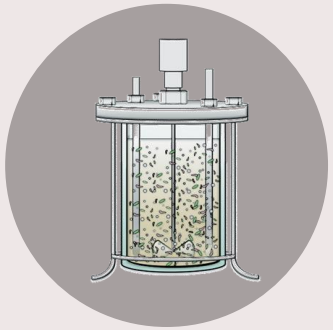
OPUS

Process monitoring software

Wasalathanthri, D.P.; Feroz, H.; Neha, P.; Hung, J.; Lane, G.; Holstein, M.; Chemmalil, L.; Both D.; Ghose, S.; Ding, J.; Li, Z. *Biotech & BioEng.* **2020**, *Accepted*

Holistic Process Understanding

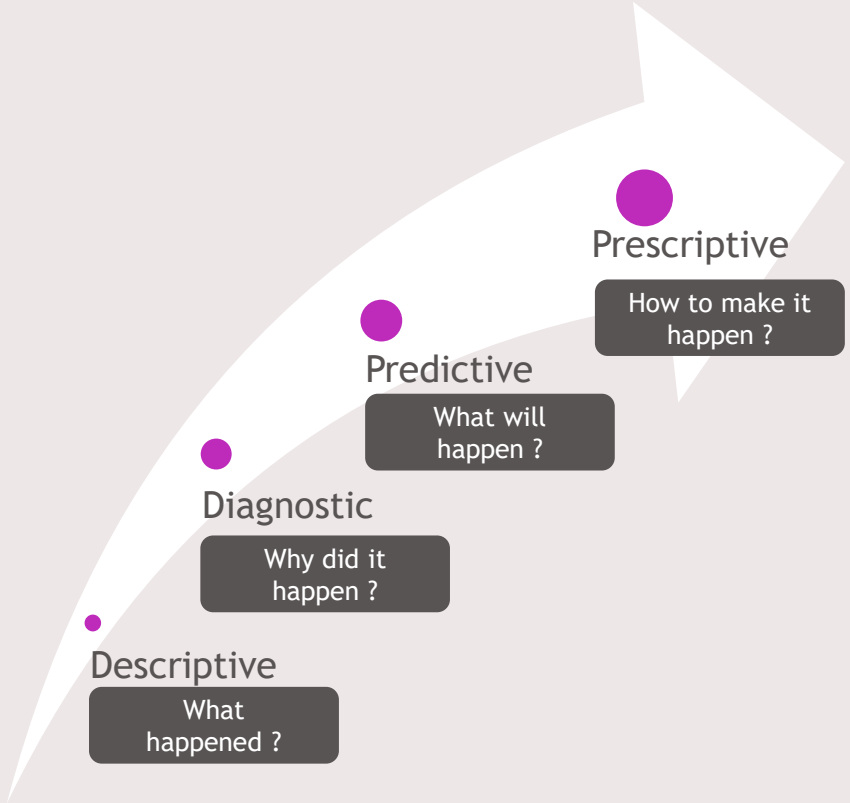
CPPs
Nutrients
Metabolites
Trace metals



CQAs
Glycan Profile
Charge Variants
Titer

Process Control..!

Quality by Design (QbD) Manufacturing



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Downstream

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thank you
danke
gracias
merci
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go raibh maith agat
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ngiyabonga
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рахмат
Баярлалаа
спасибо
mochchakkeram
arigatô
dakujem
grazie
dank je
tapadh leat
ευχαριστώ
감사합니다
ありがとう
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хвала
спасибі
дякую
hvala
mauruuru
sagolun
takk
taiku
asante
enkosi
sobodi
dėkuji
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tanemirt
rahmet
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diolch
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murakoze
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manana
mahalo
paldies
matondo
misaotra
blagodaram
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nandri
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gràcies
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sulpáy
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