IN SILICO MODELING APPROACHES TOWARDS ESTABLISHING ROBUST DESIGN AND CONTROL STRATEGIES: *BIO/PHARMA INDUSTRY PERSPECTIVE*

CENK ÜNDEY, PhD
PROCESS DEVELOPMENT

AMGEN®
Pioneering science delivers vital medicines™

4th PQRI/FDA Conference on Advancing Product Quality, Rockville, MD, Apr.9-11, 2019

OUTLINE

- **Process and product development paradigm**
  - **Prior knowledge, empirical, first principles, ML approaches**
- **Case Studies:**
  - **First principles modeling based UFDF for buffer composition predictions**
  - **Drug product T/P filling process modeling**
  - **Process monitoring and predictive control examples**
  - **Incorporating PAT and models towards control strategy**

OUTLINE

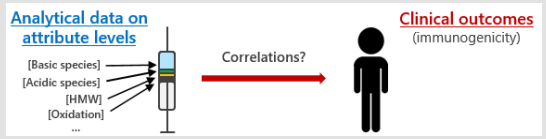
- **Process and product development paradigm**
  - **Prior knowledge, empirical, first principles, ML approaches**
- **Case Studies:**
  - **First principles modeling based UFDF for buffer composition predictions**
  - **Drug product T/P filling process modeling**
  - **Process monitoring and predictive control examples**
  - **Incorporating PAT and models towards control strategy**

IN SILICO MODELING HAS SIGNIFICANT POTENTIAL TO INCREASE SPEED AND EFFICIENCIES OF PROCESS AND PRODUCT DEVELOPMENT

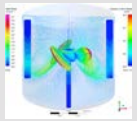
Pre-PT | FIH Development | Clinical Support | Commercial Process Development | Commercial Advancement | Commercial Support

Design | Qualification | Continued Verification

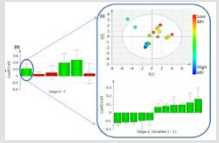
Cell Line Selection
Cell Line Development



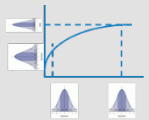
Patient centric



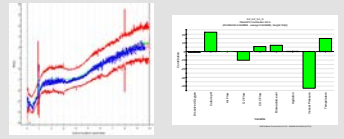
First principles predictive modeling (reduced wet exp.)



Predictive modeling for QTPP



Robust design (6σ)



Process and Product Performance Management

Increased data flow, digitalization and *in silico* model use across the product lifecycle

Feedback loop

AMGEN

RISK ASSESSMENT, DESIGN SPACE AND CONTROL STRATEGY ARE KEY IN SETTING UP PERFORMANCE-BASED CONTROL

Product Development and Realisation Case Study A-Mab*

Table 3.13 Results of the Risk Analysis Performed in the Production and N-1 Bioreactors

Process Parameter in Production Bioreactor	Quality Attributes						Process Attributes			Risk Mitigation
	Aggregate	aFucosylation	Galactosylation	Deamidation	HCP	DNA	Product Yield	Viability at Harvest	Turbidity at harvest	
Inoculum Viable Cell Concentr										DOE
Inoculum Viability										Linkage Studies
Inoculum In Vitro Cell Age										EOPC Study
N-1 Bioreactor pH										Linkage Studies
N-1 Bioreactor Temperature										Linkage Studies
Osmolality										DOE
Antifoam Concentration										Not Required
Nutrient Concentration in medium										DOE
Medium storage temperature										Medium Hold Studies
Medium hold time before filtration										Medium Hold Studies
Medium Filtration										Medium Hold Studies
Medium Age										Medium Ho
Timing of Feed addition										Not Re
Volume of Feed addition										DO
Component Concentration in Feed										DO
Timing of glucose feed addition										DOE-In
Amount of Glucose fed										DOE-In
Dissolved Oxygen										DO
Dissolved Carbon Dioxide										DO
Temperature										DO
pH										DO
Culture Duration (days)										DO
Remnant Glucose Concentration										DOE-In

Product Development and Realisation Case Study A-Mab

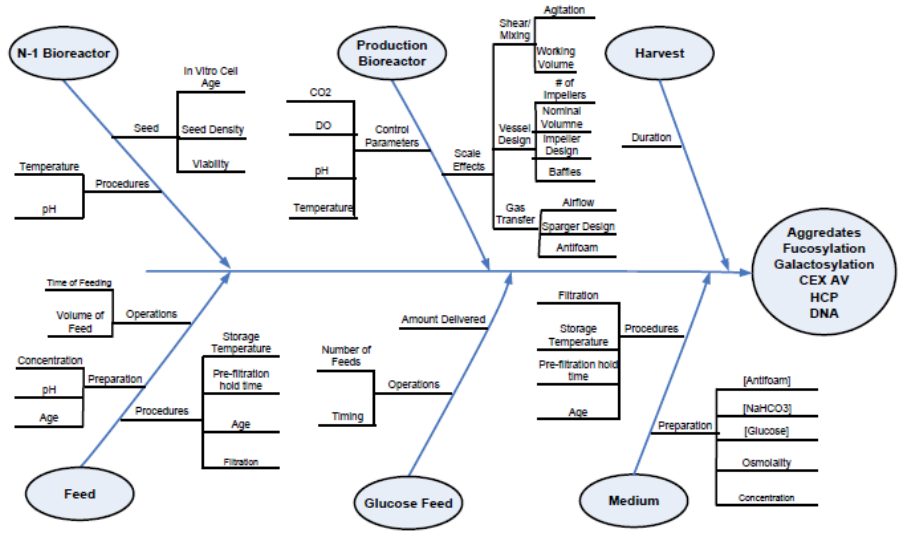
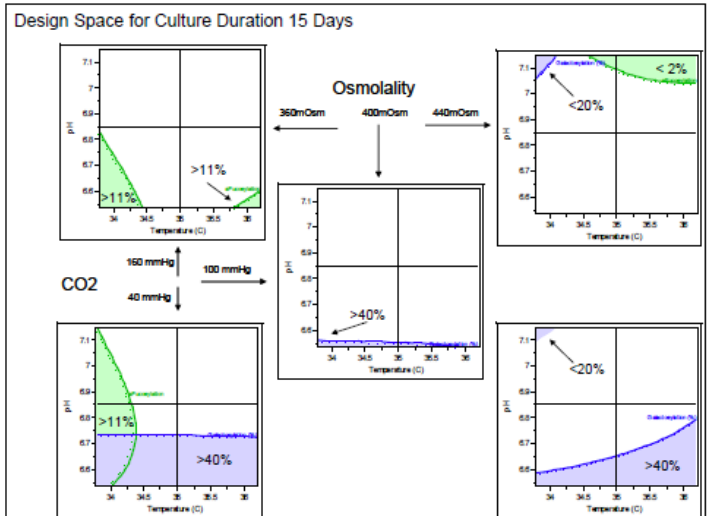


Figure 3.3 Ishikawa Diagram Indicating the Process Parameters Analyzed in the Risk Assessment of the Production and the N-1 Bioreactors

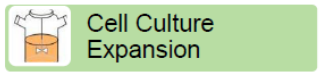


* CMC Biotech WG, 2009, A-Mab: A Case Study in Bioprocess Development. V2.1

PRIOR KNOWLEDGE ASSESSMENT AND AGGREGATING HISTORICAL DATA FOR PLATFORM PROCESSES OFFER UNIQUE ADVANTAGES TOWARDS PROCESS DESIGN AND PROCESS PERFORMANCE QUALIFICATION (PPQ)

Information can be Aggregated to Understand Variance Across Similar Process Unit Operations

Principals of Aggregating Information



Cell Culture Expansion

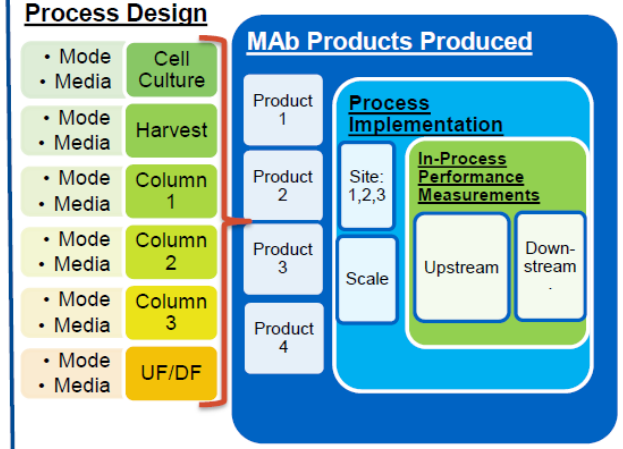
- Specific attribute
- Specific process step

Attribute	Product Modality	Process Design	Unit Operation	Raw Materials
Product Group	MAb	Similar	Similar	Common

- Assessment of the similarity of process design and implementation
- Define products contained in the Group

Operations + Equipment + Raw Materials + Analytical Measurement → **Total Variance**

Total variance is the sum of contributing sources



Catalog of process information is needed to support assessment of process design and implementation similarity

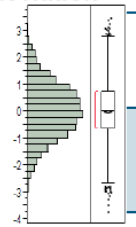
AMGEN 35 YEARS

26

Empirical Bayes approach leverages knowledge of similar attributes to improve accuracy of limits

Classical Approach	Empirical Bayes
Calculate Mean and Variance for a performance parameter for a single process used to manufacture a product to determine limits.	Use existing data to form a Bayesian model that predicts the tolerance interval of a performance parameter based on simulation for the performance parameter

1). Determine mean and standard deviation



Mean $\bar{x} = \frac{\sum x}{n}$

Standard Deviation $\sigma = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$

2). Calculate Limits Control Limits: $CL = \bar{x} \pm 3\sigma$

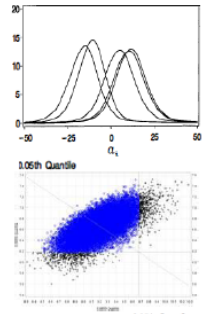
Tolerance Interval: $TL = \bar{x} \pm k\sigma$

For low run rate products, significant amount of time may be required to establish accurate variance estimates

1). Demonstrate Similarity in Variance (HOV Test)

2). Obtain Statistical Measures of Prior Information

3). Simulate to Determine Quantiles of Interest



[1]Wolfinger, (1998). Tolerance Intervals for Variance Component Models Using Bayesian Simulation. *Journal of Quality Technology*, *30* (18-32).

Use portfolio data to simulate uncertainty in reference product mean and variance. Overcome concerns with small sample sizes.

AMGEN

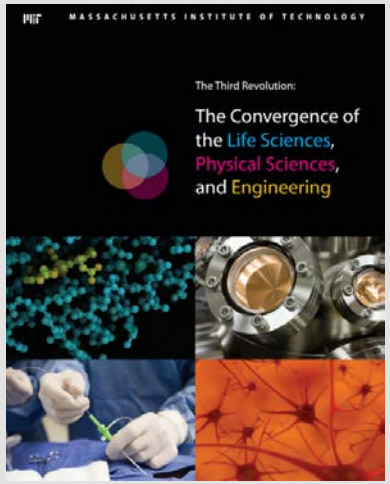
5

Courtesy of Dr. Roger Hart

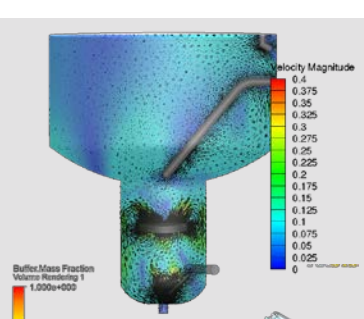
AMGEN

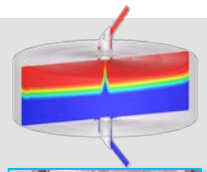
ADVANCES IN COMPUTATIONAL POWER AND SCIENTIFIC UNDERSTANDING ARE ENABLING MORE MODELING OF BIOPHARMACEUTICALS PD & MFG

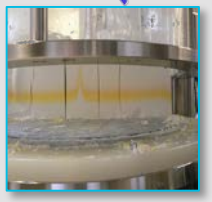
- **Much of the current modeling has its roots in engineering, biology, chemistry, physics and fluid mechanics (mass transfer, kinetics, etc.)**
- **In some cases, current scientific understanding and/or analytical resolution insufficient to utilize mechanistic modeling**

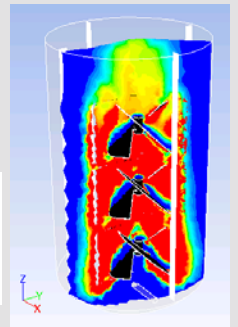


- **Convergence of disciplines**:
  in silico modeling to enable Smart PD computational platforms
  - *in silico* experiments for Process Characterization
  - Predictive modeling for RM selection and variation control
  - *in silico* tooling and device design





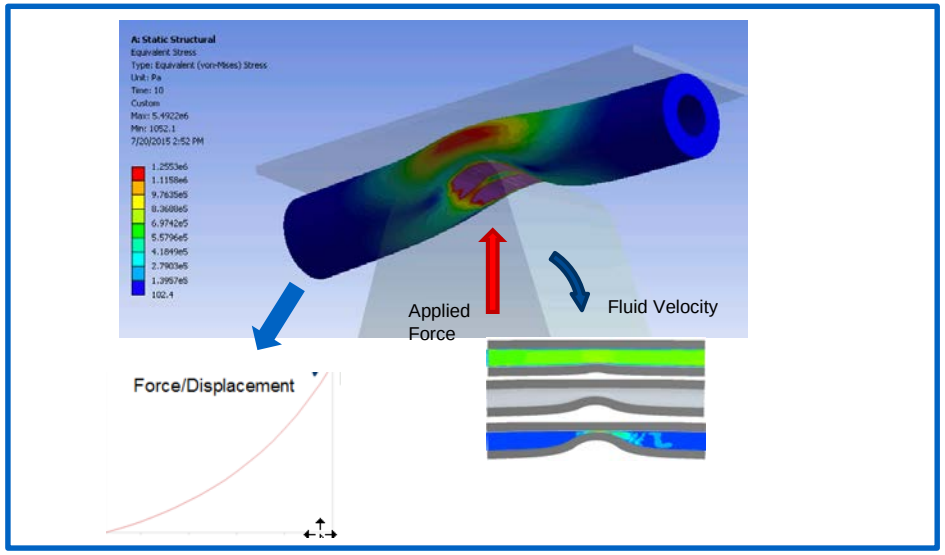


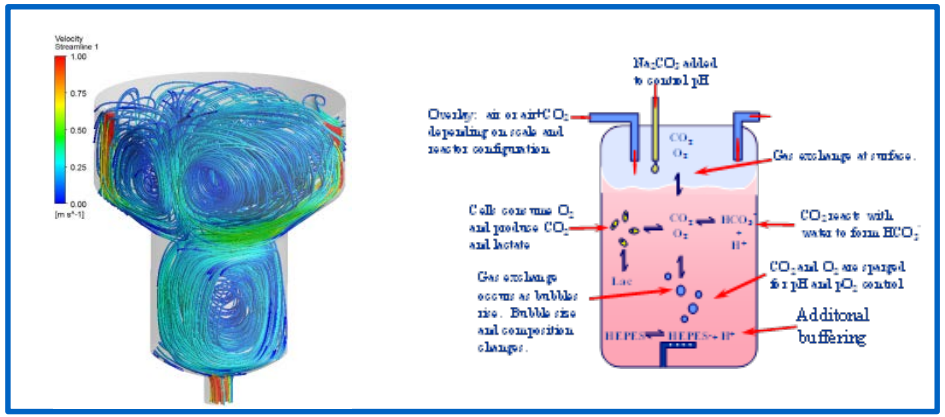


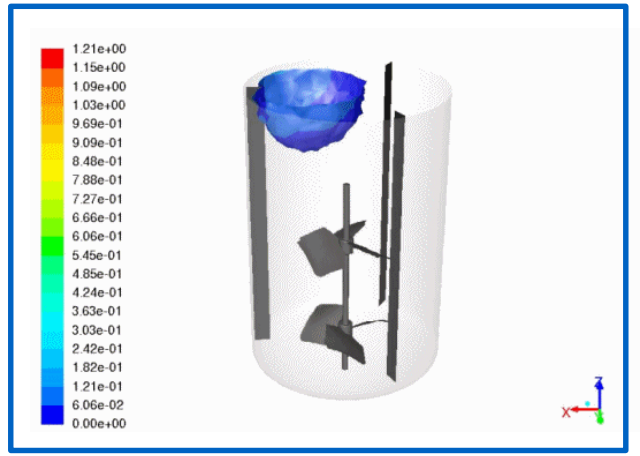
Q11 - Design and conduct studies (e.g., **mechanistic and/or kinetic evaluations**, multivariate design of experiments, **simulations, modeling**) to identify and confirm the links and relationships of material attributes and process parameters to drug substance CQAs

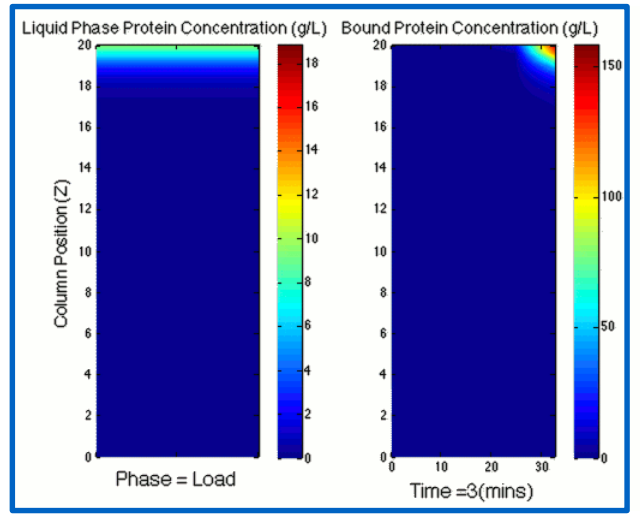
AMGEN

WE ARE ADVANCING THE USE OF FIRST PRINCIPLES MODELING IN PROCESS, PRODUCT DEVELOPMENT AND IN MANUFACTURING









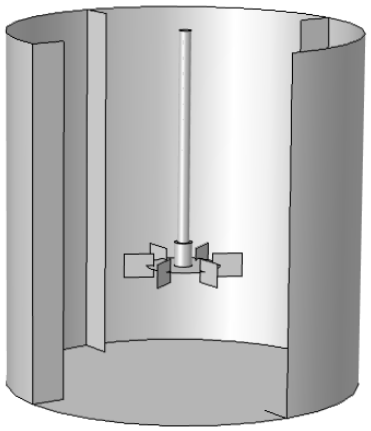
THE MODELING PROCESS (IDEALIZED)

1. Domain Definition

2. Problem Formulation

3. Numerical Approximation

4. Solution Analysis



Fluid Flow

$$\rho\frac{\partial\vec{u}}{\partial t}+\rho(\vec{u}\cdot\nabla)\,\vec{u}=-\nabla p+\nabla\cdot\tau+\vec{F}$$

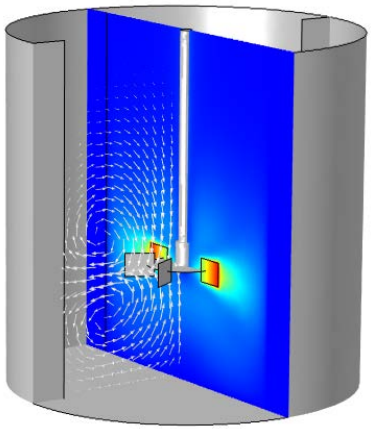
$$\frac{\partial\rho}{\partial t}+\nabla(\rho\cdot\vec{u})=0$$

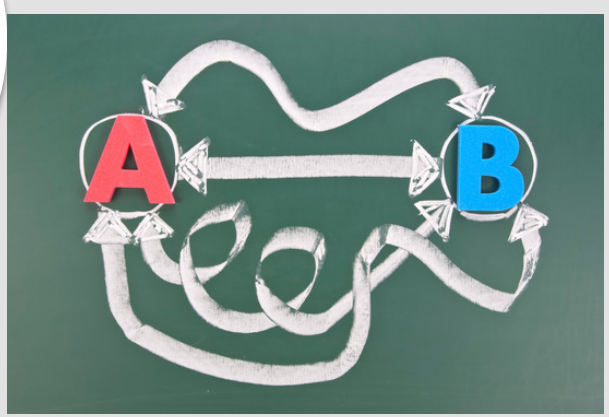
Mass Transport

$$\frac{\partial c_i}{\partial t}+\nabla\cdot\left(-D\nabla c_i+\vec{u}c_i\right)=R_i$$

Heat Transport

$$\rho C_P\frac{\partial T}{\partial t}+\rho C_P\vec{u}\cdot\nabla T=\nabla\cdot(k\nabla T)+Q$$





$$\frac{\partial}{\partial x}(\rho u\phi)-\frac{\partial}{\partial x}\left(\Gamma\frac{\partial\phi}{\partial x}\right)=0$$

AMGEN

MODEL-BASED PROCESS DEVELOPMENT

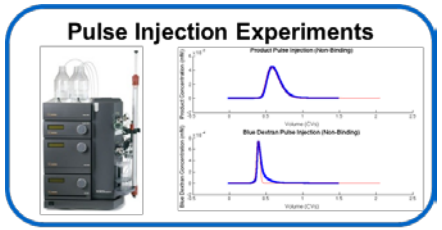
Reducing costly and time consuming experimentation

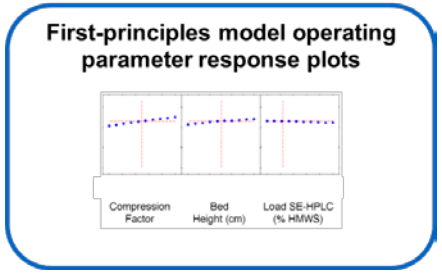
Calibration and validation of first-principles model required a small number of targeted experiments

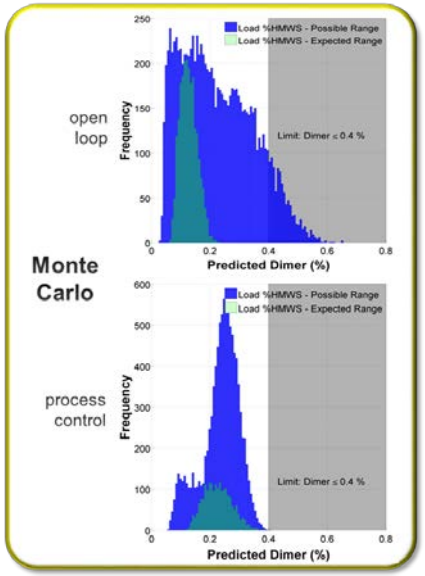
- a fraction of conventional DOE-based process characterization approaches

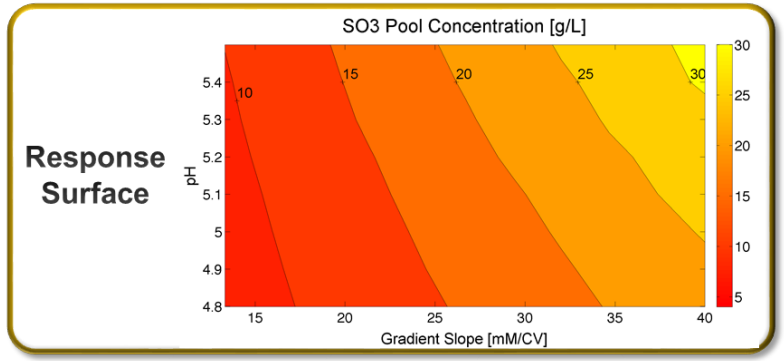
More operating parameters and wider ranges explored via fast and inexpensive "*in-silico*" experiments

- investigating parameters difficult to study experimentally (e.g., bed compaction)
- replacing costly or time-demanding experiments (e.g., column size)



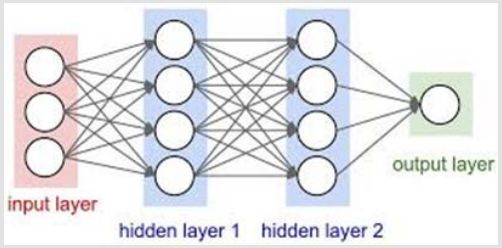




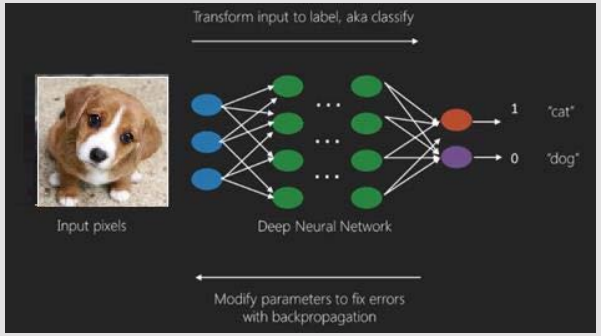


WE HAVE BEEN ADVANCING DEEP LEARNING APPLICATIONS TO CREATE SIGNIFICANT EFFICIENCIES TOWARDS ACCELERATING PD

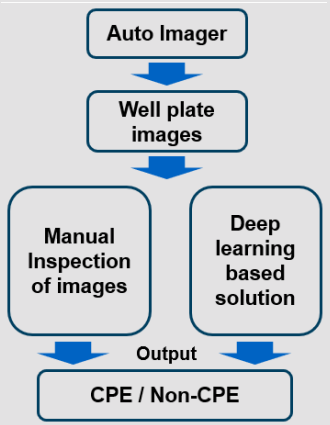
ANN

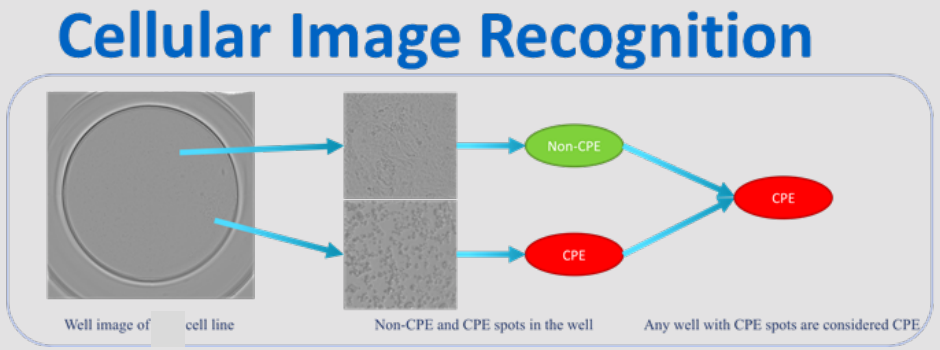


Deep CNN

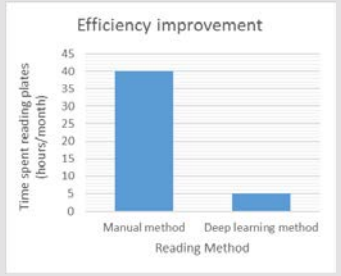


https://www.tutorialspoint.com/python_deep_learning/python_deep_learning_deep_neural_networks.htm





	Line 1	Line 2	Line 3	Line 4
Training set				
Training set				
Validation set				
False negative				
False positive				
Accuracy	99.40%	99.70%	96.90%	99.40%



Automated Cytopathic Effect (CPE) Detection via Deep Learning

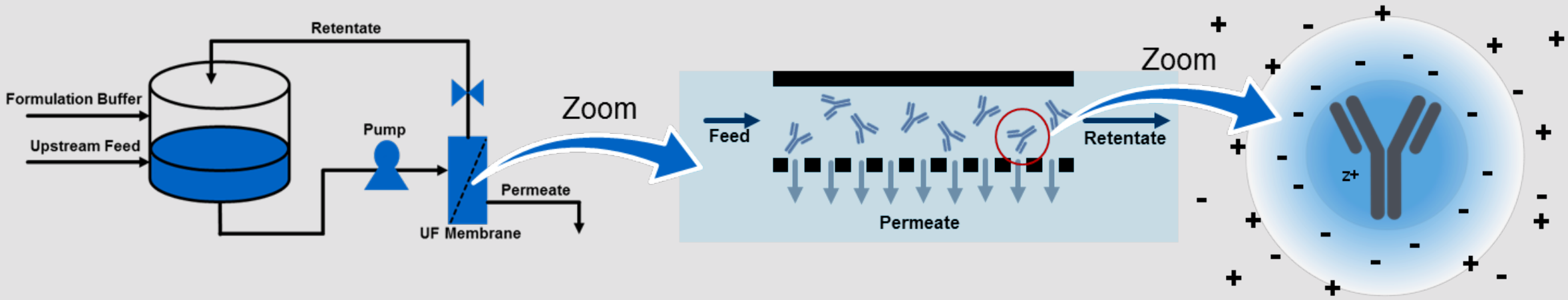
OUTLINE

- Process and product development paradigm
  - Prior knowledge, empirical, first principles, ML approaches
- Case Studies:
  - **First principles modeling based UFDF for buffer composition predictions**
  - Drug product T/P filling process modeling
  - Process monitoring and predictive control examples
  - Incorporating PAT and models towards control strategy

GOAL: ACCURATELY PREDICT pH AND EXCIPIENT CONCENTRATIONS IN PROTEIN DRUG SUBSTANCE

Challenge: High concentrations of charged mAb during UF/DF commonly result in offsets in pH/excipients between UF/DF pool and formulation buffer

- Molecular basis for this offset is the selective retention or rejection of ions due to:
  - **Charge interactions between ions and the protein: ions attracted or repelled**
  - **Volume exclusion: solutes excluded from volume occupied by high concentration of mAb**



FIRST PRINCIPLES UNDERSTANDING OF UF/DF AND BUFFER EXCIPIENTS WAS USED VIA IN SILICO MODELING TO REDUCE WET EXPERIMENTS DURING PC

PREDICTIVE MECHANISTIC UF/DF PROCESS MODEL

- Building on earlier work[1,2], a predictive UF/DF model based on Poisson-Boltzmann theory has been developed at Amgen
- Mechanistic features of the Amgen UF/DF model include:
  1. Species equilibrium for both solutes and protein with pH calculation using a charge balance approach
  2. Distribution of ions and protein surface potential using Poisson-Boltzmann theory
  3. Mass transfer of solutes through the UF/DF membrane

A predictive tool to support UF/DF development and process understanding

1. "Theoretical Analysis of Excipient Concentrations During the Final UF/DF Step of Therapeutic Antibody", Fudu Miao et. al., Biotechnology Progress, June 2009
2. "Predicting Diafiltration Solution Compositions for Final Ultrafiltration/Diafiltration Steps of Monoclonal Antibodies", Mark Teeters et. al., Biotechnology and Bioengineering, June 2011

AMGEN

PH CALCULATED BY CHARGE BALANCE[3] METHOD

- Conceptual example using H_3PO_4 dissociation
- Known: K_{a1}, K_{a2}, K_{a3}, $C_{H_3PO_4}$ (sum of phosphate species), electroneutrality ($Z = 0$)
- Equilibrium relationships:

$$K_{a1} = \frac{[H^+][H_2PO_4^-]}{[H_3PO_4]},\ K_{a2} = \frac{[H^+][H_2PO_4^{2-}]}{[H_2PO_4^-]},\ K_{a3} = \frac{[H^+][H_2PO_4^{3-}]}{[H_2PO_4^{2-}]},\ C_{H_3PO_4} = [H_3PO_4] + [H_2PO_4^-] + [HPO_4^{2-}] + [PO_4^{3-}]$$

- Charge neutrality constraint:

$$Z = -[OH^-] - [H_2PO_4^-] - 2\cdot[HPO_4^{2-}] - 3\cdot[PO_4^{3-}] + [H^+] = 0,\quad [H^+] = 10^{-pH},\quad [OH^-] = 10^{pH-pKw}$$

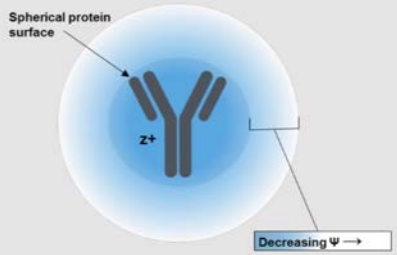
- Activity coefficients are calculated using the Davies Equation and lumped into K_a values
- Protein treated as an ion family with many pK_a values (amino acid residues)

Provides full accounting of ion species concentrations

3 Advanced pH Measurement and Control 3rd Ed, ISA 2005, McMillan, Greg, Cameron, Robert, p 49

AMGEN

ELECTROSTATIC INTERACTION OF PROTEIN AND IONS DESCRIBED USING POISSON-BOLTZMANN THEORY



Poisson-Boltzmann equation solved numerically to describe the electrical potential outside of a charged protein as a function of radius $\Psi(r)$:

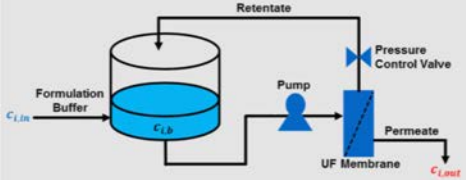
$$\frac{d^2\psi(r)}{dr^2} + \frac{2}{r}\frac{d\psi(r)}{dr} = -\frac{e}{\epsilon}\sum_{i=1}^{n} c_{i,\infty} z_i e^{-\frac{ez_i\psi(r)}{kT}}$$

$\psi(r)$ can then be used to calculate the local ion concentrations using the Boltzmann distribution:

$$C_i(r) = C_{i,\infty}\exp\left(-\frac{ez_i\psi(r)}{kT}\right)$$

Poisson-Boltzmann Theory is applied to establish the distribution of solutes around the protein

MASS TRANSFER AND SIMULATION OF UF/DF PHASES



Process model for all UF/DF phases:

1) Initial batch concentration of upstream protein pool
2) Exchange protein into formulation buffer (Diafiltration)
3) Over-concentration and recovery flush to achieve the target final protein concentration

Diafiltration: constant volume buffer exchange – inlet and outlet flow of solvent and solutes:

$$V\frac{dc_{i,b}}{dt} = Q * (c_{i,in} - c_{i,out})$$

Ultrafiltration: concentration stages –solvent and solutes permeate membrane with no inlet flow:

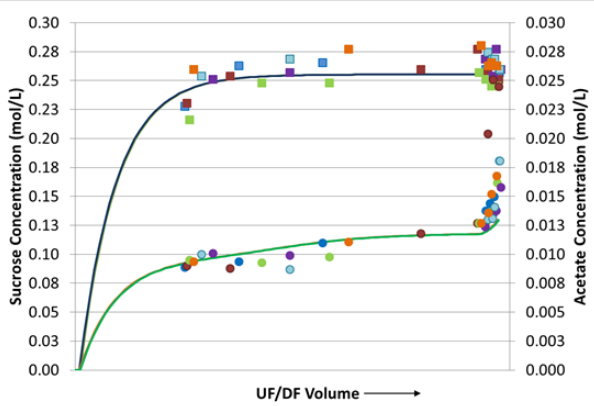
$$V\frac{dc_{i,b}}{dt} = Q * (c_{i,b} - c_{i,out})$$

where $c_{i,out}$ is dependent on:

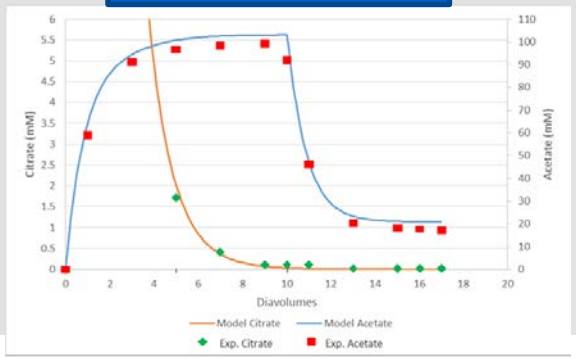
- Chemical speciation from the pH calculation
- Ion distribution from the Poisson-Boltzmann calculation

Model Verification

Diafiltration and Over-concentration



Model Prediction

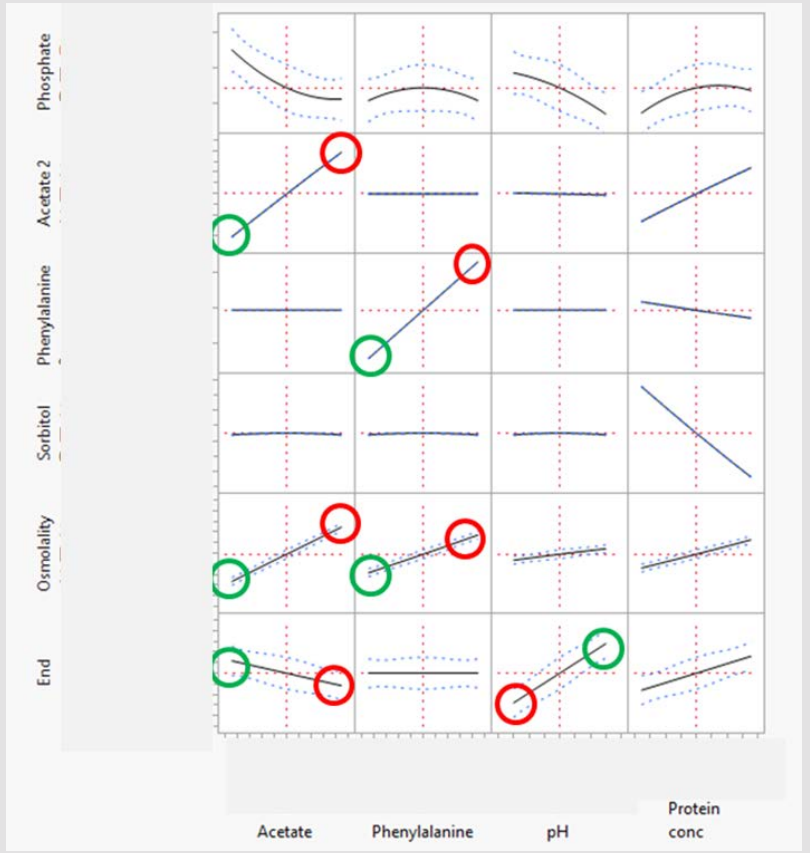


AMGEN

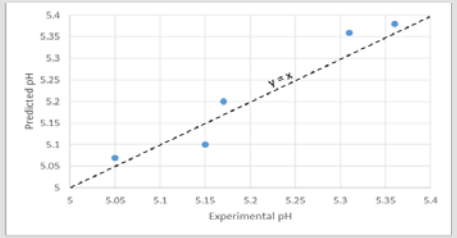
IN SILICO DOE: MECHANISTIC MODEL OF EXCIPIENT EXCHANGE DURING PROTEIN ULTRAFILTRATION & DIAFILTRATION (MUD)

- (Right→) In-silico DoE performed in MUD to explore the formulation buffer design space for targeted experimentation
- (Below↓) Worst-case buffer conditions were tested experimentally and results agreed with MUD predictions

Buffer Conditions	Result Source	Acetate (mM)	Phe (mM)	Sorbitol (%)	Osmolality (mOsm)	pH
Buffer Formulation #1	| Exp. – Pred. |	2.0	2.1	0	3	0.02
Buffer Formulation #2		0.3	0.4	0.31	7	0.02



Process robustness:
Model accurately predicts UF/DF pool pH



Correlation Factor	coefficient	p-value	95% Confidence Limits	
0.97	1.11	6.5E-03	0.60	1.62

OUTLINE

- Process and product development paradigm
  - Prior knowledge, empirical, first principles, ML approaches
- Case Studies:
  - First principles modeling based UFDF for buffer composition predictions
  - **Drug product T/P filling process modeling**
  - Process monitoring and predictive control examples
  - Incorporating PAT and models towards control strategy

TIPCOM USE IN DP FILLING PROCESS DEVELOPMENT

Design Space

SKU Characteristics

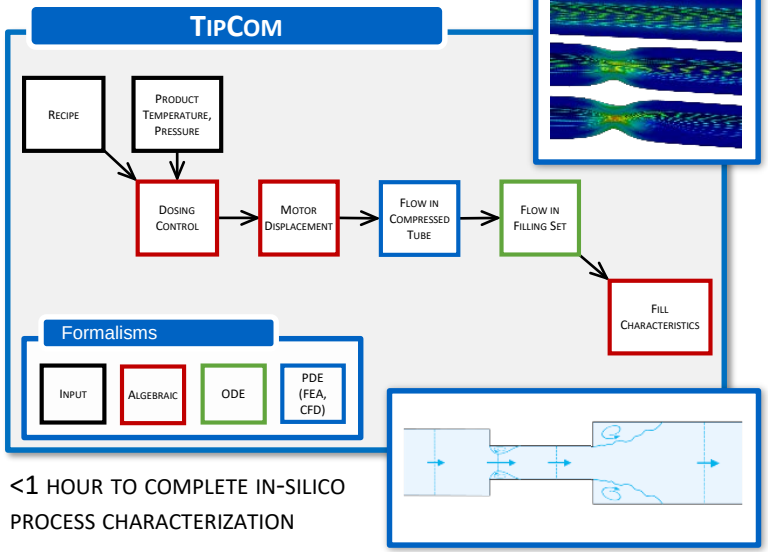
- Target fill volume
- Viscosity
- Density
- Vial geometry

Hardware Characteristics

- Orifice geometry
- Needle dimensions
- Tubing dimensions
- Pinch Valve geometry

In-Silico Process Characterization

TipCom



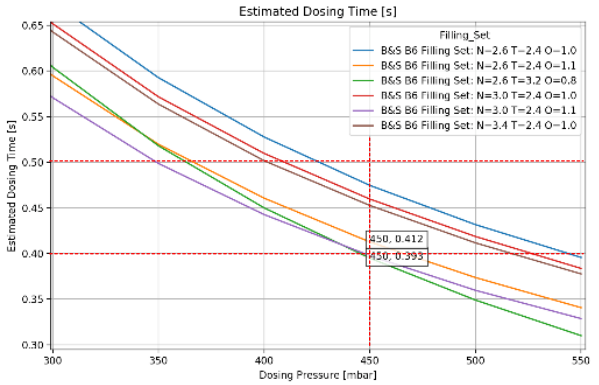
<1 hour to complete in-silico process characterization

Design Candidates

TipCom-Recommended Recipes

32 Filling sets, 6720 recipe settings explored

- 6 usable filling sets identified
- 2 filling sets w/ recipes recommended



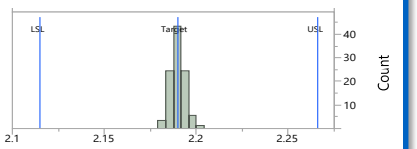
Offline Confirmation

Benchtop Filler

TipCom recommendations followed, substituting logistically preferred tubing

Extended dosing time to accommodate tubing (T_{DOSE} > 0.6 s)

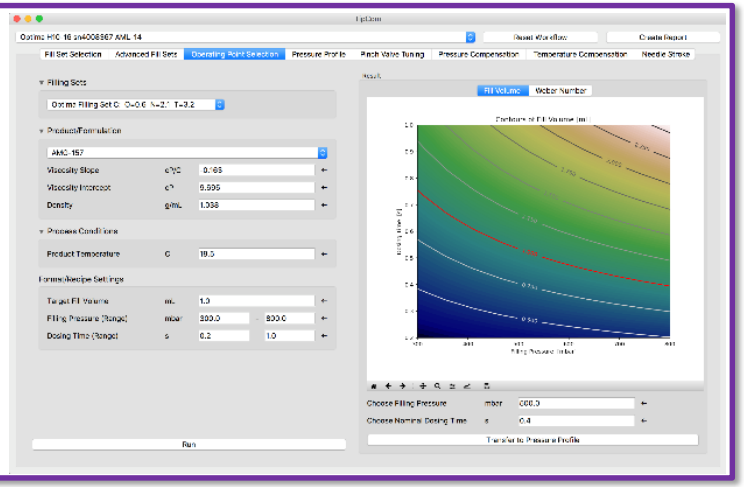
C_{PK}: 5.0-9.0



TipCom 3.0

An evolution in deployment

- Improved user interface
- Customized equipment-based apps
- Site- and Line-specific workflows
- Auto-generated PDF reports
- Cross-platform
- No installation required
- Validated (Tech Report)



TipCom filling process characterization prior to B6 benchtop characterization enabled:

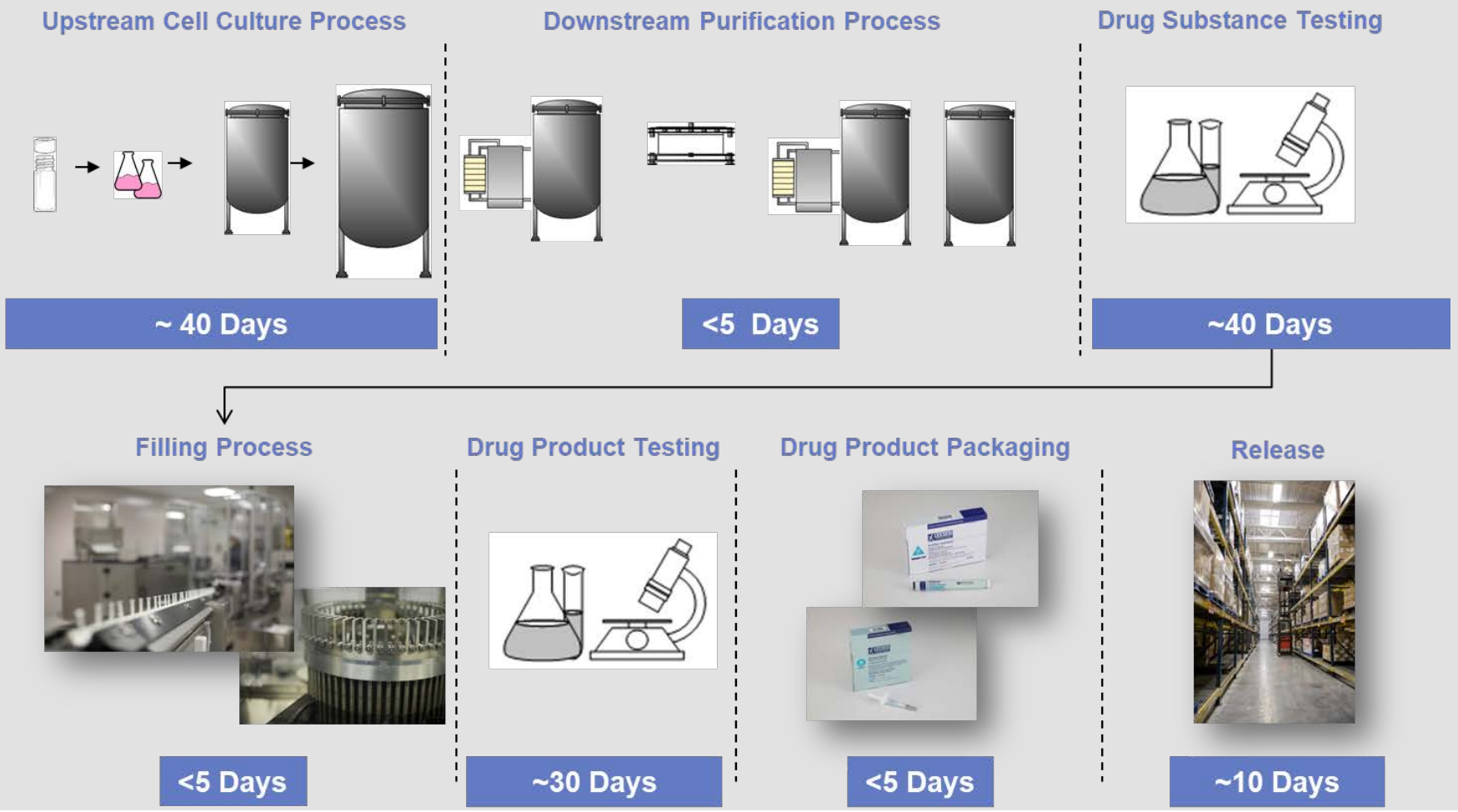
- ✓ **33% time savings** in Wet experiments
- ✓ **Elimination of experiments** at Commercial Line
- ✓ Assurance of **optimal** recipe selection
- ✓ Highly capable filling process **(C_{PK}: 5.0-9.0)**

AMGEN

OUTLINE

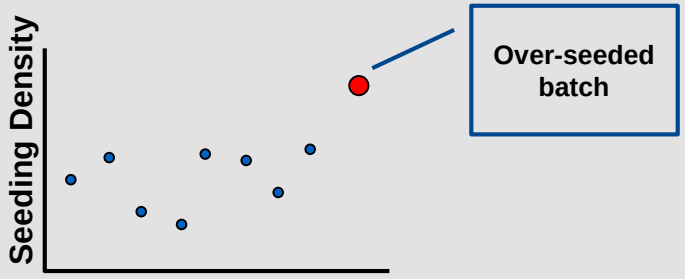
- Process and product development paradigm
  - Prior knowledge, empirical, first principles, ML approaches
- Case Studies:
  - First principles modeling based UFDF for buffer composition predictions
  - Drug product T/P filling process modeling
  - **Process monitoring and predictive control examples**
  - Incorporating PAT and models towards control strategy

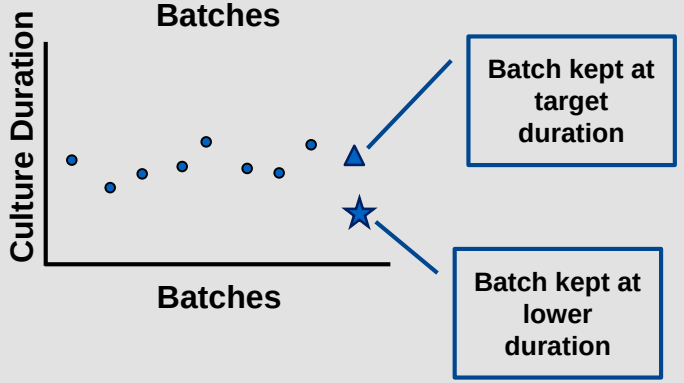
BIOPHARMACEUTICAL PROCESSES, COMPRISED OF CONSECUTIVE UNITS, GENERATE ABUNDANT DATA: PERFORMANCE-BASED CONTROL IS CRITICAL

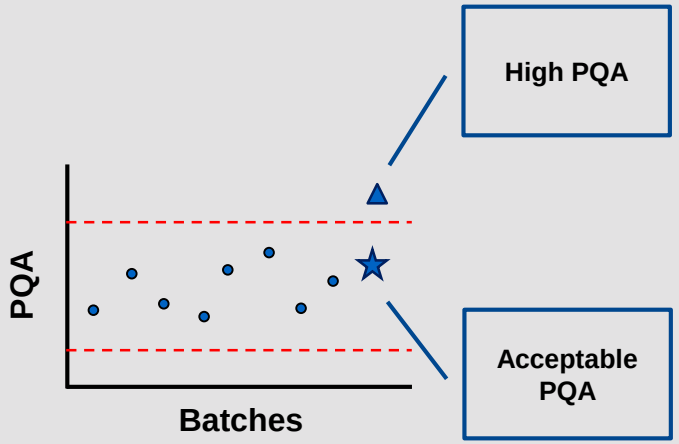


AMGEN

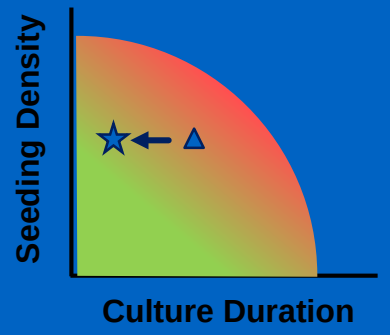
PERFORMANCE PREDICTION MODEL CAN BE USED TO ADJUST CULTURE DURATION FOR OVER SEEDED BATCHES





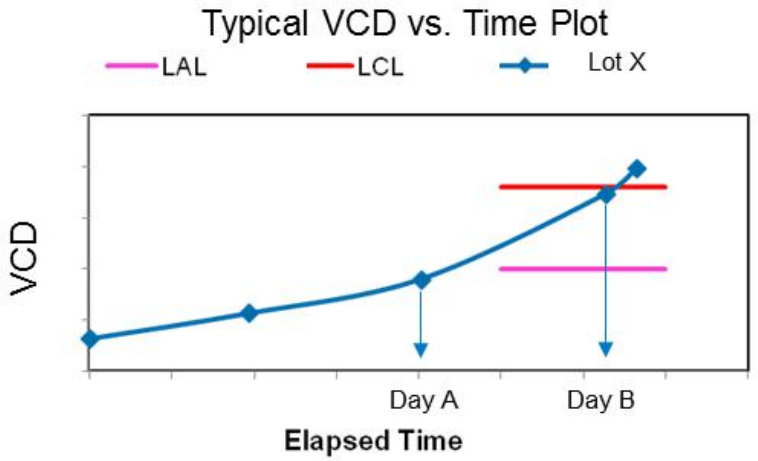


- Per process characterization, culture duration and seeding density are positively correlated to PQA



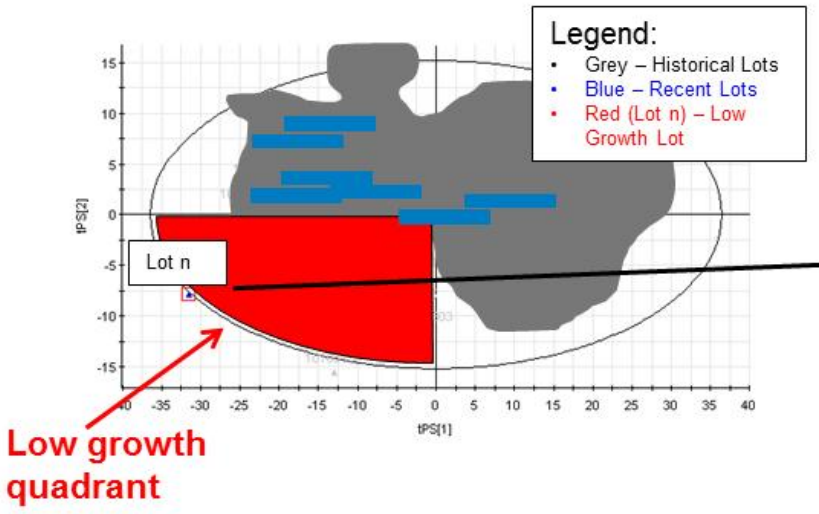
- A reliable real-time prediction model for PQAs enables improved control

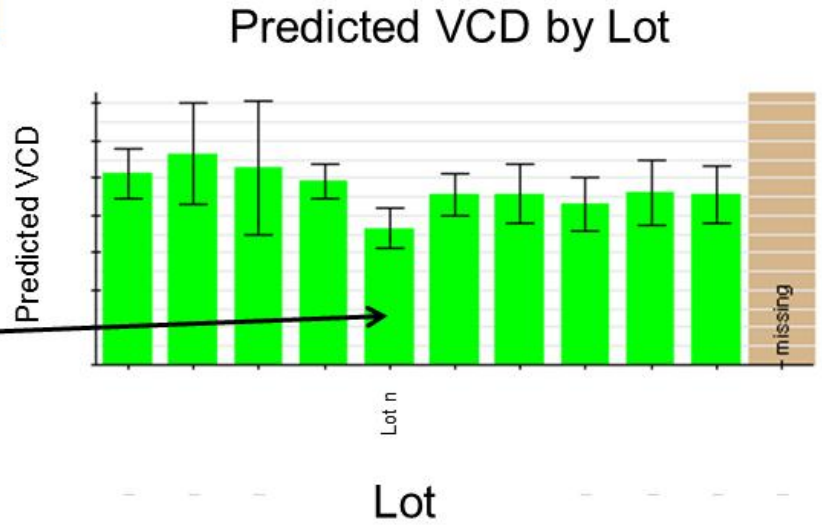
MULTIVARIATE PREDICTIVE MODEL DEVELOPED AND DEPLOYED FOR PERFORMANCE-BASED CONTROL FOR SEED BIOREACTORS



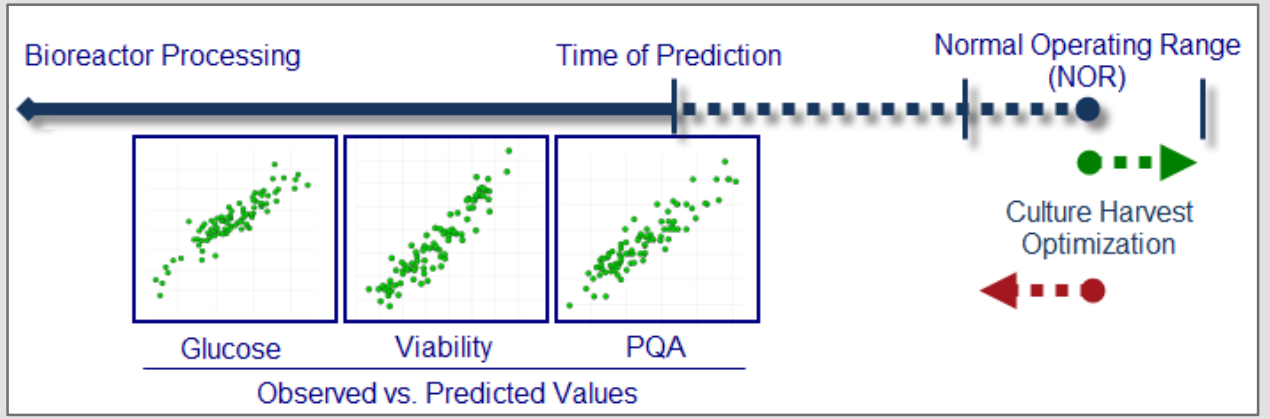
- Accurate Final VCD prediction will
  - Prevent unnecessary samples
  - Enable scheduling early or late transfer outs in advance
  - Schedule support activities early

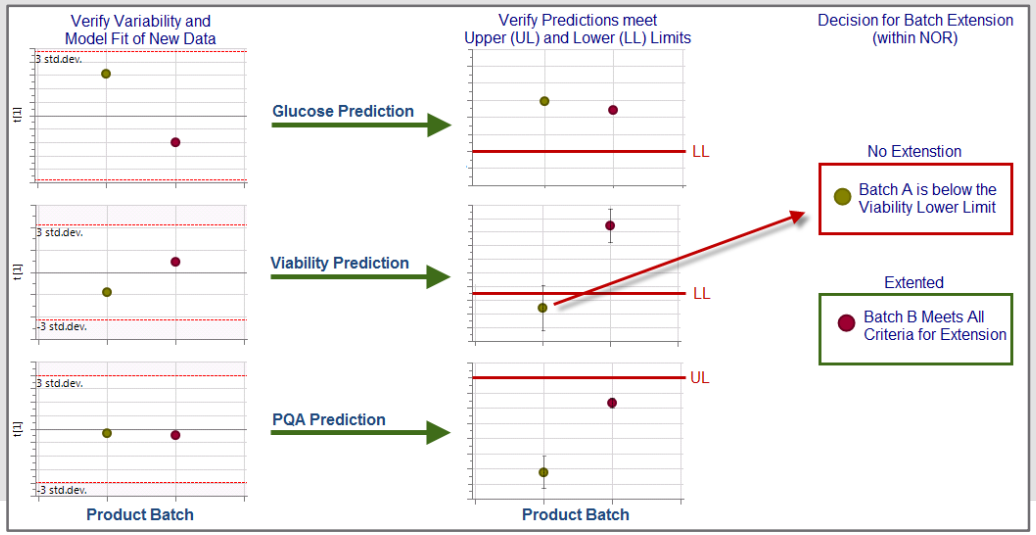
Day B VCD prediction model @ Day A





KPI'S AND PQA'S ARE PREDICTED TO CONTROL BIOREACTOR CULTURE HARVEST*

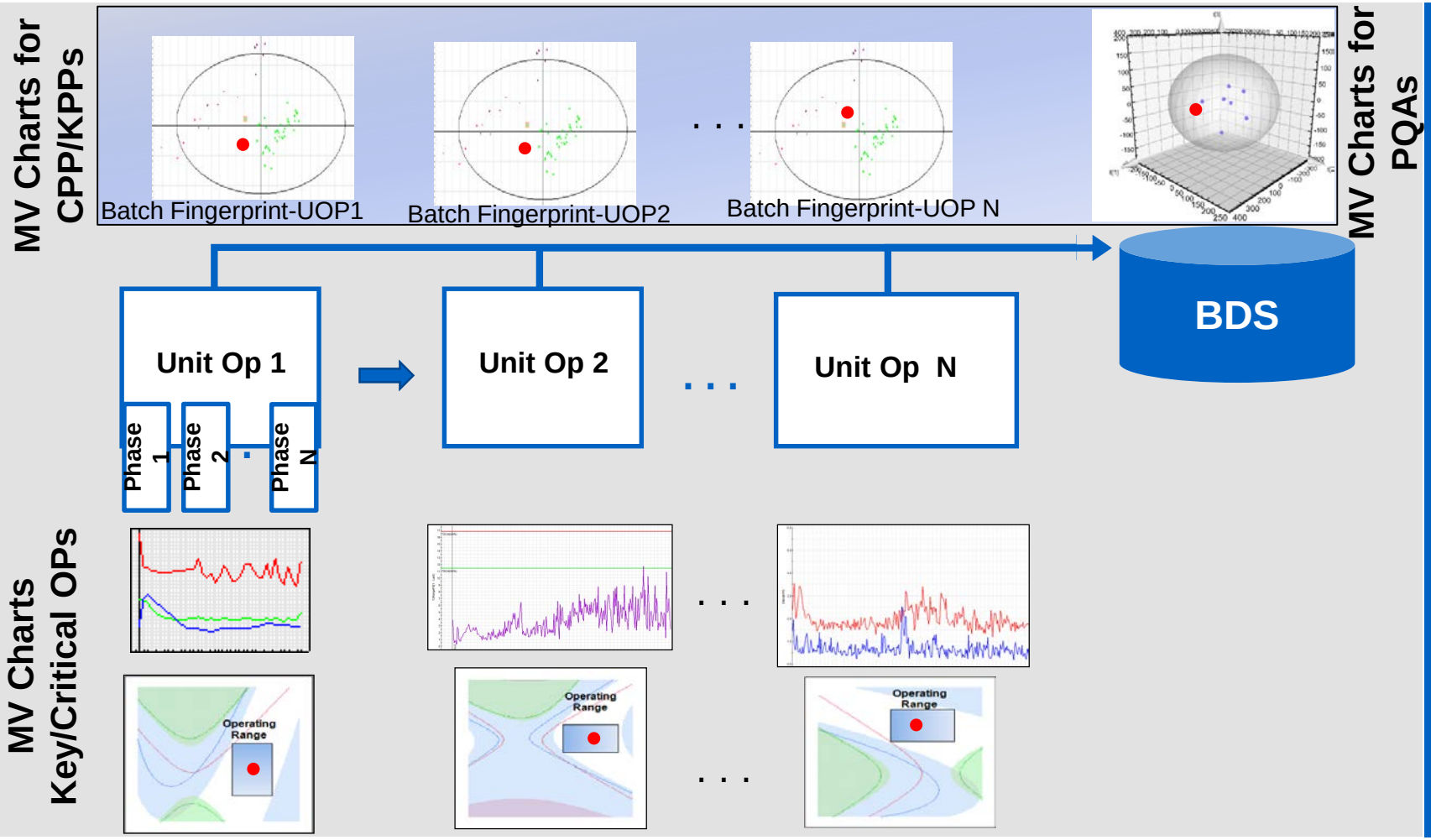




** Undey et al., 2015, Predictive Monitoring and Control Approaches in Biopharmaceutical Manufacturing, European Pharmaceutical Review, 20(4), pp. 63-69 .*

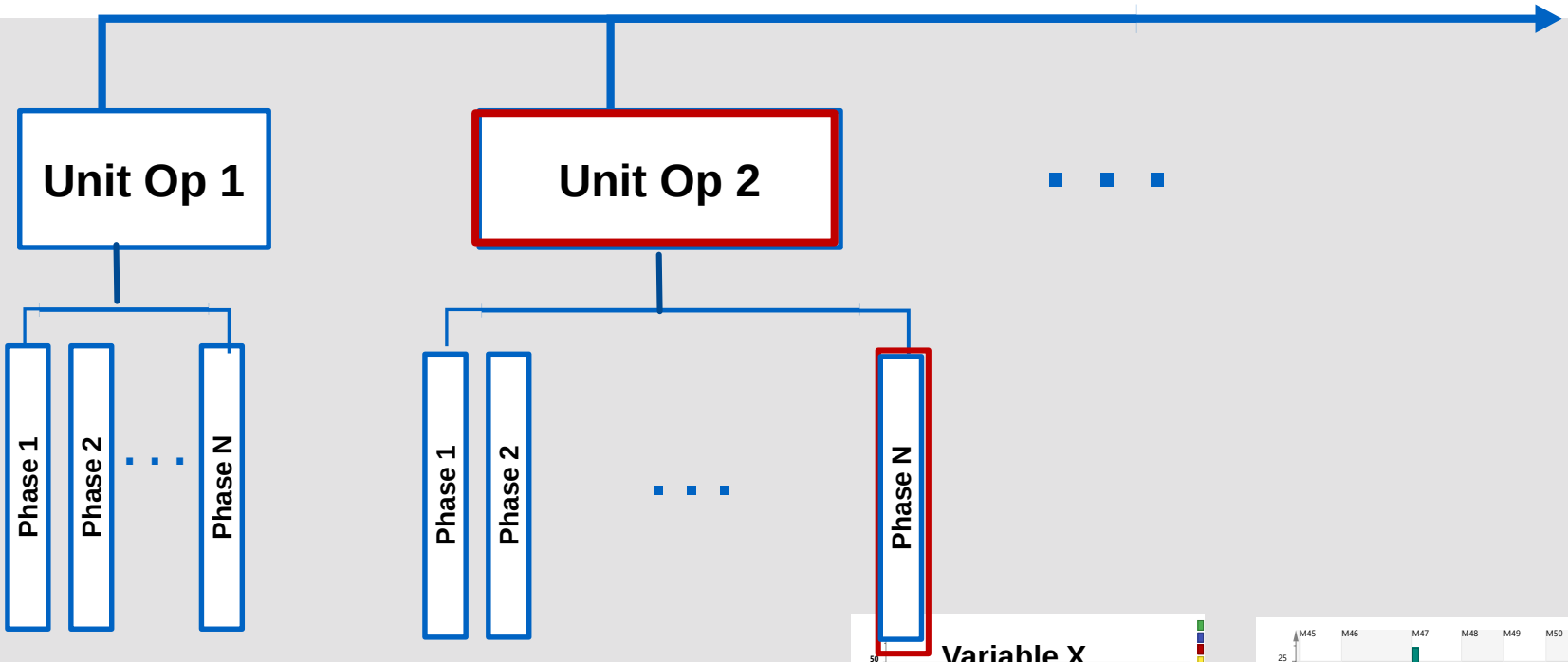
AMGEN

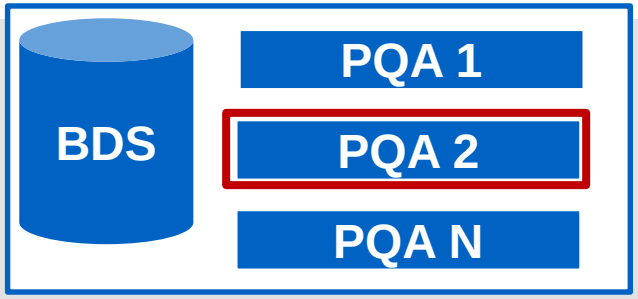
ENHANCED CONTINUED PROCESS VERIFICATION (eCPV) CAN ENABLE HOLISTIC PERFORMANCE-BASED MONITORING AND CONTROL

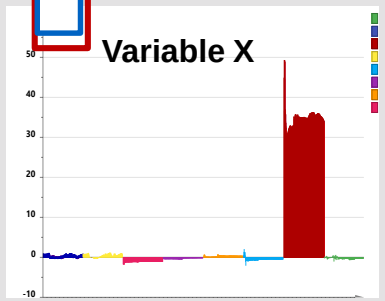


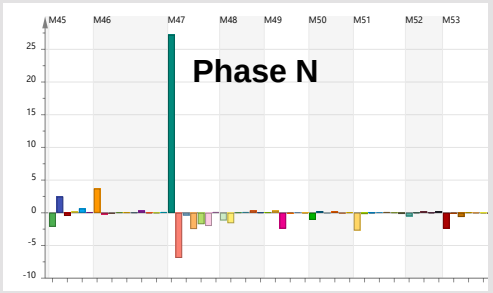
- Hierarchical modeling helps identifying variability within and across unit operations between process and product performance variables in real time
- Batch fingerprints are generated to compare batch behavior to historical batches

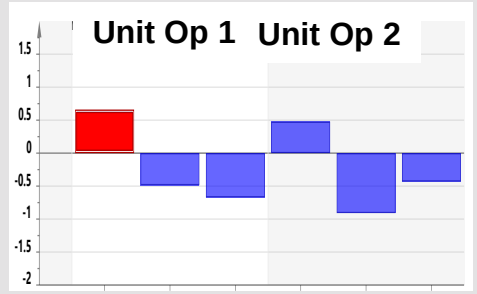
eCPV HELPS IDENTIFYING VARIABILITY WITHIN AND ACROSS UNIT OPERATIONS BETWEEN PROCESS AND PRODUCT PERFORMANCE VARIABLES





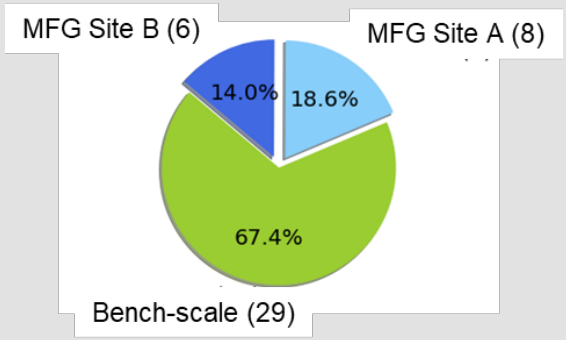


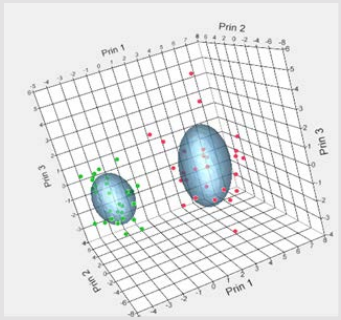




Model suggested an increase in PQA2 in BDS pool was correlated to a Phase N in Unit Operation 2

MACHINE LEARNING-BASED PREDICTIVE METHODS ARE PROVEN PROMISING:
COMBINING DATA FROM DIFFERENT SCALES IMPROVED THE CQA PREDICTIONS

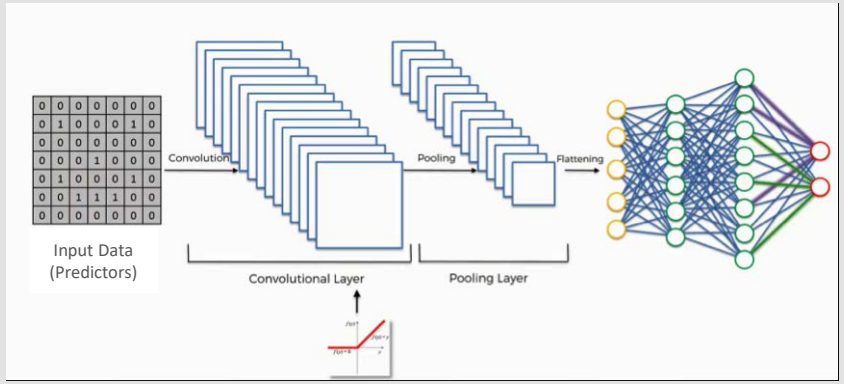


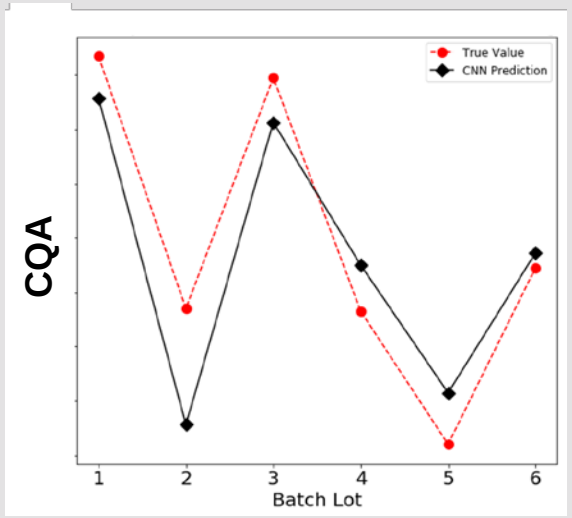


	MFG Scale Only	Combined
Training	MFG Site A (8)	MFG Site A (8) + Bench-scale (29)
Testing	MFG Site B (6)	MFG Site B (6)

Method	RMSE	Performance
PLS (MFG data)	38.577	-
PLS (Combined data)	23.519	↑
SVM (Combined data)	35.170	↑
GP (Combined data)	30.565	↑
RF (Combined data)	47.050	↓
CNN (Combined data)	22.414	↑

Convolutional Neural Networks





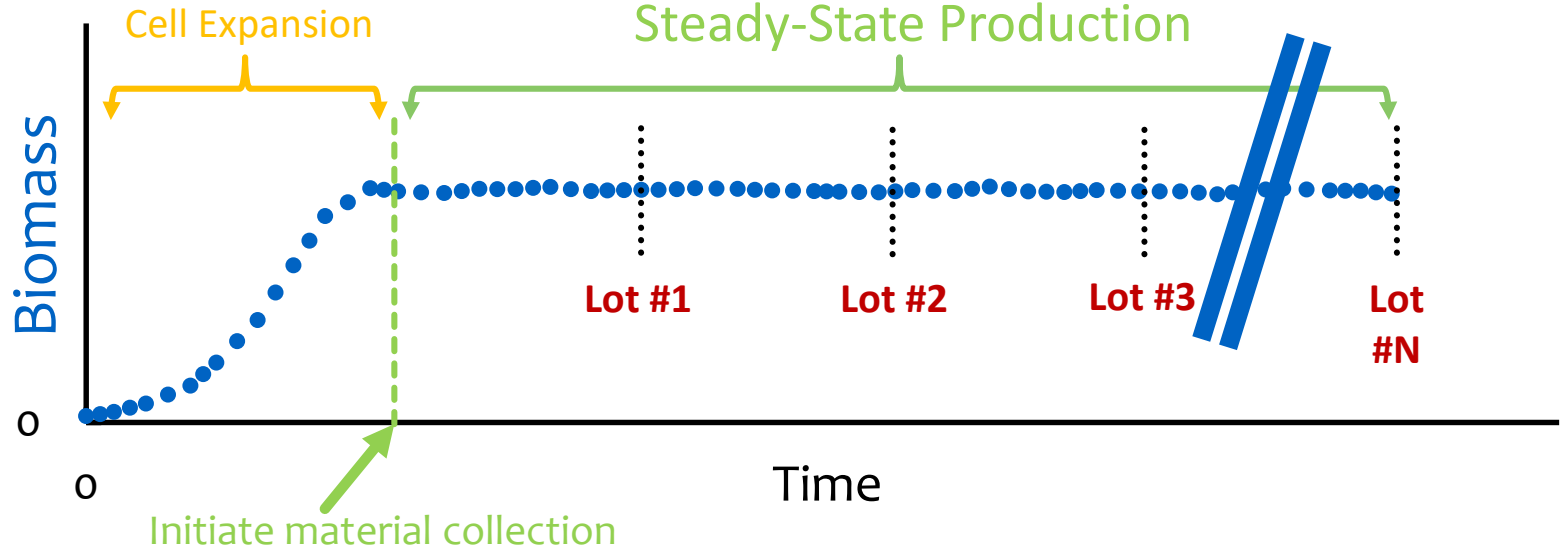
OUTLINE

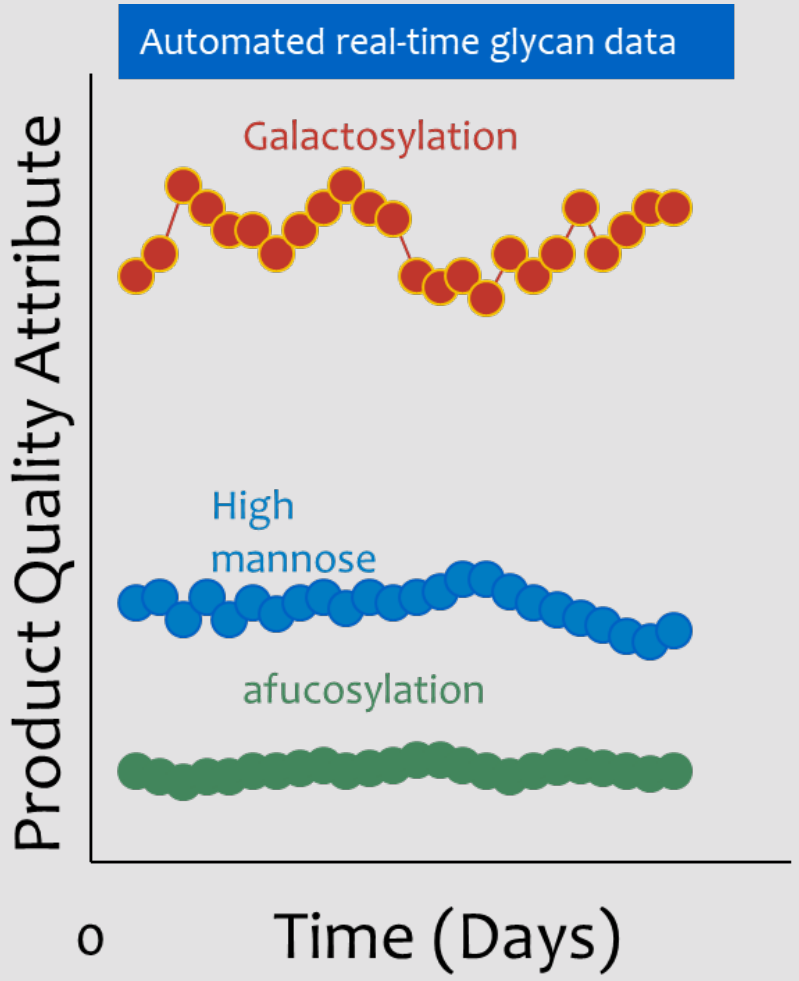
- Process and product development paradigm
  - Prior knowledge, empirical, first principles, ML approaches
- Case Studies:
  - First principles modeling based UFDF for buffer composition predictions
  - Drug product T/P filling process modeling
  - Process monitoring and predictive control examples
  - **Incorporating PAT and models towards control strategy**

CONTINUOUS MANUFACTURING BIOREACTOR OPERATION: CONTROL AND LOT STRATEGY

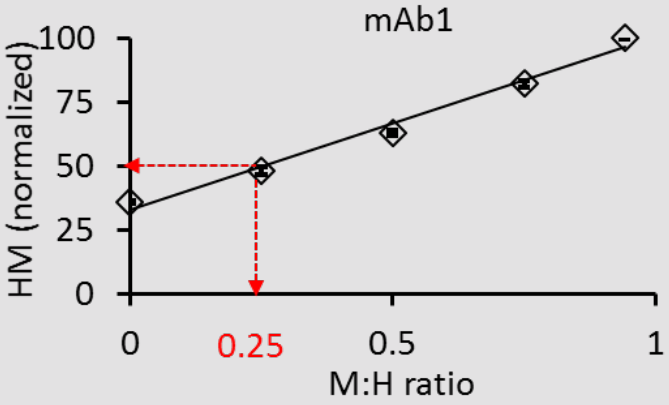
Key considerations for the Cell Culture process

- Supporting high cell densities for extended durations
- Cell separation at high cell densities
- Perfusion rates, media formulation, liquid handling
- Lot strategy
- Detect and segregate NC material





TARGETED HIGH MANNOSE CONTROL IS ACHIEVED USING MPC METHOD



(1) $\frac{dN}{dt} = \frac{\mu N(N_m - N)}{N_m}$

(2) $\frac{dP}{dt} = q_p N - S\ D\ P$

(3) $\frac{dM}{dt} = D(M_f - M) - q_M N$

(4) $q_M = \frac{V_M M}{K_M + M}$

(5) $\frac{dH}{dP} = F_H M$

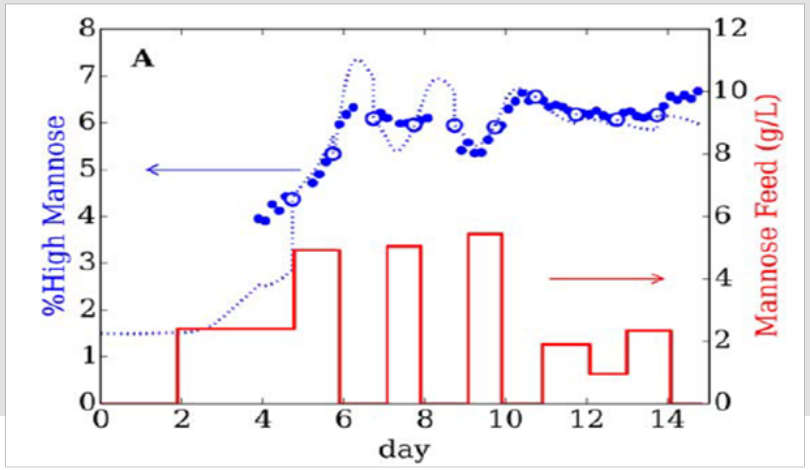
(6) $F_H = K_1 * (K_2 + N)$

(7) $\frac{dH}{dt} = \frac{dH}{dP}\frac{dP}{dt} = q_p K_1 (K_2 + N) MN$

Slide courtesy of Jack Huang

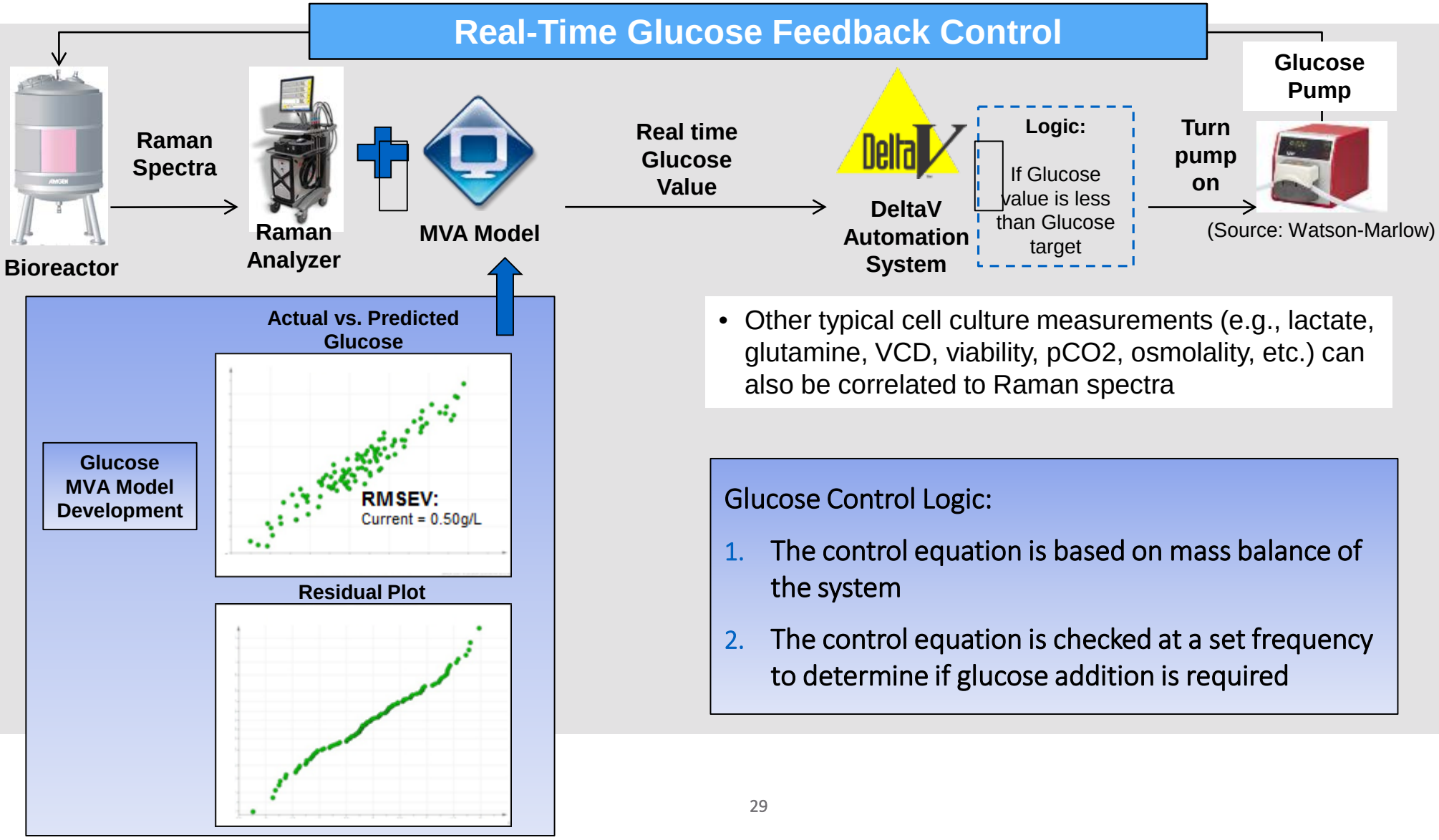
Input:
[Mannose], VCD, Titer, %HM
↓
Adjust %HM target
↓
Mannose feed rate

Target HM level: 6±1%



(Zupke et al. 2015, Biotechnol Prog)

OVERVIEW OF GLUCOSE FEEDBACK CONTROL STRATEGY

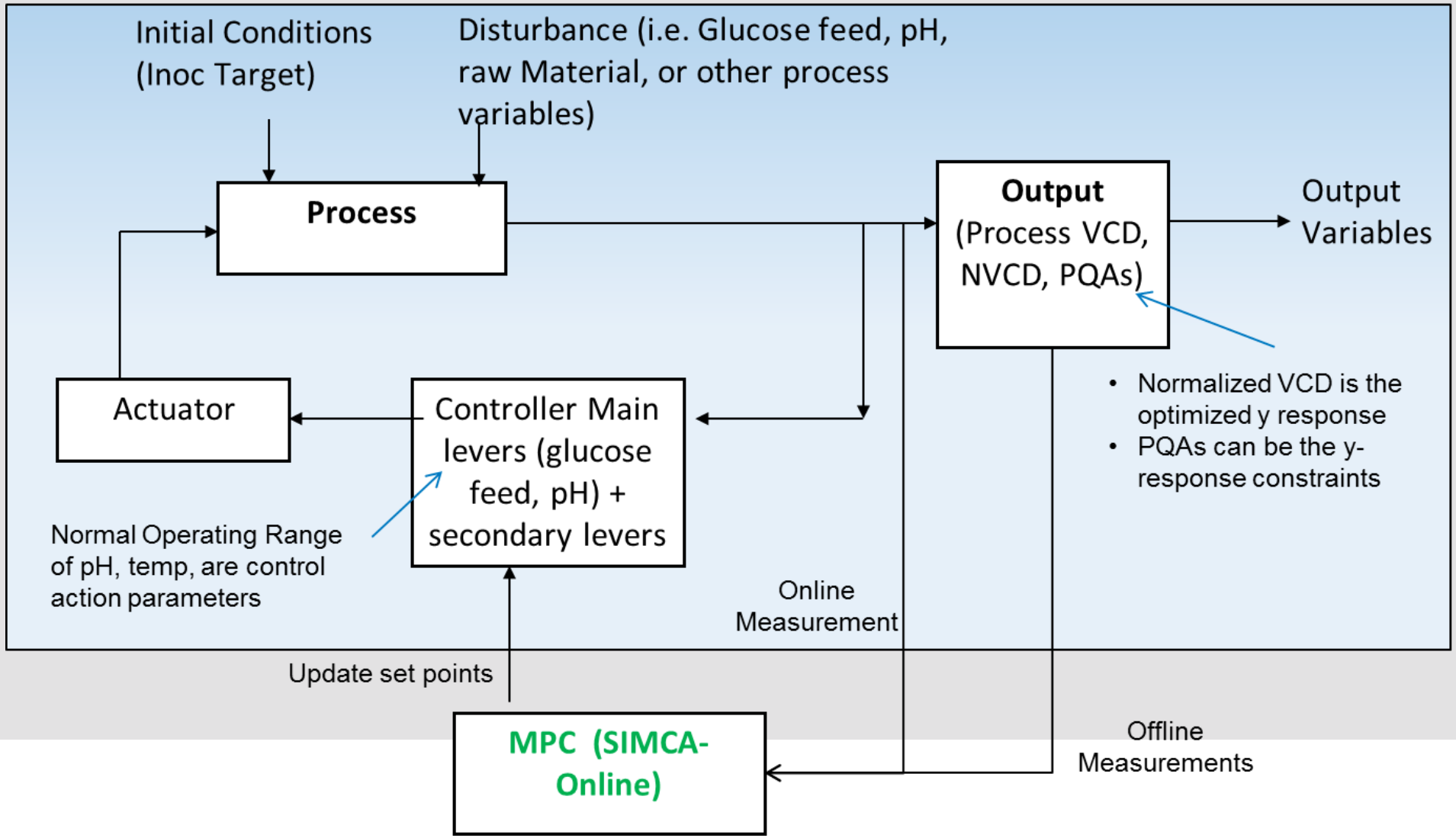


- Other typical cell culture measurements (e.g., lactate, glutamine, VCD, viability, pCO2, osmolality, etc.) can also be correlated to Raman spectra

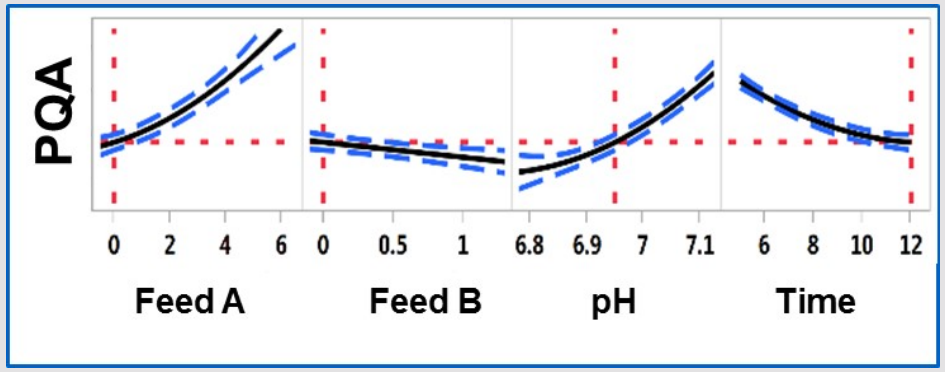
Glucose Control Logic:

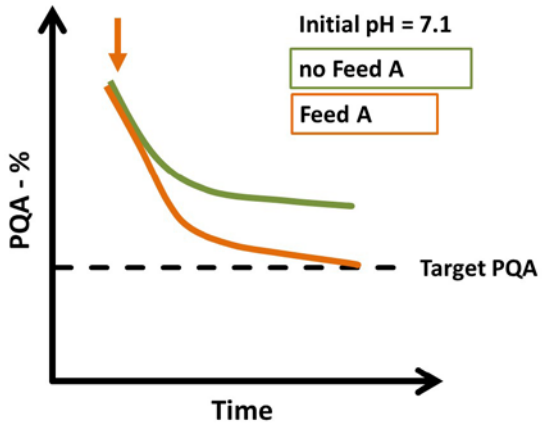
1. The control equation is based on mass balance of the system
2. The control equation is checked at a set frequency to determine if glucose addition is required

MODEL PREDICTIVE CONTROL FRAMEWORK ENABLES PERFORMANCE-BASED CONTROL

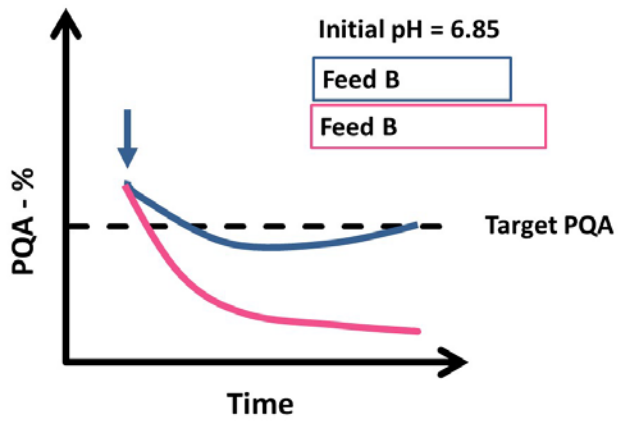


EXPERIMENTS WERE USED TO DETERMINE THE APPROPRIATE LEVERS TO CONTROL PQA; FEED A AND FEED B ACT IN OPPOSITE DIRECTIONS AS IDEAL LEVERS FOR MPC



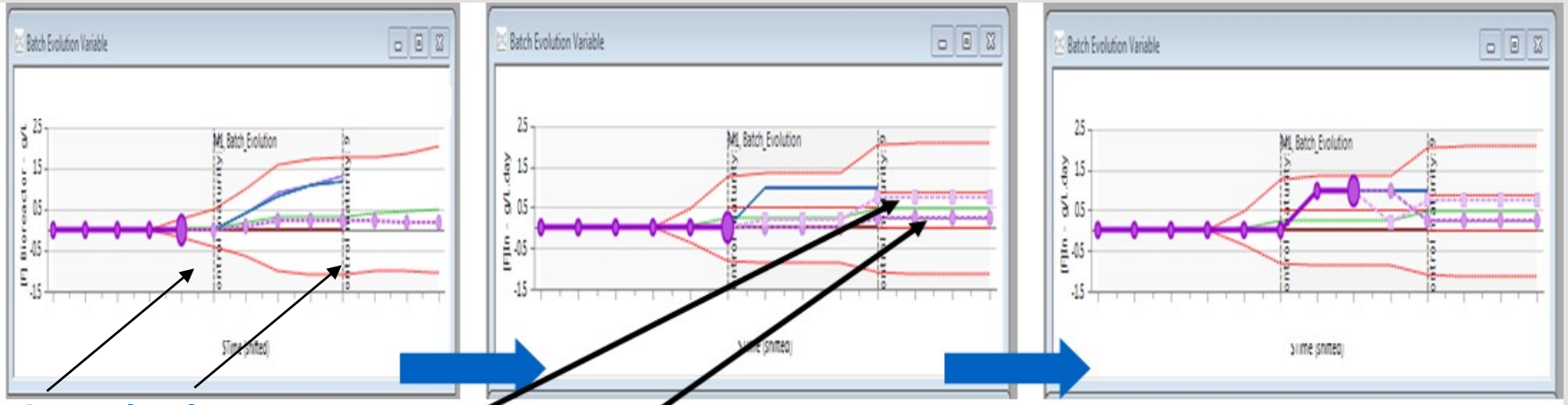


High initial pH results in a high PQA trajectory. This could be corrected by using feed A as shown with the arrow.



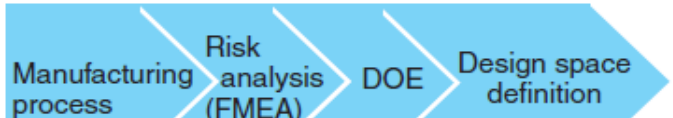
Low initial pH results in a low PQA trajectory. This could be corrected by using Feed B as shown with the arrow.

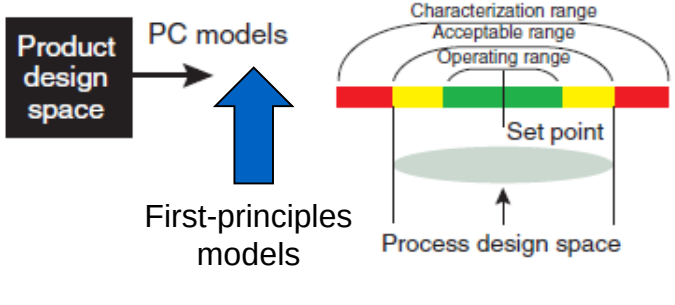
WE WERE ABLE TO MEET PQA TARGET WITHIN +/- 2.5% OF ITS DESIRED VALUE USING MPC IN PRODUCTION BIOREACTOR

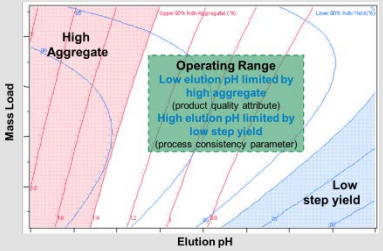


- Two control points were available in this run
- MPC used to add Feed A and/or Feed B at control points

ROBUSTNESS AND CONTROL OF OPERATING SPACE CAN BE IMPROVED USING PAT AND FIRST PRINCIPLES MODELS







PAT Method 1: MALS for Controlling %HMW species

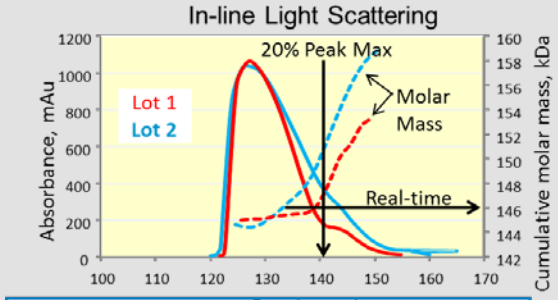
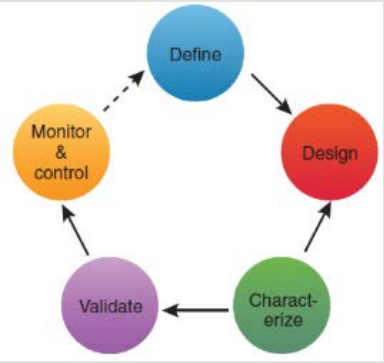
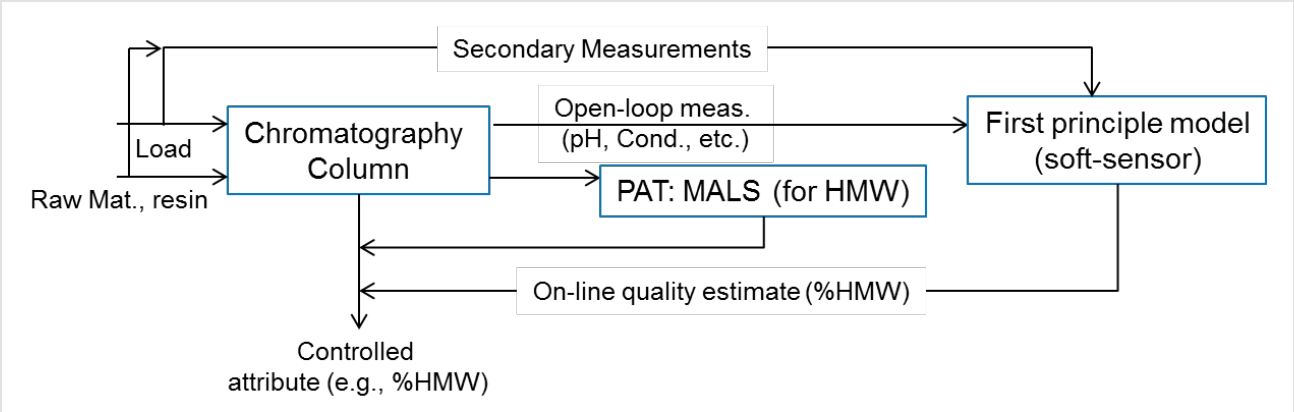


Table 2. Effect of Purity of Load Material on Pool Purity and Percent Yield of the HIC Process Column for Pooling Based on Absorbance and PAT for Experiments Performed at Laboratory Scale *

		A280-Based Pooling		PAT Pooling	
Run	% Load Purity	% Pool Purity	% Yield	% pool Purity	% Yield
1	62.8	81.3	91.7	91.6	81.9
2	72.2	85.5	85.6	91.1	83.8
3	81.6	95.4	83.1	90.2	87.8



** Rathore et al., 2010, Large Scale Demonstration of a Process Analytical Technology Application in Bioprocessing, Biotechnology Progress, 26(2), 448.*



PAT Method 2: First principles model for controlling %HMW species

Mass Transport in Column

$$\frac{\partial c_i}{\partial t} = -u\frac{\partial c_i}{\partial z} + D_{ax}\frac{\partial^2 c_i}{\partial z^2} - \frac{1}{\beta_c}\frac{3}{r_p}k_{f,i}\left(c_i - c_{p,i}[r_p]\right)$$

Mass Transport in Bead

$$\frac{\partial c_{p,i}}{\partial t} + \frac{1}{\beta_p}\frac{\partial q_i}{\partial t} = D_{p,i}\left(\frac{\partial^2 c_{p,i}}{\partial r^2} + \frac{2}{r}\frac{\partial c_{p,i}}{\partial r}\right)$$

AMGEN

CONCLUSIONS

In silico first principles modeling:

- is an instrumental tool for rapid process design and knowledge-based manufacturing
- enables an efficient use of experimental efforts
- enables a richer characterization of the robust design space
- can enable next-generation process monitoring and control applications

Augmented with PAT, sensors and _in silico_ models offer advanced process performance management capabilities

Artificial Intelligence and Machine Learning-based _in silico_ models are emerging, offering unique opportunities in bio/pharma

Every patient, every time

AMGEN

ACKNOWLEDGEMENTS

- Tony Wang
- Seyma Bayrak
- Sinem Oruklu
- Pablo Rolandi
- Xiaoxiang Zhu
- Fabrice Schlegel
- Richard Wu
- Jack Huang
- Will Johnson
- Chris Garvin
- Myra Coufal
- Gerd Kleemann
- Deirdre Piedmonte
- Stephen Brych
- Justin Ladwig
- Roger Hart
- Karin Westerberg

AMGEN