Simulated Moving Bed Technologies for High-Purity and High Yield Multi-component Separations

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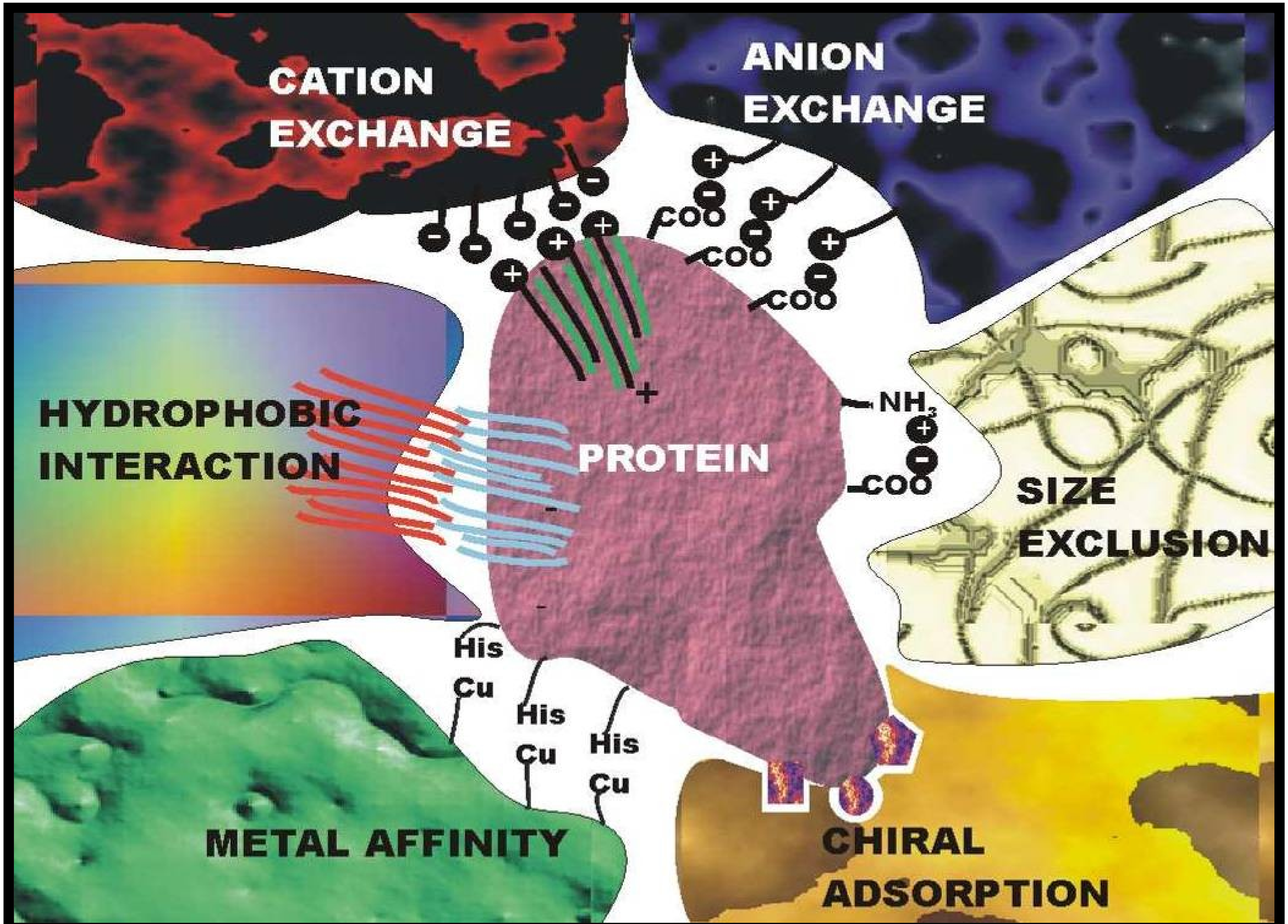
Overview

- Chromatography and SMB
  - Principles
  - Key Barriers
- Purdue SMB Technologies
  - Standing Wave Design & Optimization
  - VERSE Dynamic Simulations
  - Versatile SMB Equipment
  - Model Based Design Approach
- Applications
  - Tandem SMB for insulin purification
  - A Five Zone SMB for Isolation of Six Sugars from Biomass Hydrolysates (Mixtures of 10 or more components)

Chromatography- Advantages

- High selectivity – 1 in 10,000.
- Versatile mechanisms of separation – adsorption, ion exchange, size exclusion, etc.
- Compact volume compared to extraction.
- Lower solvent usage than extraction.
- Mild operating conditions – suitable for fragile compounds.

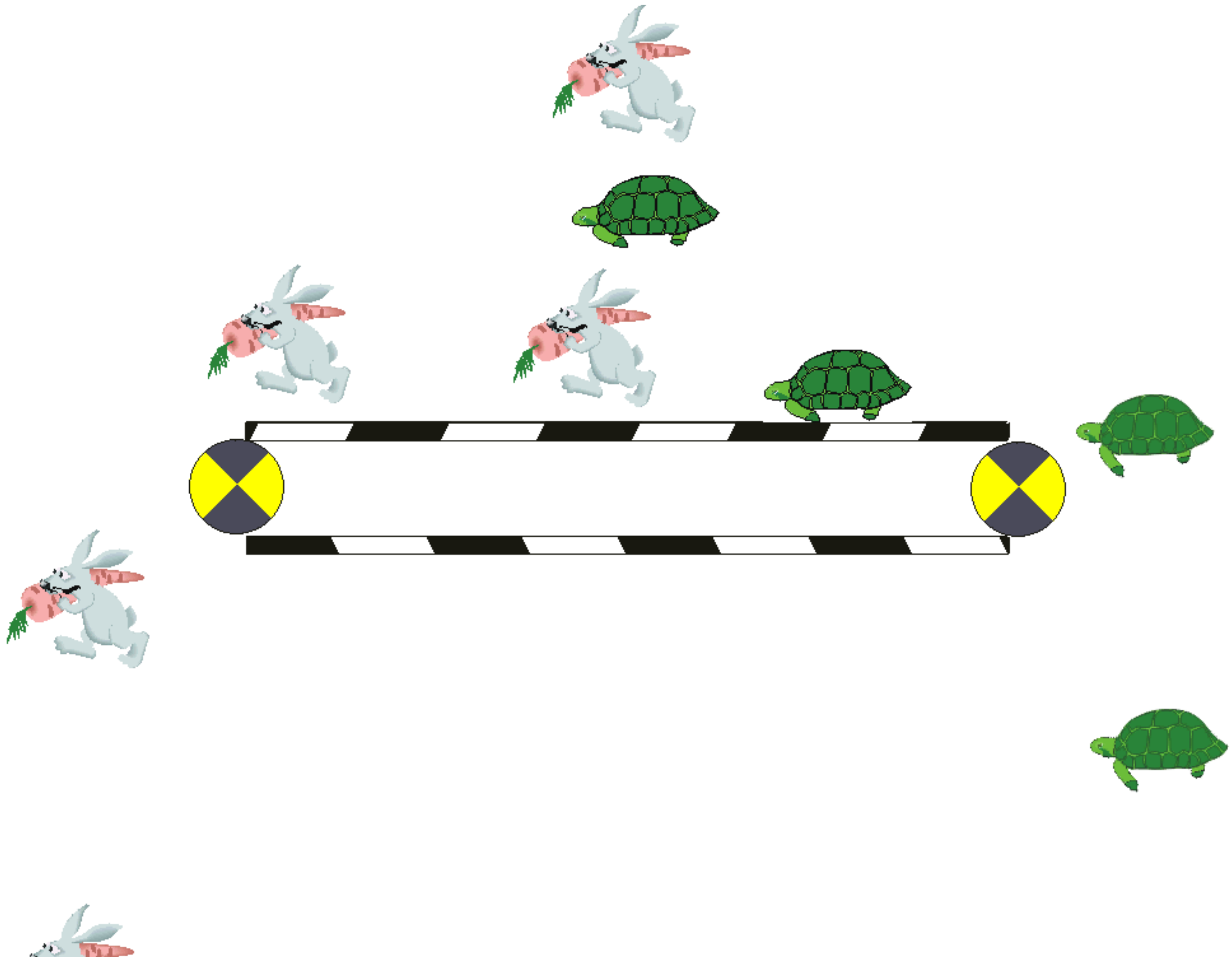
Mechanisms of Adsorption



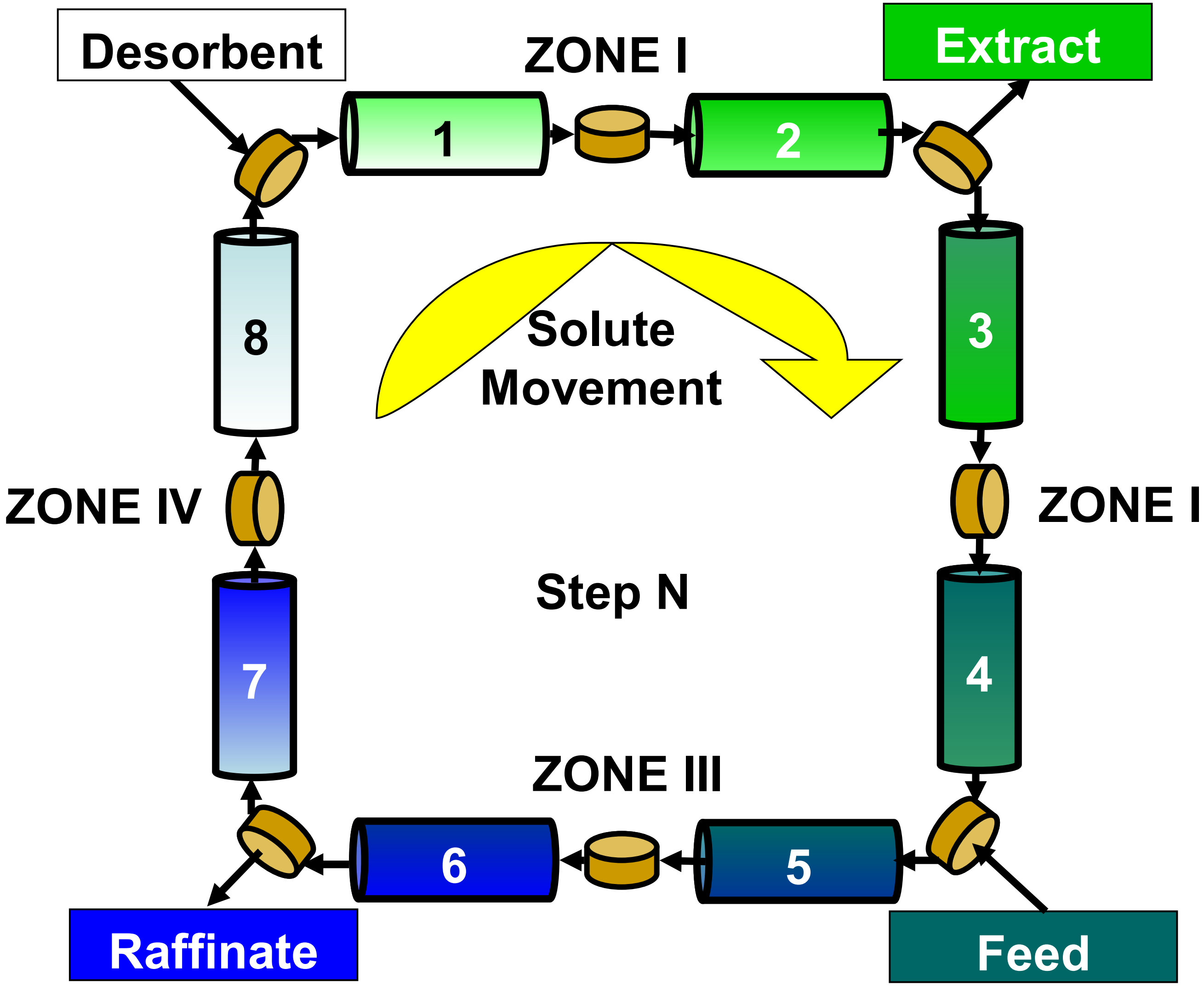
Limitations of Batch Chromatography

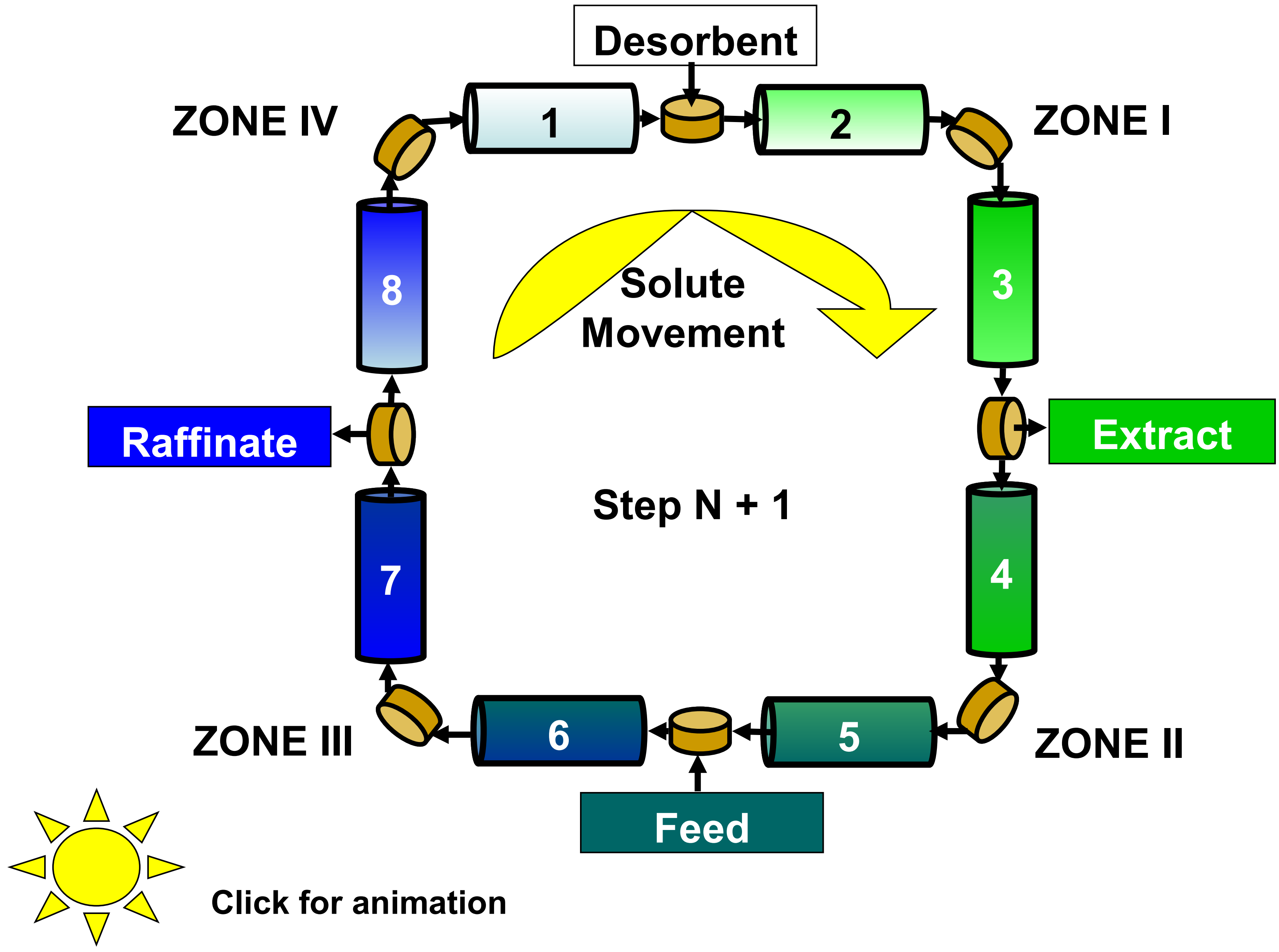
- Difficult to achieve both high purity and high yield.
- Low adsorbent utilization.
- High solvent consumption and product dilution.
- Protein aggregation and instability.
- Not a continuous process.

Solution I- Binary Separation in a Continuous Moving Bed

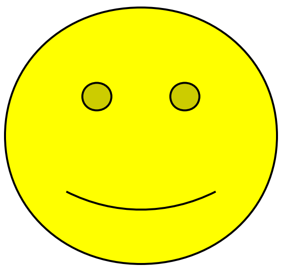


Solution II–Moving Port or SMB




Desorbent
ZONE IV
1
2
ZONE I
8
Solute
Movement
3
Raffinate
Extract
Step N + 1
7
4
ZONE III
6
5
ZONE II
Feed
Click for animation

VERSE Simulation of Separation of Insulin from Zinc Chloride in Tandem SMB (Ring II)



Clickport-r2.pptm

Advantages of SMB over Batch

- Only partial separation of solutes is required to obtain high purity.
- Higher yield than batch – 10% more than batch.
- High purity achievable without sacrificing yield.
- High productivity– 5 to 10 fold increase.
- Less solvent – 5 to 10 fold less.
- Reduced environment impact.
- Reduced footprint, equipment size, and manpower.
- Continuous process-high throughput.
- Economical for large scale separations.

Commercial Applications of SMB

- Hydrocarbons – Molex, Parex (1970)
- Sugars – Tate & Lyle (1980)
- Chiral Drugs (1990)
- Antibiotic drug (2000)

* All binary separations of low MW chemicals in four-zone SMB, except the antibiotic recovery

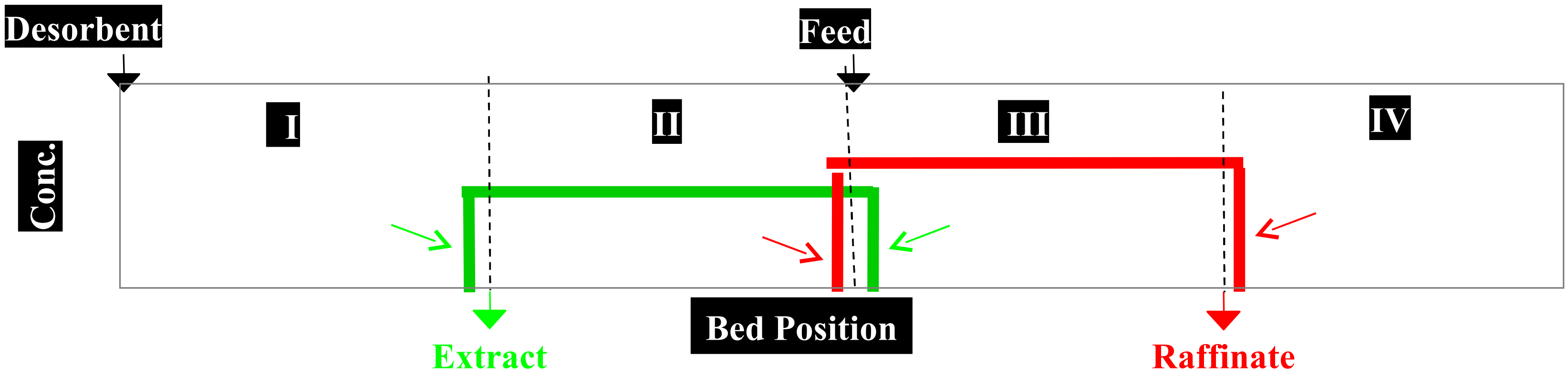
Key Barriers in SMB

- Complex transient and cyclic steady state phenomena.
- A four-zone SMB has 9 design parameters - 2^9 to 3^9 trials.
- Large number of system & operating parameters to be optimized.
- Method for multi-component separation not well developed.
- Equipment more complex than batch chromatography.
- No commercial equipment for multi-component separation.
- Control of batch identity and residence time

Purdue's Platform SMB Technologies

1. Standing wave design and optimization.
2. VERSE simulations.
3. Versatile SMB equipment.
4. A systematic model-based approach for process design and optimization.

Standing Wave Design: Binary, Ideal, Linear System



$$\nu = u_{w,slow}^{I}$$

$$\nu = u_{w,fast}^{II}$$

$$\nu = u_{w,slow}^{III}$$

$$\nu = u_{w,fast}^{IV}$$

$$F^{Feed} = S\varepsilon_b \left(u_0^{III} - u_0^{II} \right)$$

$u_{w,i}^{\alpha} = u_0^{\alpha} / (1 + P\delta_i)$

= wave velocity of component i in zone α

$\nu = L_c / t_s$ = port movement velocity

F^{feed} = feed flow rate

u_0^{α} = interstitial velocity in zone α

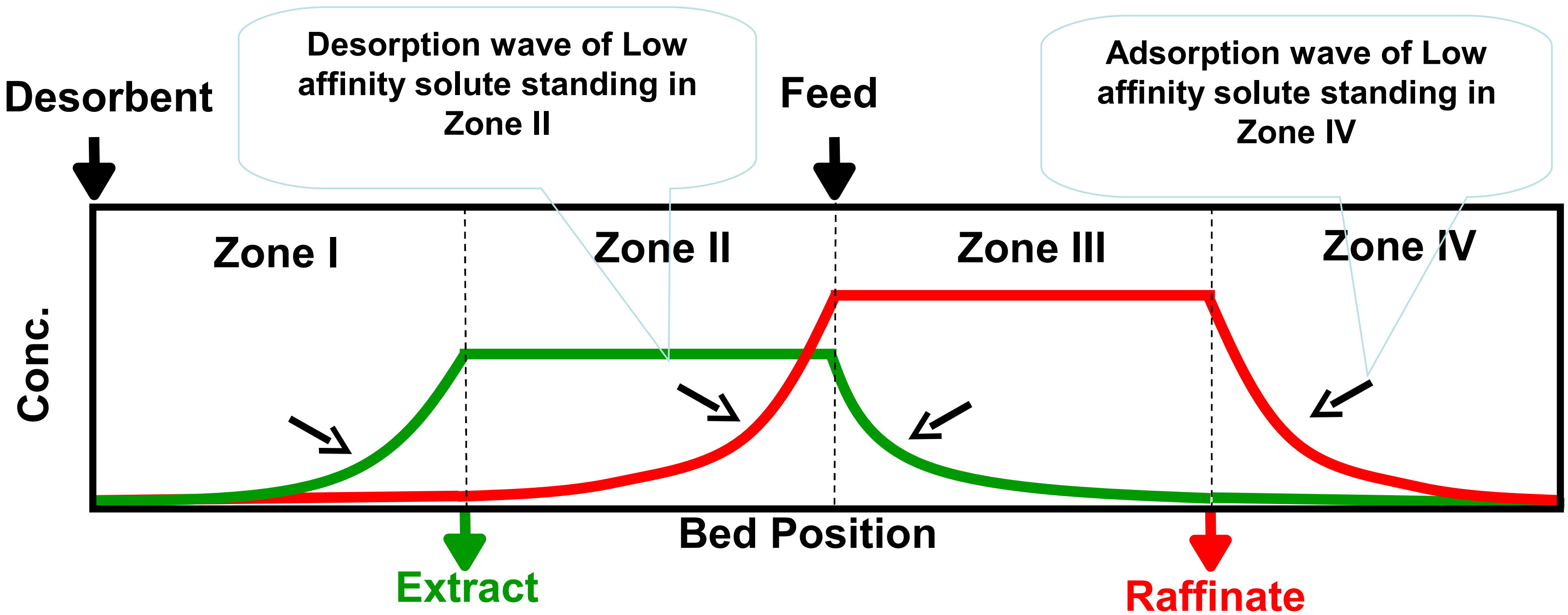
ε_b = inter-particle void fraction

$P = (1 - \varepsilon_b) / \varepsilon_b$ = bed phase ratio

δ_i = distribution coefficient of i

S = column cross-sectional area

Standing Wave Design for Linear, Nonideal Systems



- *Matching wave velocities to port velocity to ensure high purity and high yield*
- *Difference in wave velocity and port velocity allows focusing for nonideal systems*

Standing Wave Design & Optimization-Advantages

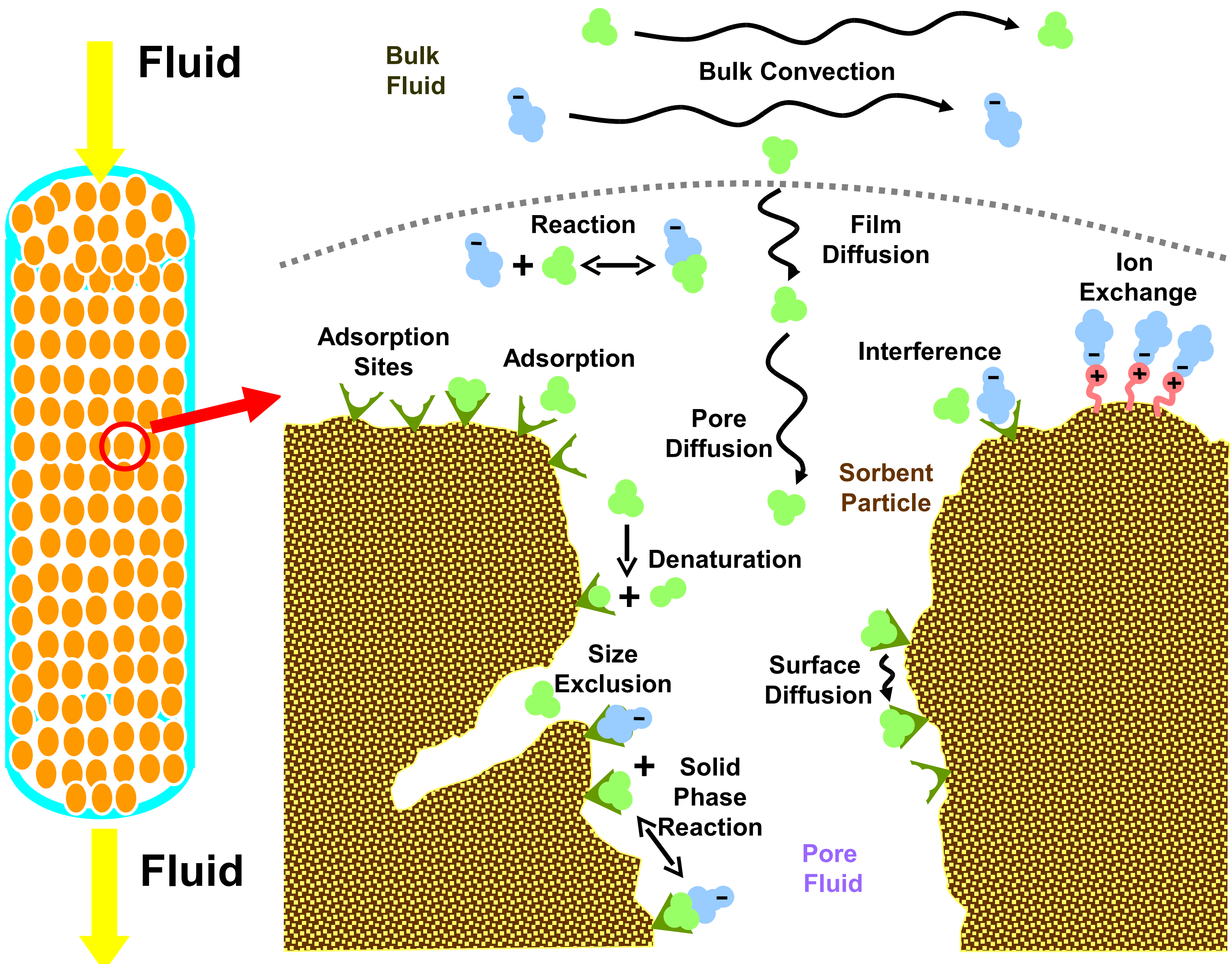
- Four zone flow rates and port velocity are solved easily.
- Little computation time required.
- Achieving maximum productivity and minimum solvent consumption for a given configuration.
- Easy extension to nonlinear, multi-component, multi-zone separations.
- Reduce search space by five dimensions or more for optimization.

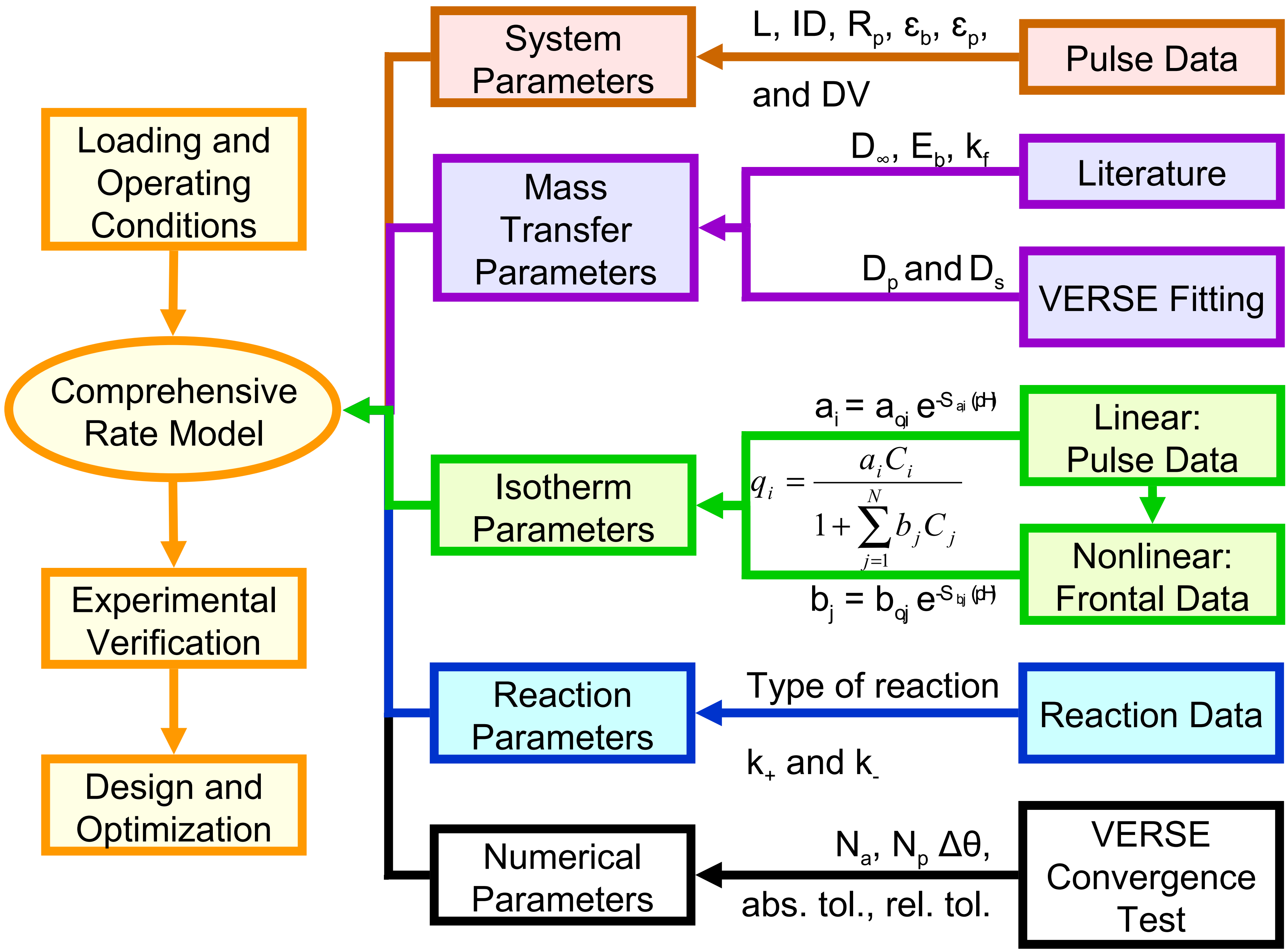
VERSE

VErsatile Reaction SEparation Simulator

- Simulation based on a detailed dynamic rate model (transient differential mass balances)
- Thousands of equations solved at each instance
- To predict column profiles and histories
- To understand transient phenomena in batch chromatography, carousel, and SMB
- To understand residence time and batch integrity issues in SMB
- To reduce the number of costly experiments

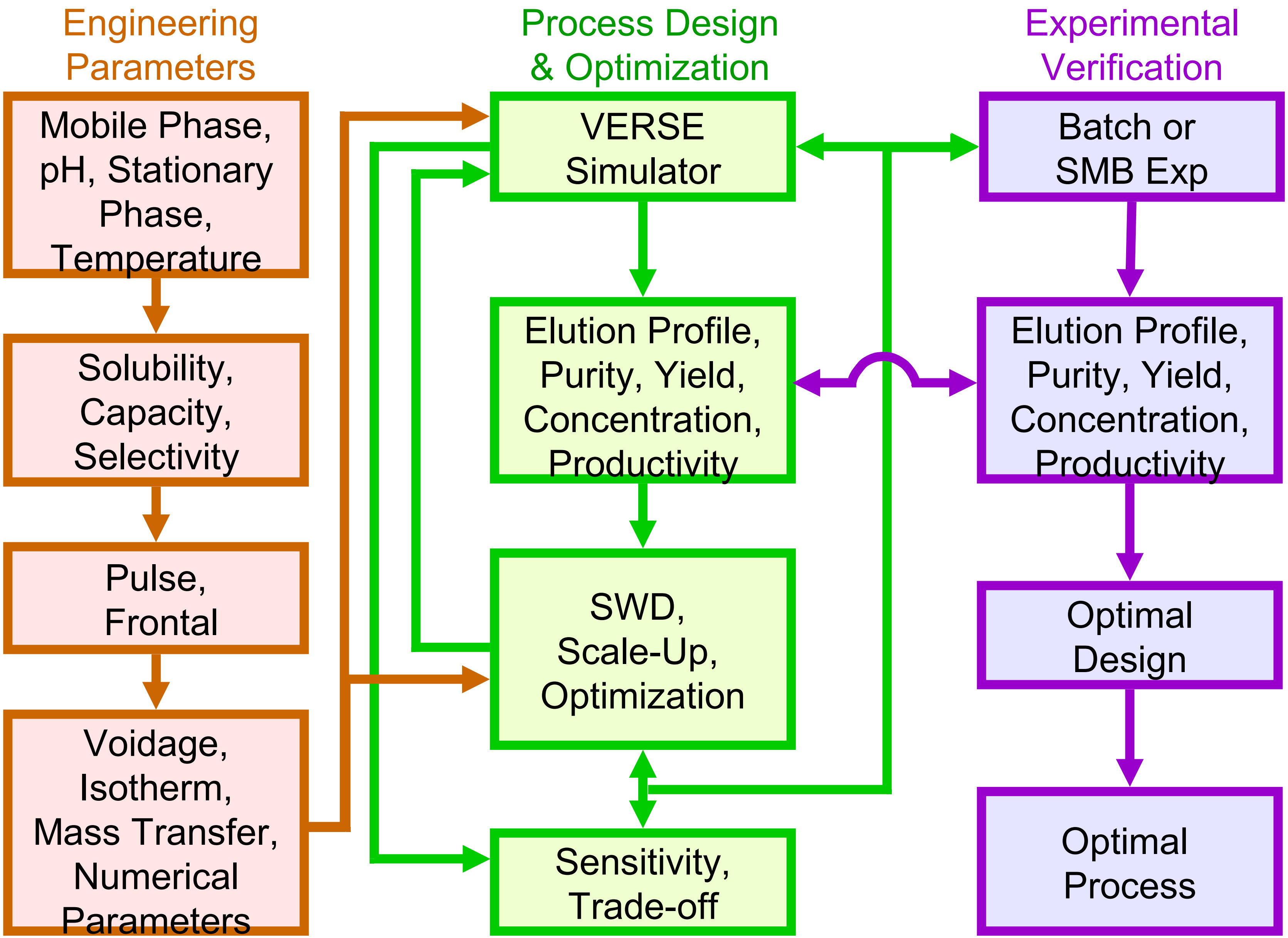
Mechanisms Considered in VERSE





Loading and Operating Conditions
Comprehensive Rate Model
Experimental Verification
Design and Optimization
System Parameters
L, ID, R_p, ε_b, ε_p, and DV
Pulse Data
Mass Transfer Parameters
D_∞, E_b, k_f
Literature
D_p and D_s
VERSE Fitting
Isotherm Parameters
$a_i = a_{qi} e^{-S_{ai}(pH)}$
$q_i = \frac{a_i C_i}{1 + \sum_{j=1}^{N} b_j C_j}$
$b_j = b_{qj} e^{-S_{bj}(pH)}$
Linear: Pulse Data
Nonlinear: Frontal Data
Reaction Parameters
Type of reaction
k_+ and k_-
Reaction Data
Numerical Parameters
N_a, N_p $\Delta\theta$, abs. tol., rel. tol.
VERSE Convergence Test

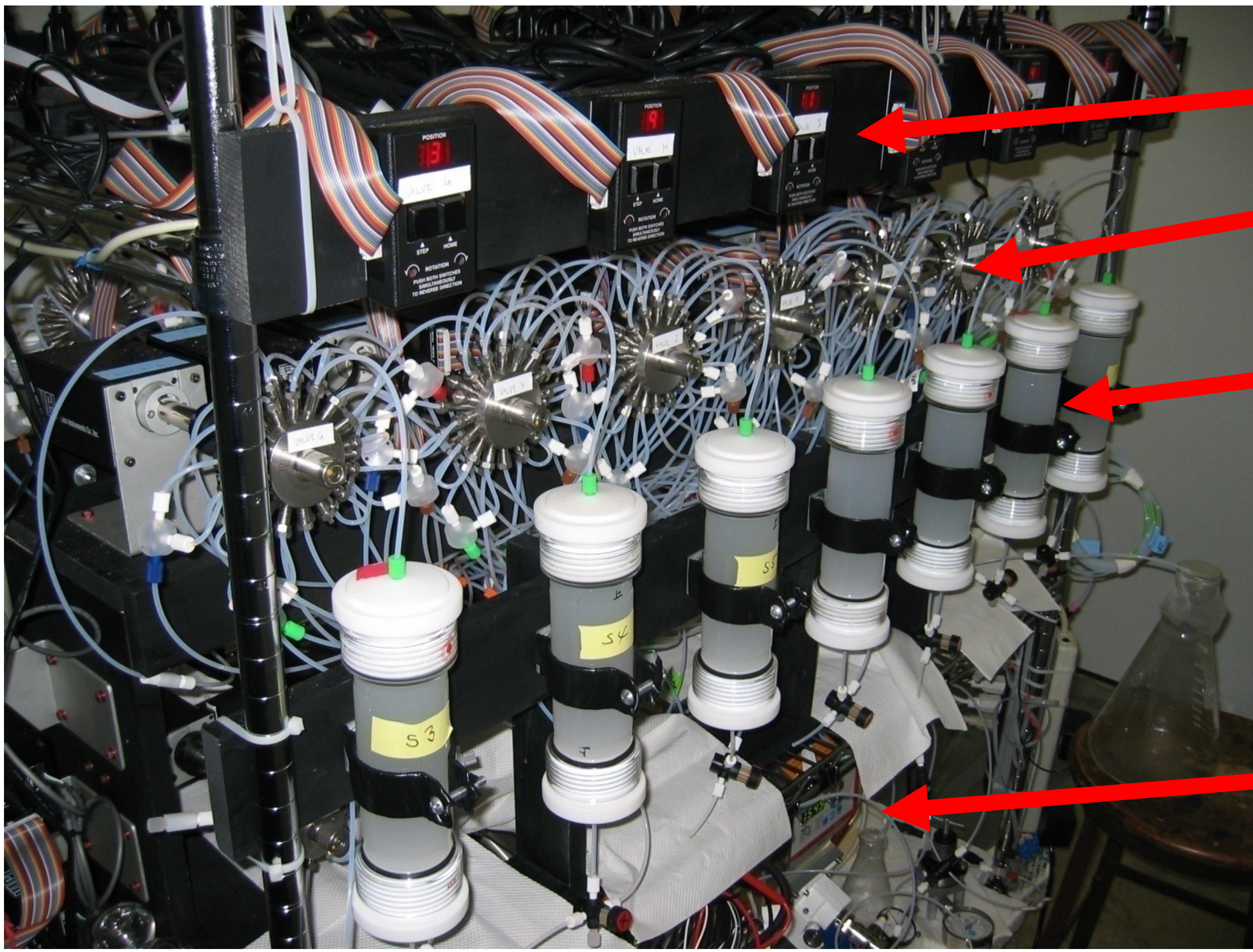
Knowledge-Based Design & Optimization



(Hirtzko et al., 1999; Mun et al., 2005; Wu et al., 1997; Xie et al., 2002)

Versatile SMB

To implement complex processes for multicomponent separations



Valve Controls

Valves

Sephadex G50 Columns

Pumps

Features of Versatile SMB

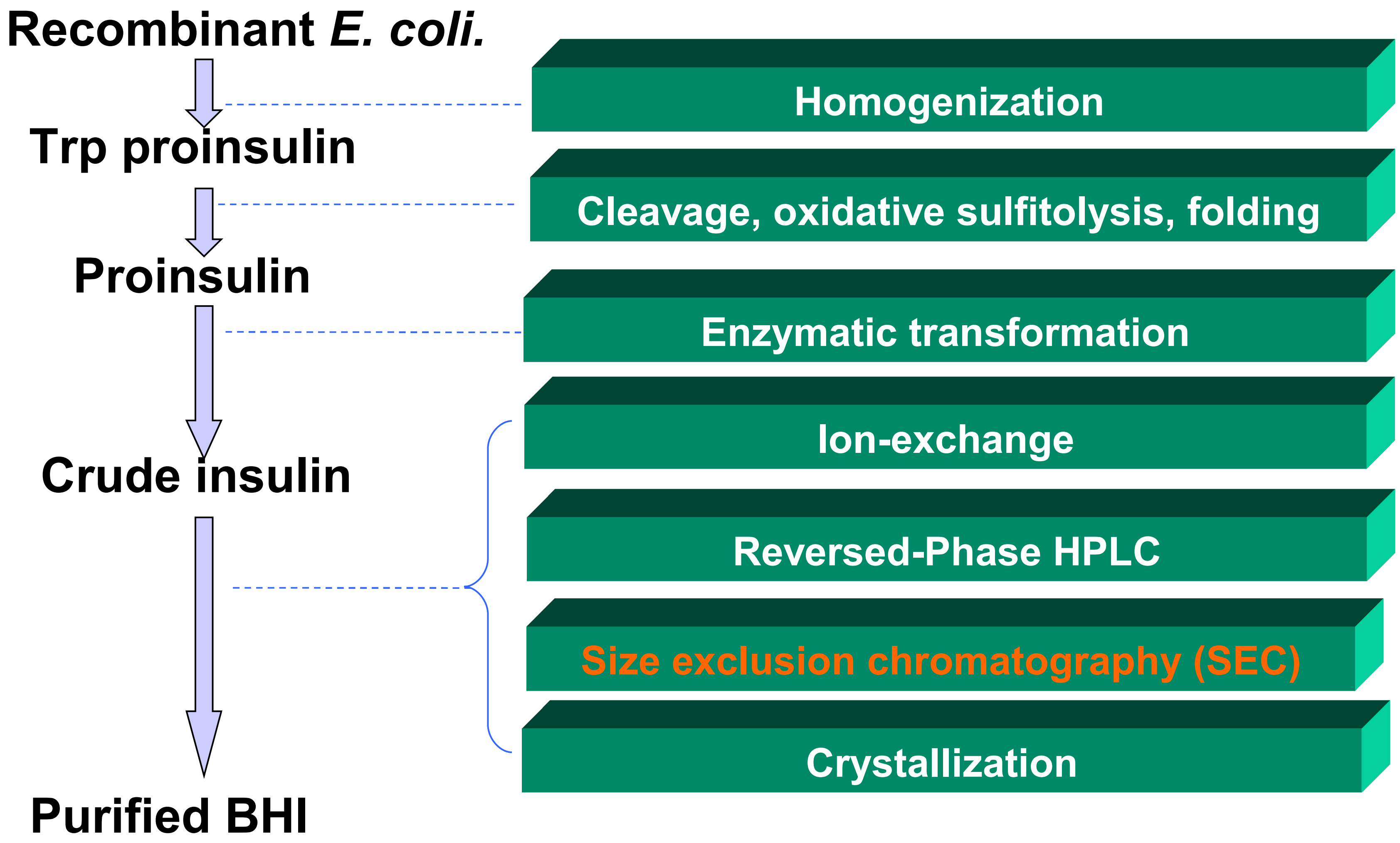
- *Dedicated valves and manifolds for high purity and high yield*
- *Allows zone bypass, open loop, multizone, multisolvent ,and multicomponent separation.*
- *Easy column expansibility.*
- *Moving port chromatography.*
- *Online decoupled regeneration.* ***Animation***
- *Independent column switching for variable step time*

Novel SMB Processes Developed at Purdue

- Pilot Scale
  - Insulin
  - Sugars from Biomass
- Lab Scale
  - Antibiotic Drug
  - Amino Acids and Derivatives
  - Lactic Acid
  - Paclitaxel (Anticancer Drug)
  - Chiral Drugs

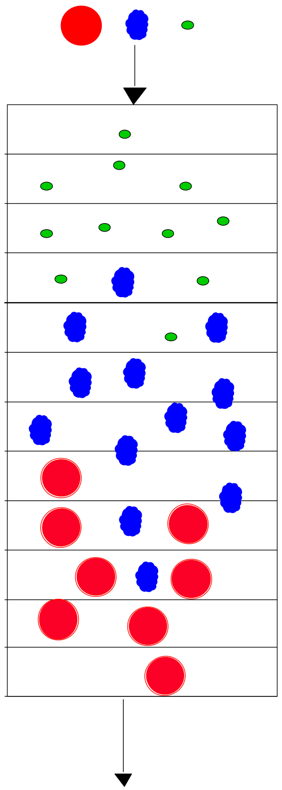
Model-Based Design of Tandem SMB for Insulin Purification

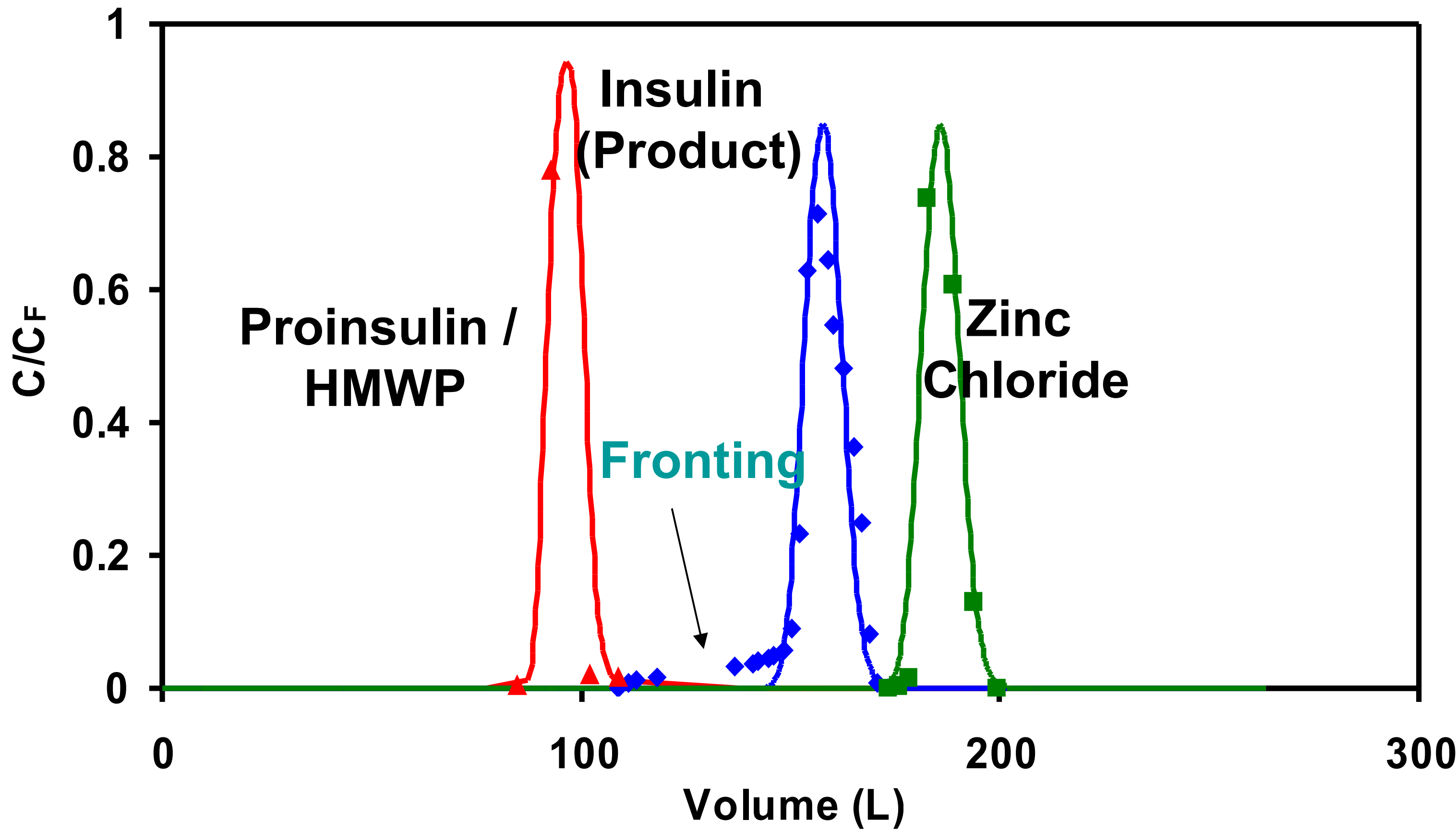
Biosynthetic Human Insulin (BHI) Process



Isolation & purification steps take 10 to 12 weeks.

Conventional Size Exclusion Chromatography



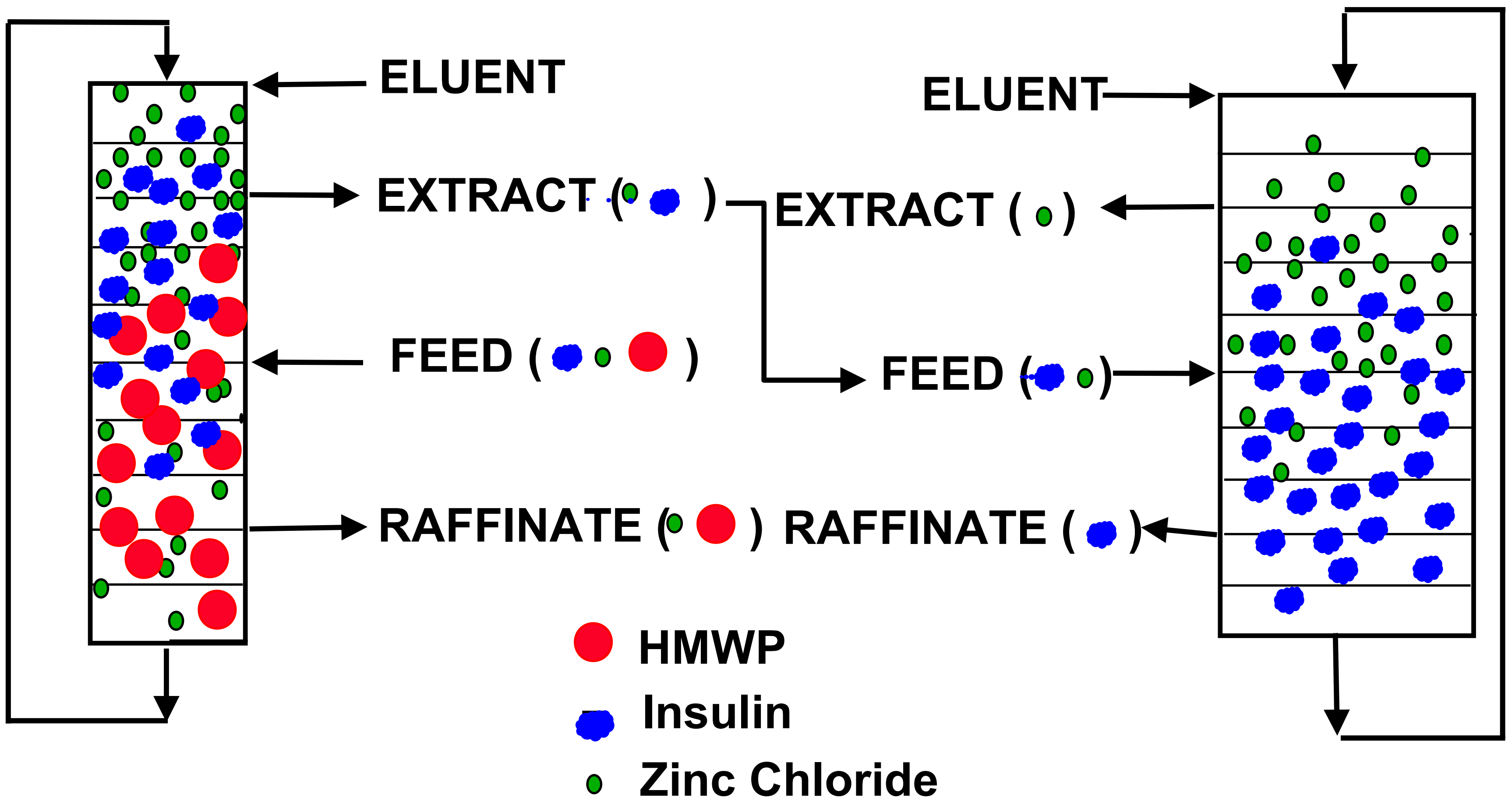


Proinsulin / HMWP
Insulin (Product)
Zinc Chloride

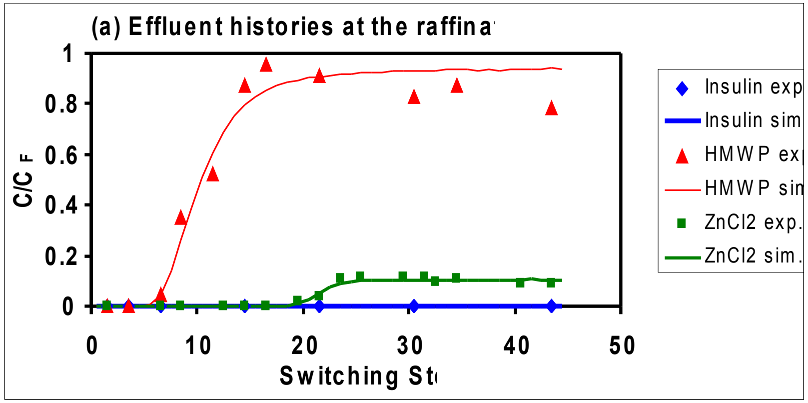
Animation

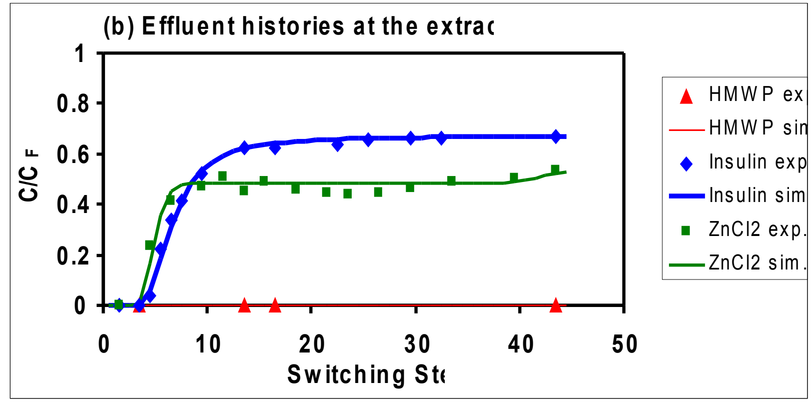
- Existing SEC batch process
  - Yield < 90%
  - Purity >99%
  - Resin productivity = 0.3 L / hr/100 L BV

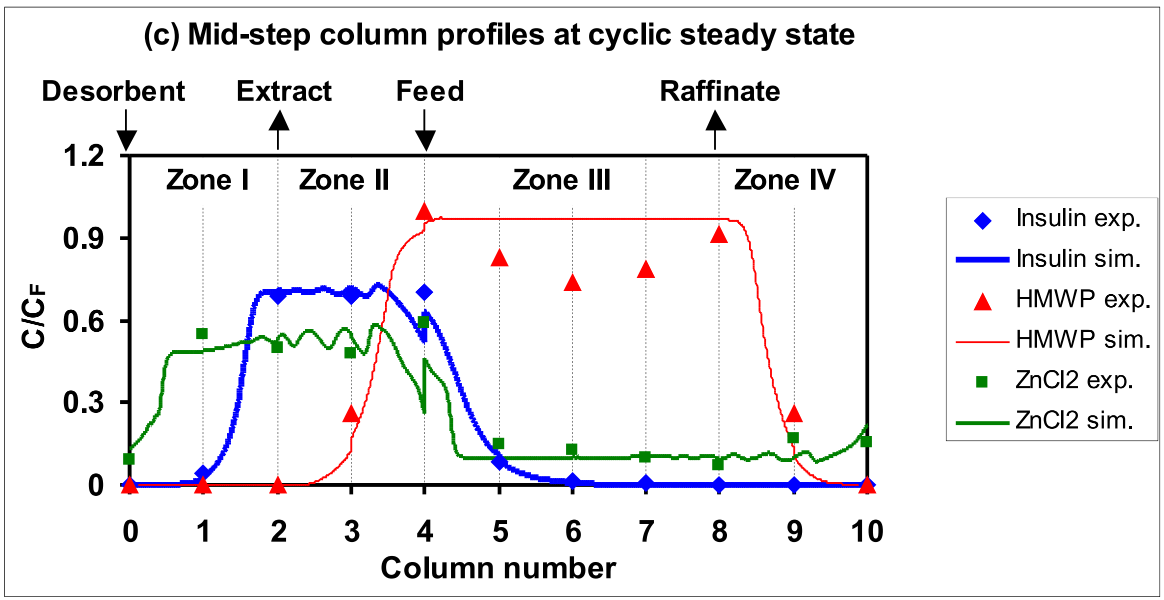
Tandem SMB for Insulin Purification



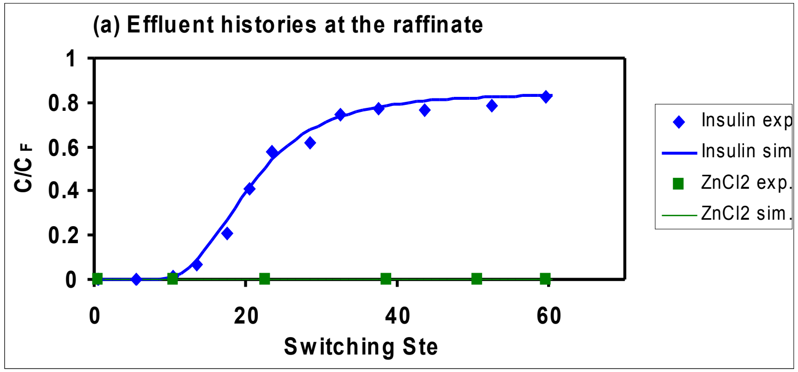
SMB Experimental Validation : Ring I

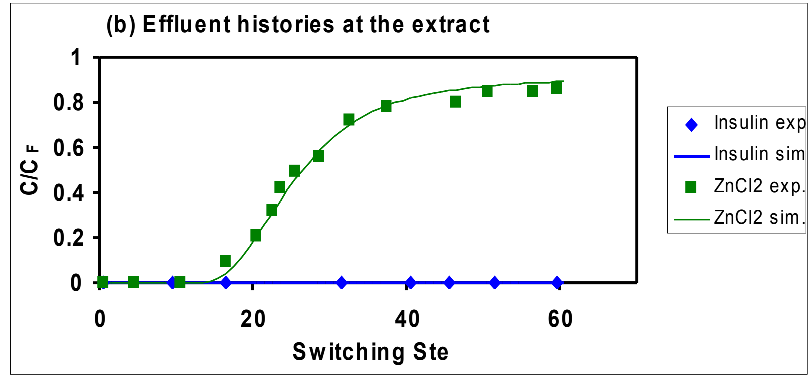


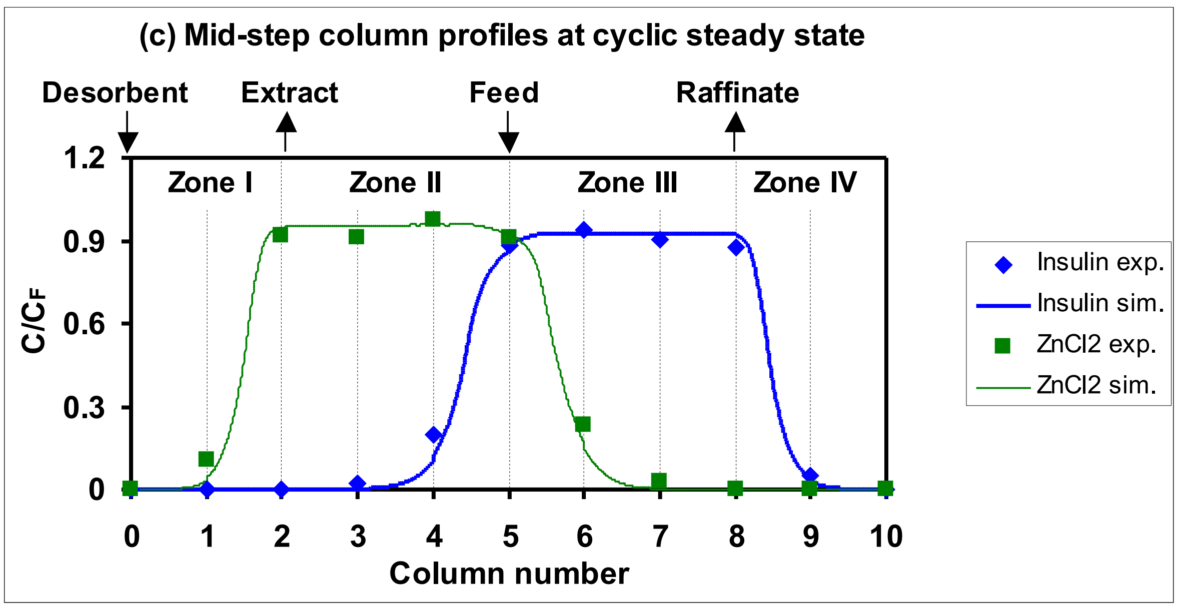




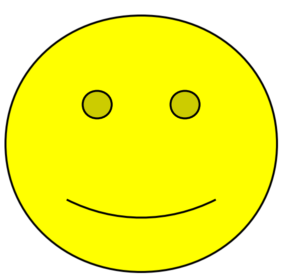
SMB Experimental Validation: Ring II







VERSE Simulation of Insulin Separation from Impurities (High Molecular Weight Proteins and Zinc Chloride) in Tandem SMB (Ring I)



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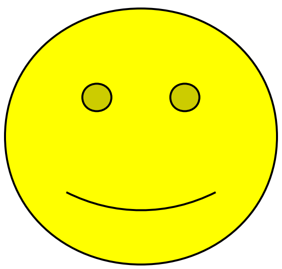
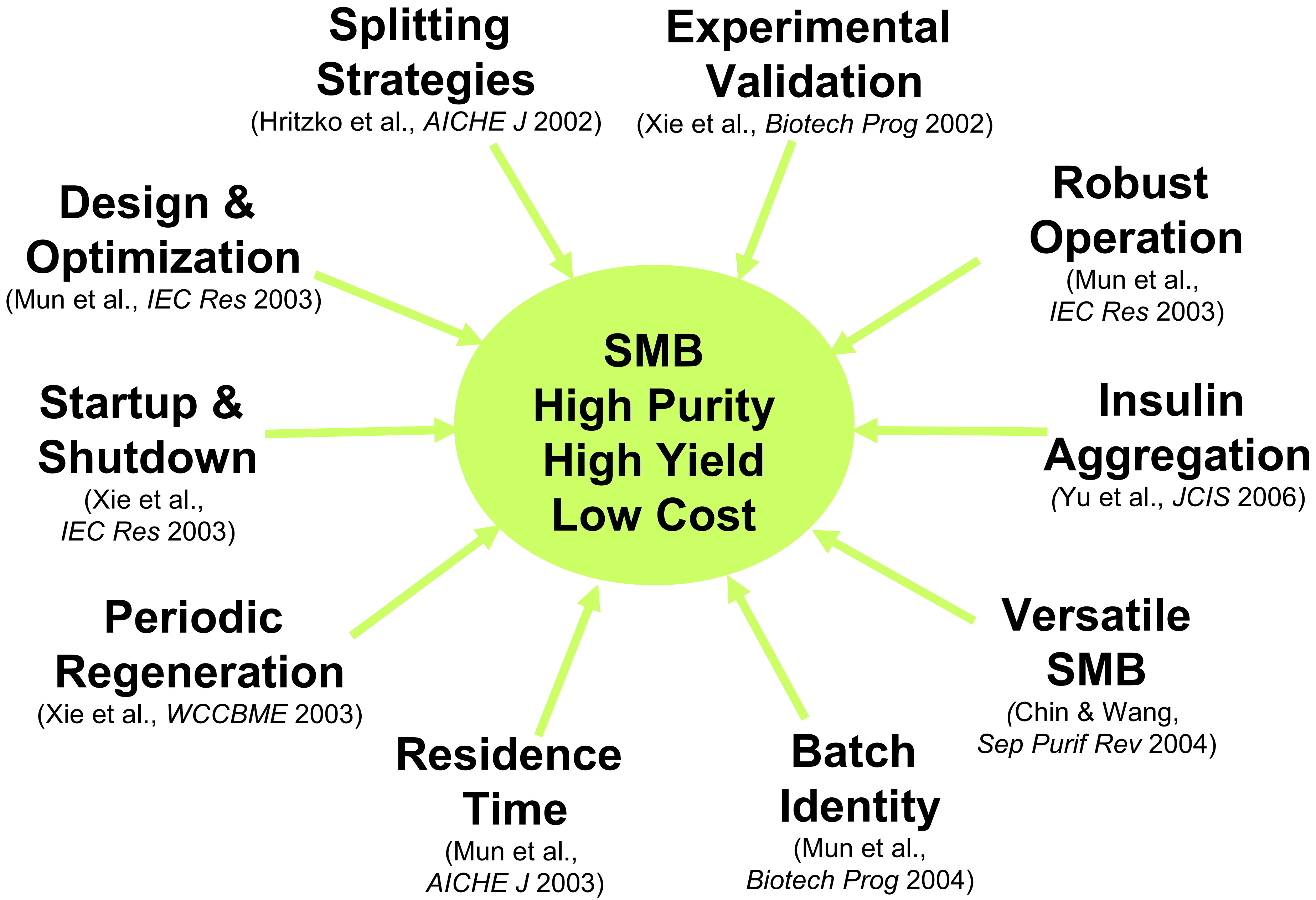
VERSE Simulation of Separation of Insulin from Zinc Chloride in Tandem SMB (Ring II)



Clickport-r2.pptm to activate

Key Issues Solved



Insulin Purification

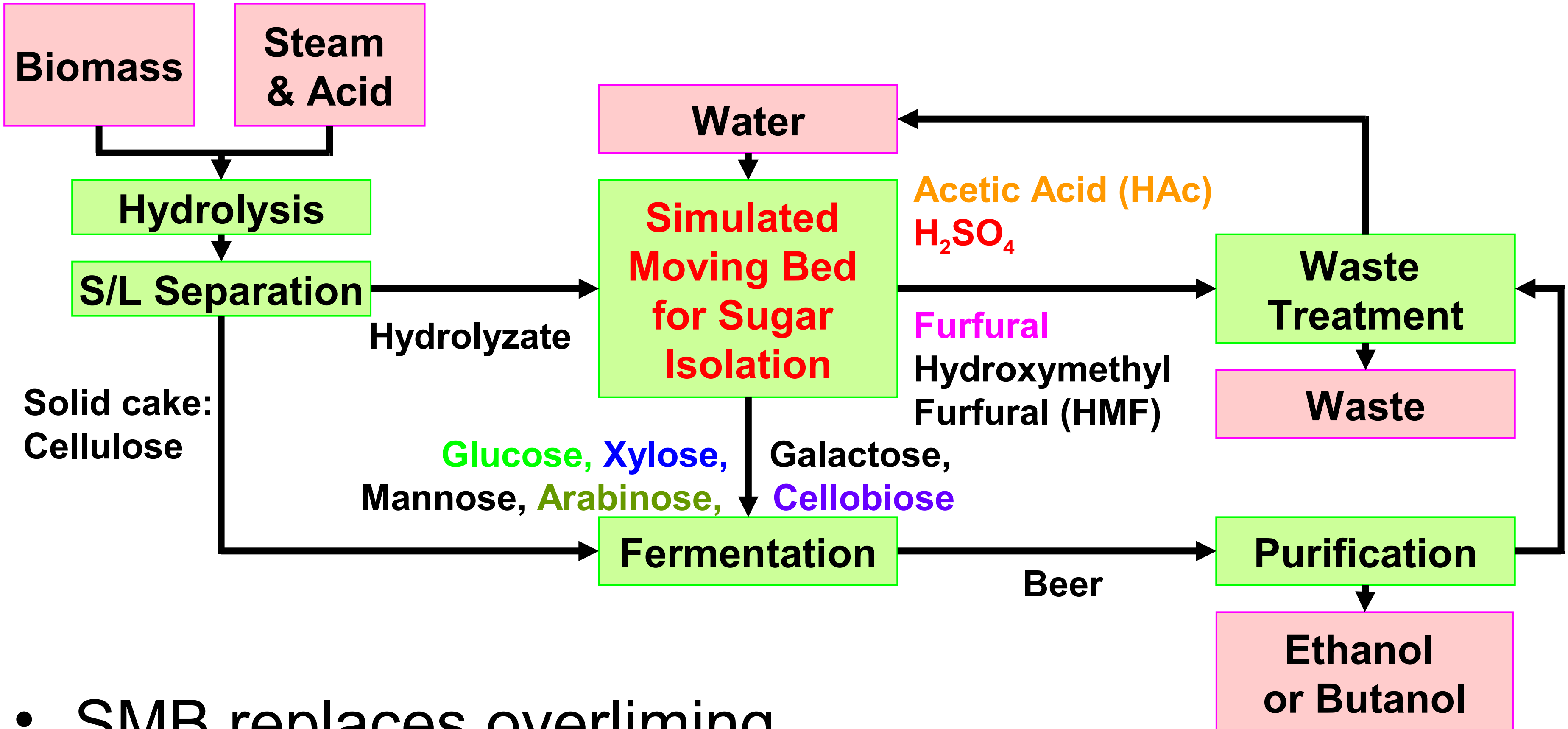
- Tandem SMB for ternary separation designed and validated with experiments
- >99% yield, 5X throughput, and 1/3 solvent consumption
- Robust and optimal Standing Wave Design
- Novel strategies created to reduce protein residence time and maintain batch identity
- Technology licensed to a major company

A Five-zone Simulated Moving Bed for Isolation of Six Sugars from Biomass Hydrolyzate

Yi Xie, Chim Yong Chin, Diana S.C. Phelps, Chong Ho Lee, Ki Bong Lee, Sungyong Mun,
N.-H. Linda Wang.

Ind. Eng. Chem. Res. 2005, 44, 9904-9920

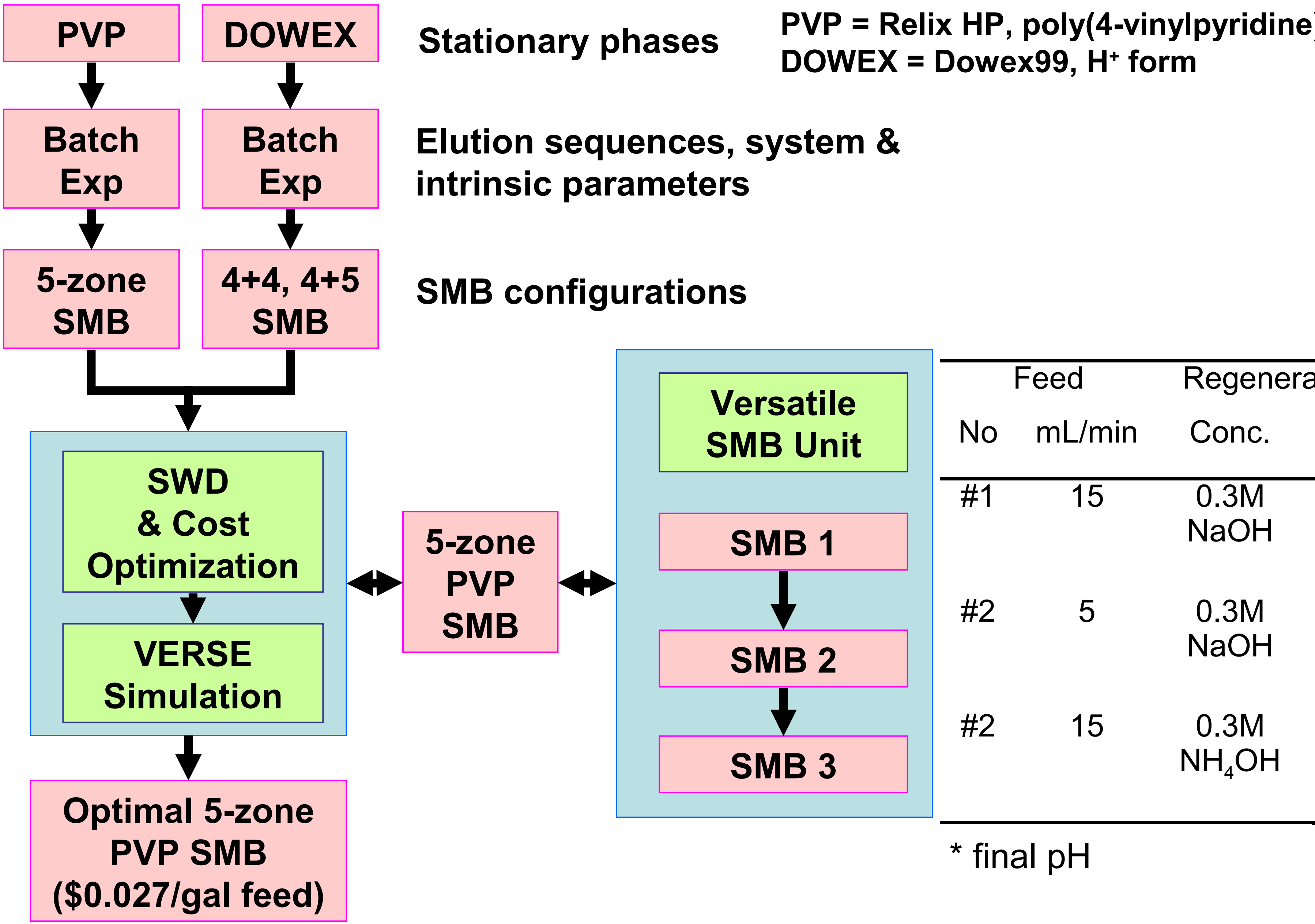
Sugars Isolated using Simulated Moving Bed



- SMB replaces overliming
  - Reduce steps & process time
  - Removes known fermentation inhibitors
  - Reduce gypsum waste disposal

Objective: An economical SMB for sugar recovery

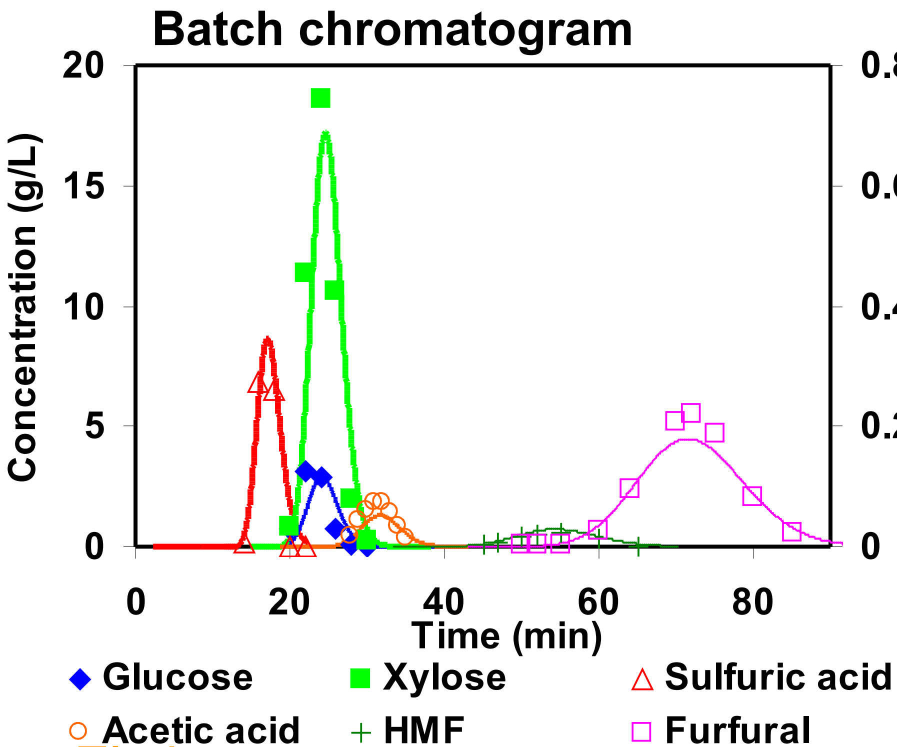
Overview



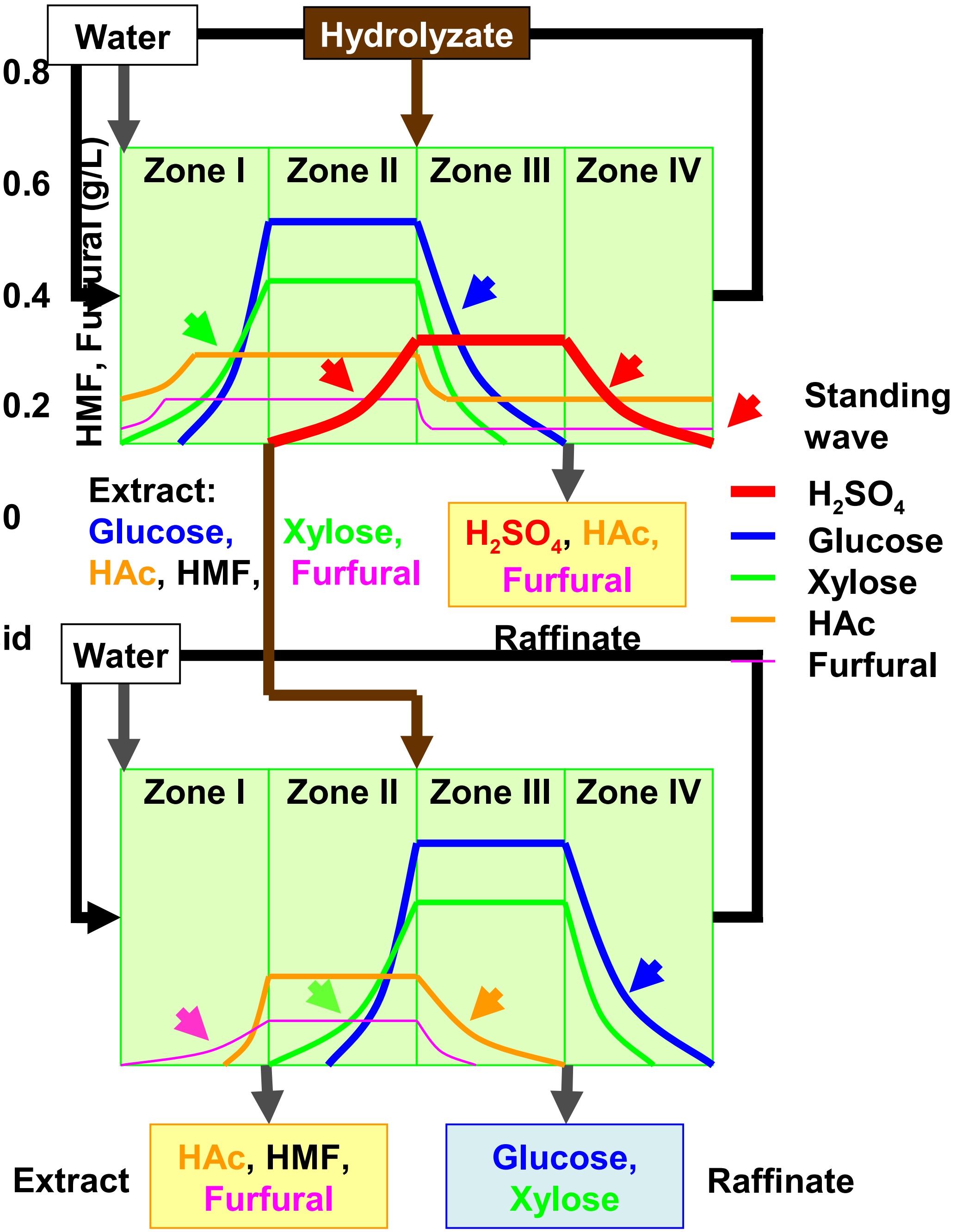
	Feed	Regeneration	
No	mL/min	Conc.	pH*
#1	15	0.3M NaOH	7
#2	5	0.3M NaOH	7
#2	15	0.3M NH_4OH	9

* final pH

DOWEX 99 Tandem SMB

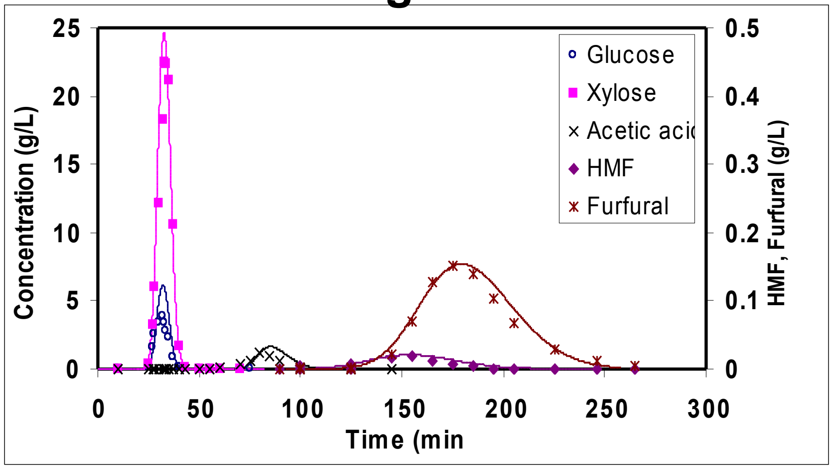


- Elution sequence:
  - H_2SO_4
  - Sugars (Glucose … Xylose)
  - HAc, HMF, Furfural
- Sugars – Linear isotherms
- Water for desorbent
- 4+5 SMB uses 0.3N HCl



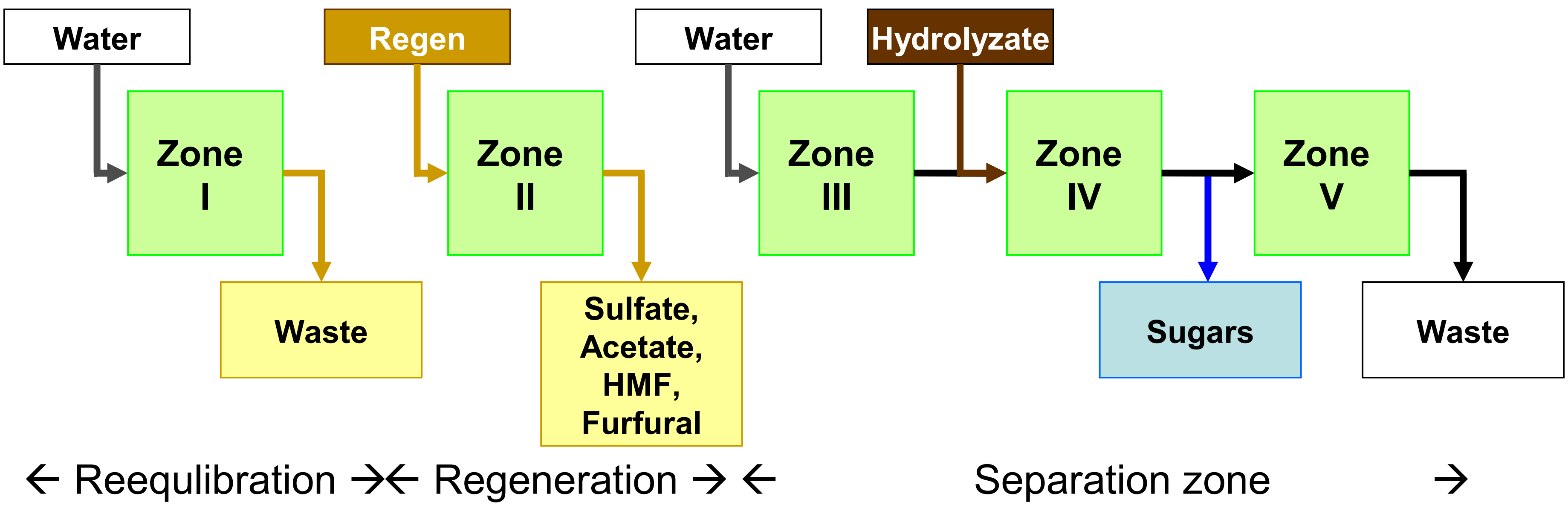
5-zone Non-isocratic PVP SMB

Batch Chromatogram

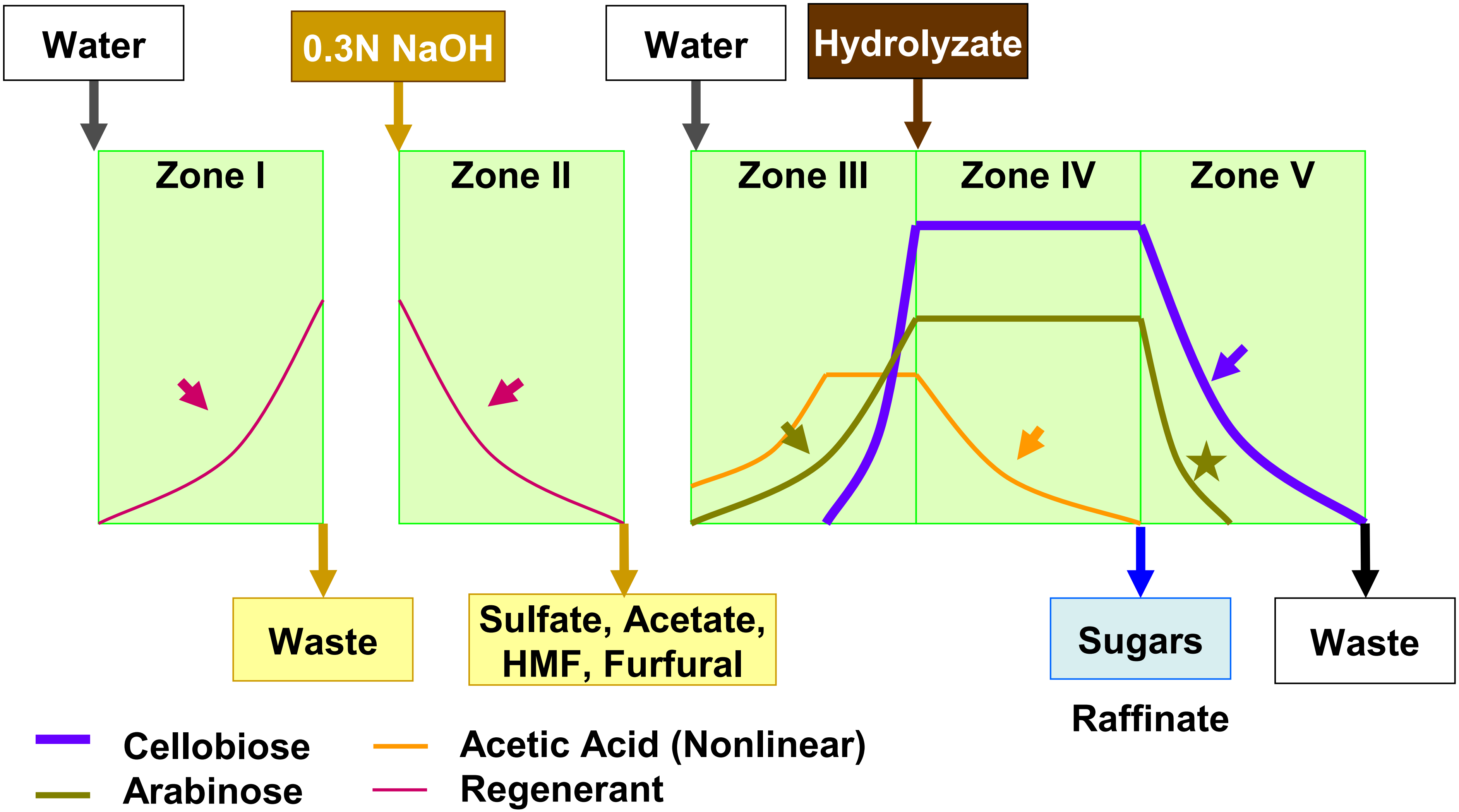


- Elution sequence:
  - Sugars (Cellobiose … Arabinose)
  - Impurities (HAc, HMF, Furfural, H_2SO_4)
- Sugars - Linear isotherms
- HAc, HMF, Furfural, H_2SO_4 – Nonlinear isotherms
- 0.3N NaOH regenerant
- Water desorbent

5-zone Non-isocratic Open-loop PVP SMB

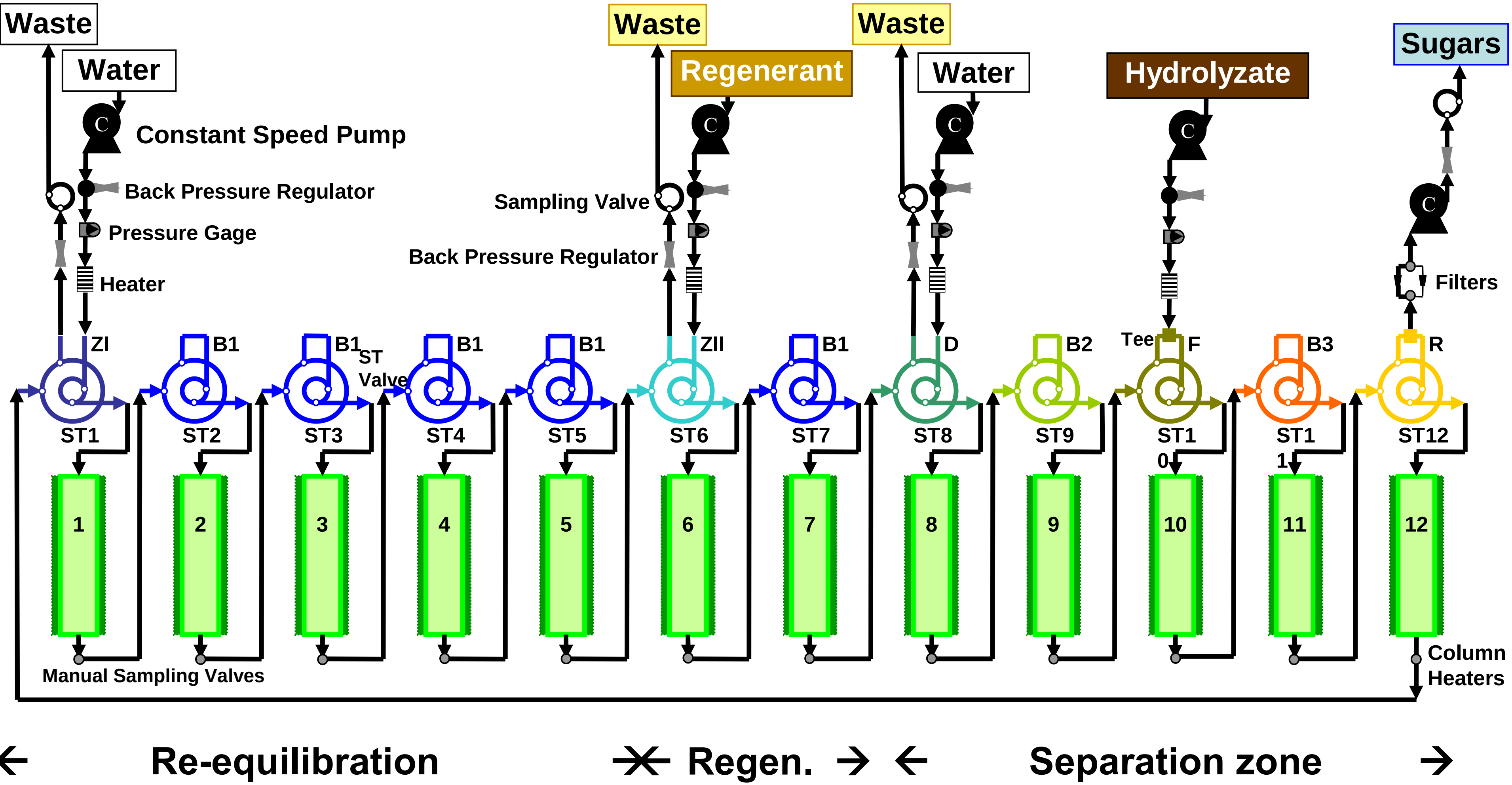


Standing Wave Design: 5-zone PVP SMB



Apparent "*a*" of acetic acid obtained from shock wave velocity of acetic acid from frontal simulation of feed

Experimental Setup: 5-2-2-2-1 PVP-SMB

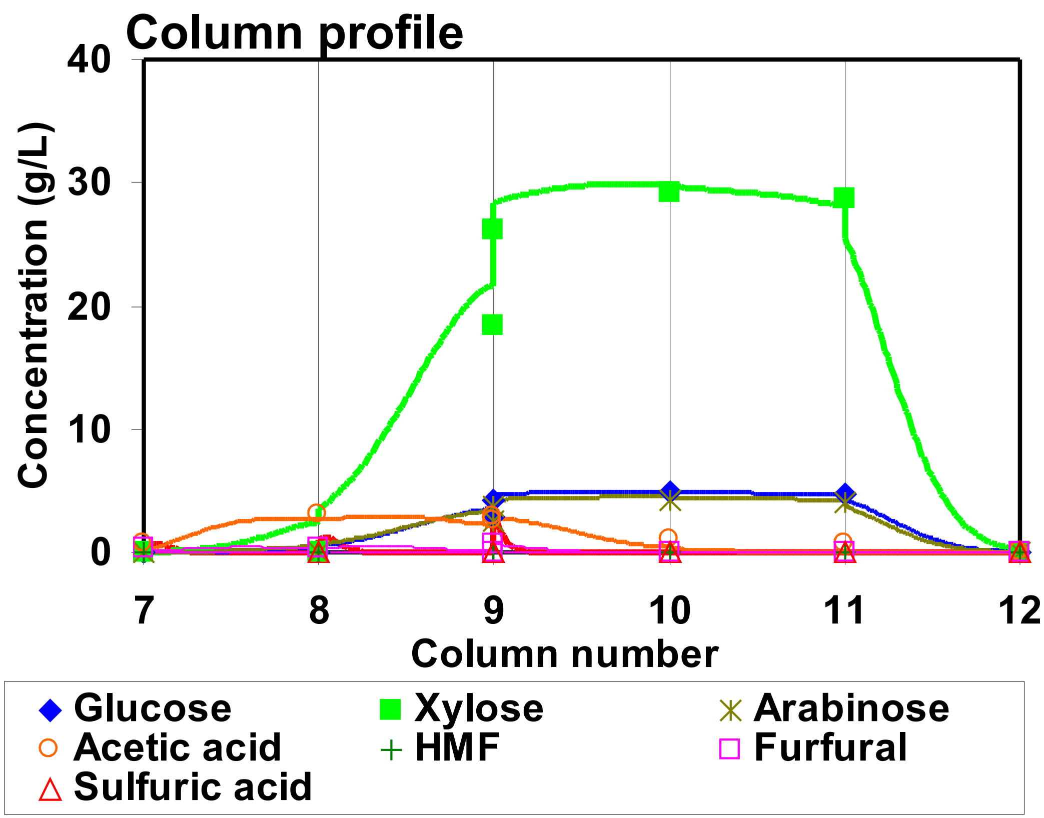


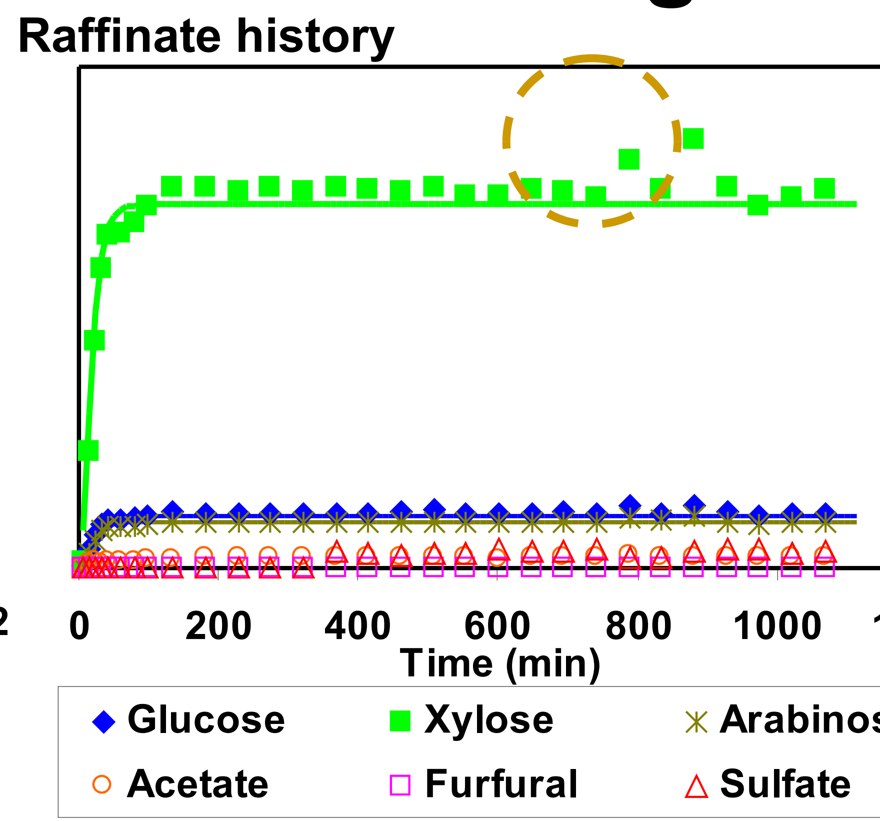
Column: 2.69 cm ID x 30.5 cm L

Temperature: 65°C (Reduces viscosity, prevent growth)

HPLC Assays: See Xie et al., Ind. Eng, Chem. Res. 2005, 44, 6816.

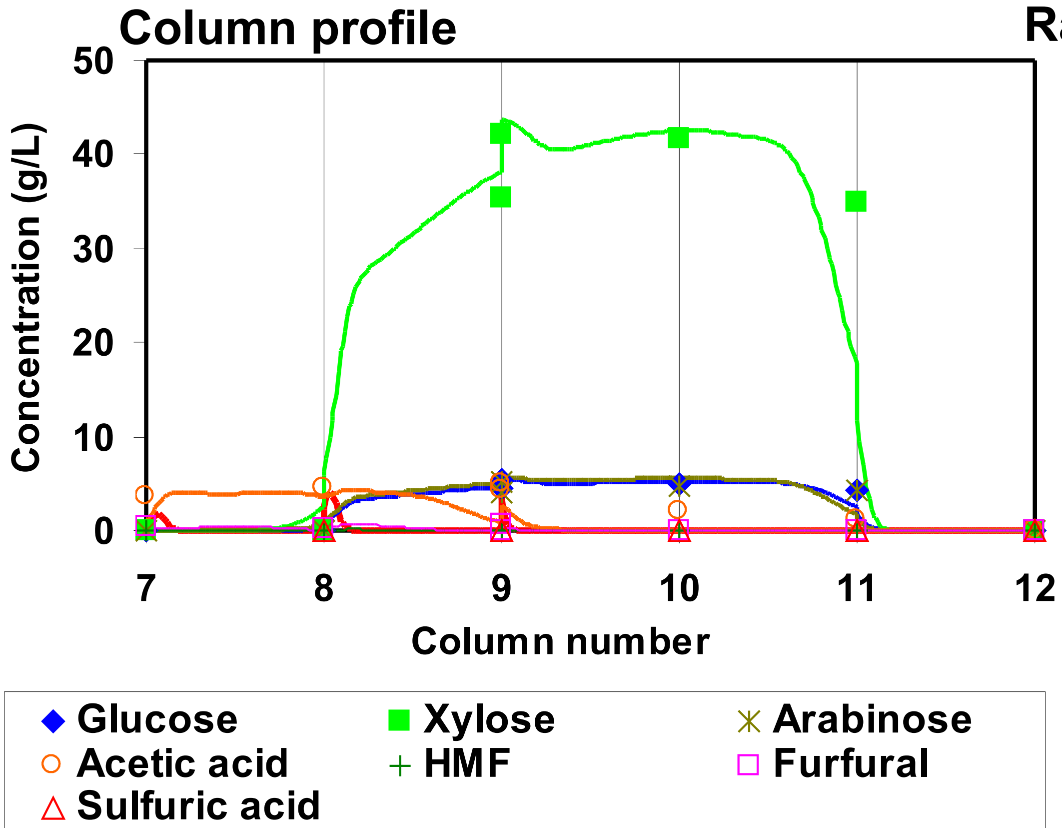
SMB Run 1: Validate Model & Design

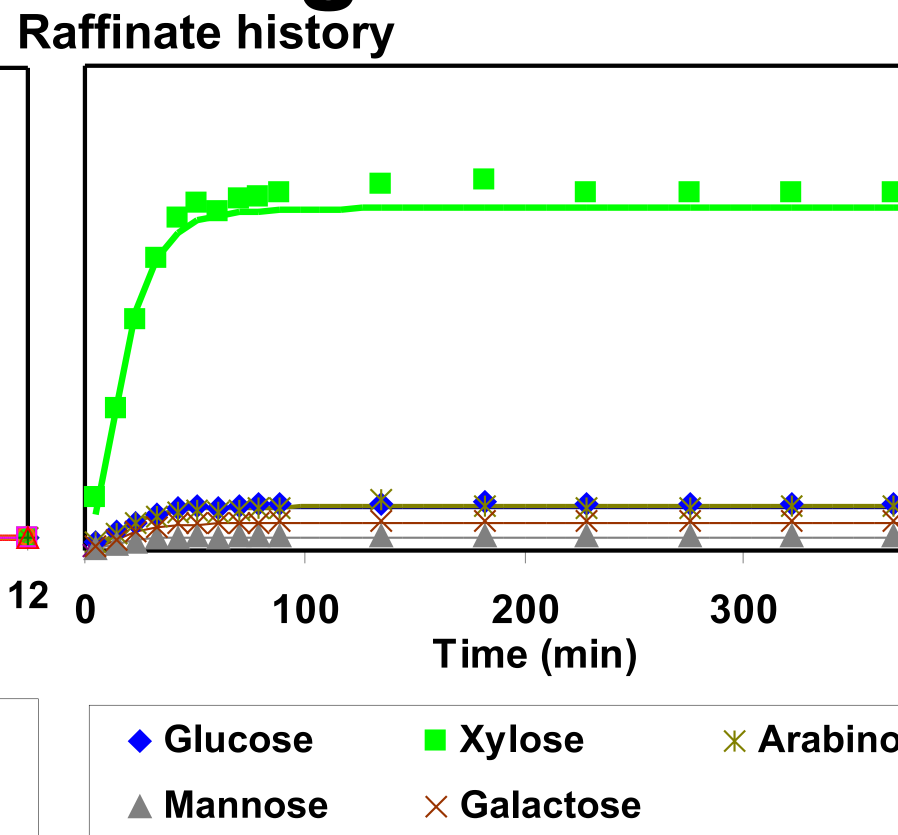




- Feed #1 (Less sugars) at 15 mL/min
- 0.3M NaOH as regenerant
- Reequilibrate to pH 7.0
- Fluctuations due to precipitate formation – use filter
- Raffinate at 94.5% purity & 99.5% yield
- Purity loss due to acetate and sulfate salts

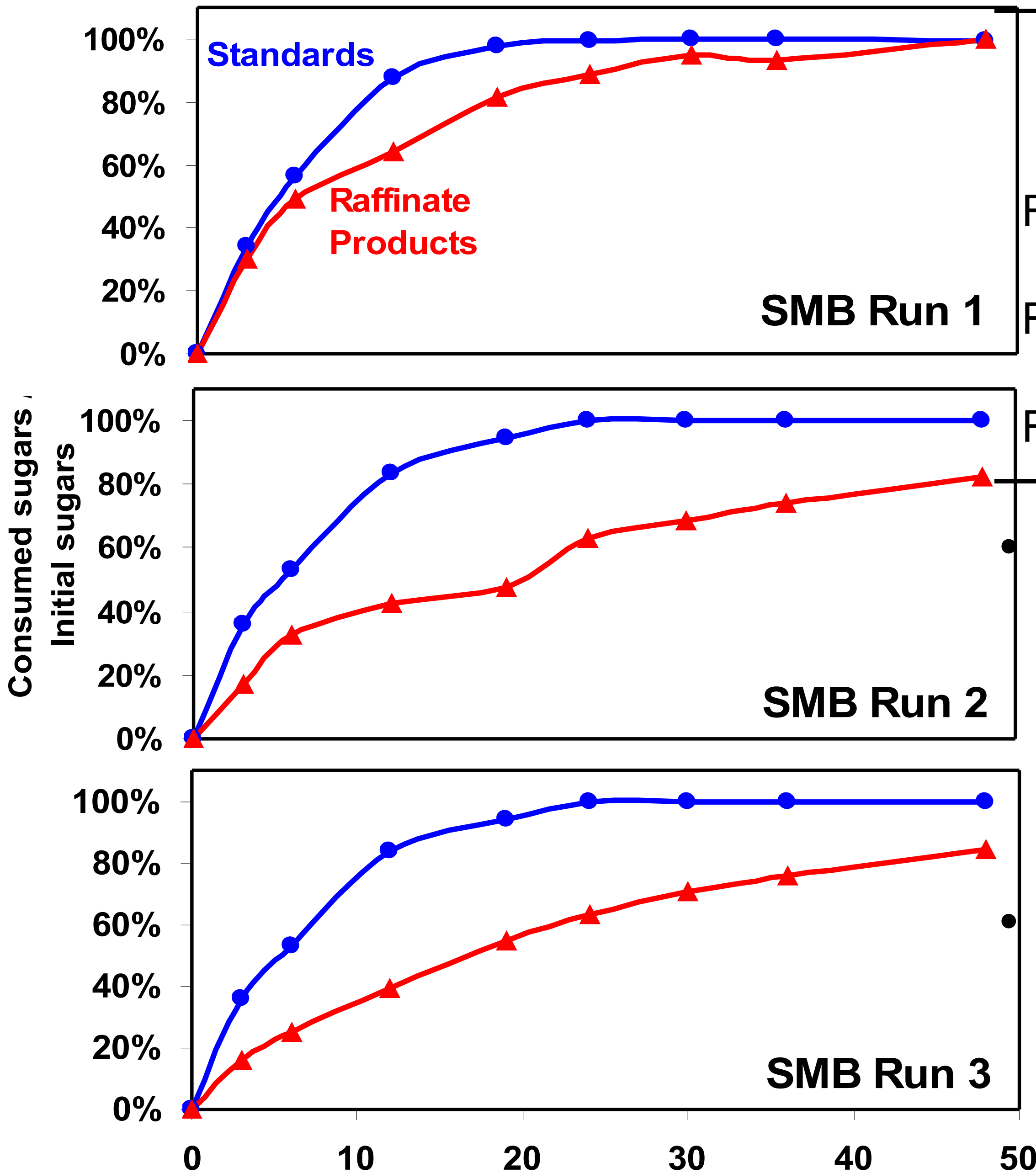
SMB Run 3: Test New Regeneration





- Feed #2 (higher conc. of sugars) at 15 mL/min
- 0.3M NH_4OH as regenerant
- Re-equilibrate to pH 9.0 (not pH 7, to reduce cost)
- Raffinate at 94.0% purity & 100% yield
- SMB performance unaffected by changes

Fermentation Test of Raffinate Sugars



	% Sugar Fermented in 48 hrs	Ethanol Yield
Run 1	98	0.42
Run 2	85	0.32
Run 3	87	0.36

- Feed #2 (Runs 2 & 3) has higher sugars concentrations and probably higher unknown impurities too
- Unknown impurities may adversely affect fermentation

Comparison of SMB Results

	Run 1	Run 2	Run 3
Purity (%)	94.5	93.4	94.0
Yield (%)	99.5	99.7	100.0

- Lower purities because unanticipated acetate and sulfate co-eluted with sugars
  - Discounting salts results in 99+% purities
- Fermentability: Run 1 (Feed #1) >> Runs 2 & 3 (Feed #2)
- Optimal 5-zone PVP SMB for 50 gal feed/min
  - 10% Dilution (Lab exp at 20%)
  - $0.027 / gal feed (21% lower than early estimate)

Five Zone SMB for Sugar Recovery Summary

- Model based approach applied successfully
- Standing wave design for ten-component separation validated
- 5-zone open-loop V-SMB validated
- 6 sugars isolated from 10-identifiable-component feedstock with high purity and high yield

Conclusions

- SMB has higher yield, purity, throughput, and requires less solvent than batch chromatography.
- Conventional SMB technologies are limited to binary, isocratic, four-zone separations. Transient phenomena are not well understood.
- Large number of parameters to be specified and optimized in SMB.

Conclusions

- Purdue SMB technologies
  - Software tools for design, simulation, and optimization.
  - Versatile SMB equipment for multi-component separation.
- Used in developing high purity, high yield separation processes for the purification of biochemicals and pharmaceuticals.

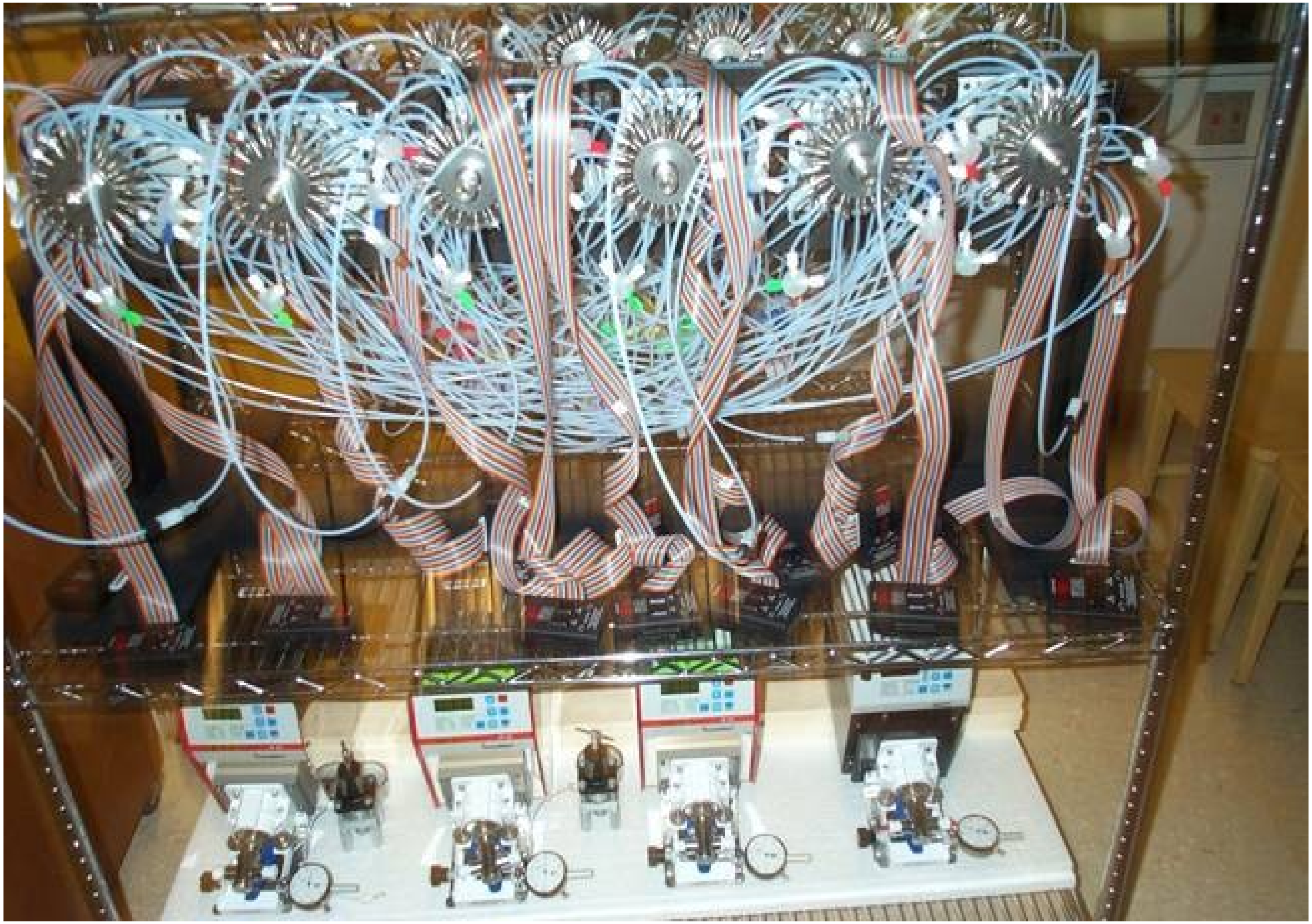
Acknowledgements

- Dr. N. Ho, Laboratory of Renewable Resources Engineering, Purdue University for fermentation test s of sugars recovered from five-zone SMB
- 21st Century Indiana Research and Technology Fund (28)
- Department of Energy (DE-FC36-01GO11071)
- Purdue TTI-IRL (NSF IGERT 9987576)
- SWD: Z. Ma, Y. Xie, K.B. Lee
- VERSE: R. Whitely, Y. Xie
- V-SMB equipment: C. Chin
- Biofuel: Y. Xie, C. Chin, K. B. Lee, D. Phelp

Motivation for V-SMB

- *Existing SMB systems were designed for binary, isocratic separation.*
- *They have limited column, zone, pump and solvent configurations.*
- *The columns rotate in the ISEP system which is impractical in production scale.*
- *They cannot accomplish online decoupled regeneration.*
- *They cannot implement optimal temperature in each zone*

Versatile SMB Prototypes



Comparison of SMB Units

	Calgon Carbon (ISEP)	UOP (1SD1S)	US Filter (1SD1C)	UOP & Novasep (Two-Way)	Purdue Versatile SMB
Columns	Rotate	Stationary	Stationary	Stationary	Stationary
Column Expansible	No	No	Yes	Yes	Yes
Contamination	None	Substantial	Some	Substantial	None
Multiple Zones	Good	Good	Limited	Excellent	Excellent
Multiple SMB Schemes	No	No	No	Potential	Yes
Variable Zone Length	No	Potential	Potential	Yes	Yes
Online Decoupled Regeneration*	No	No	No	No	Yes

SMB vs. Plant-Scale Batch SEC for Insulin Purification

	SMB	Plant-Scale Batch
Overall yield (%)	> 99.0	< 90
Overall throughput (L/hr/100L BV)	1.2	< 0.3
Overall solvent consumption (L/Kg BHI)	42.0	> 120