Continuous Chromatography: Simulated Moving Bed Systems and Operation

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SED Group Meeting Presentation

History of Chromatographic Technology

- 1903, M.S. Twsett, coined ‘Chromatography’ (writing with colors), separation of chlorophyll substances
- 1930, Lederer & Kuhn, separation of carotin & zeaxanthin
- 1940’s, GC introduced
- 1950’s TLC & Size Exclusion Chromatography (SEC) developed
- 1960’s, HPLC introduced
- 1970’s, commercial availability of reverse phase (RP) HPLC columns
- 1980’s, HPLC developed for process scale separations, SFC introduced
- 1990’s, process scale enantioseparation via HPLC, SMB developed
- 2000-present, Capillary Electrochromatography (CEC), advanced SMB operation

Ditz, R. Introduction. *Preparative Chromatography*, Henner Schmidt-Traub; Wiley-VCH: Weinheim, 2005

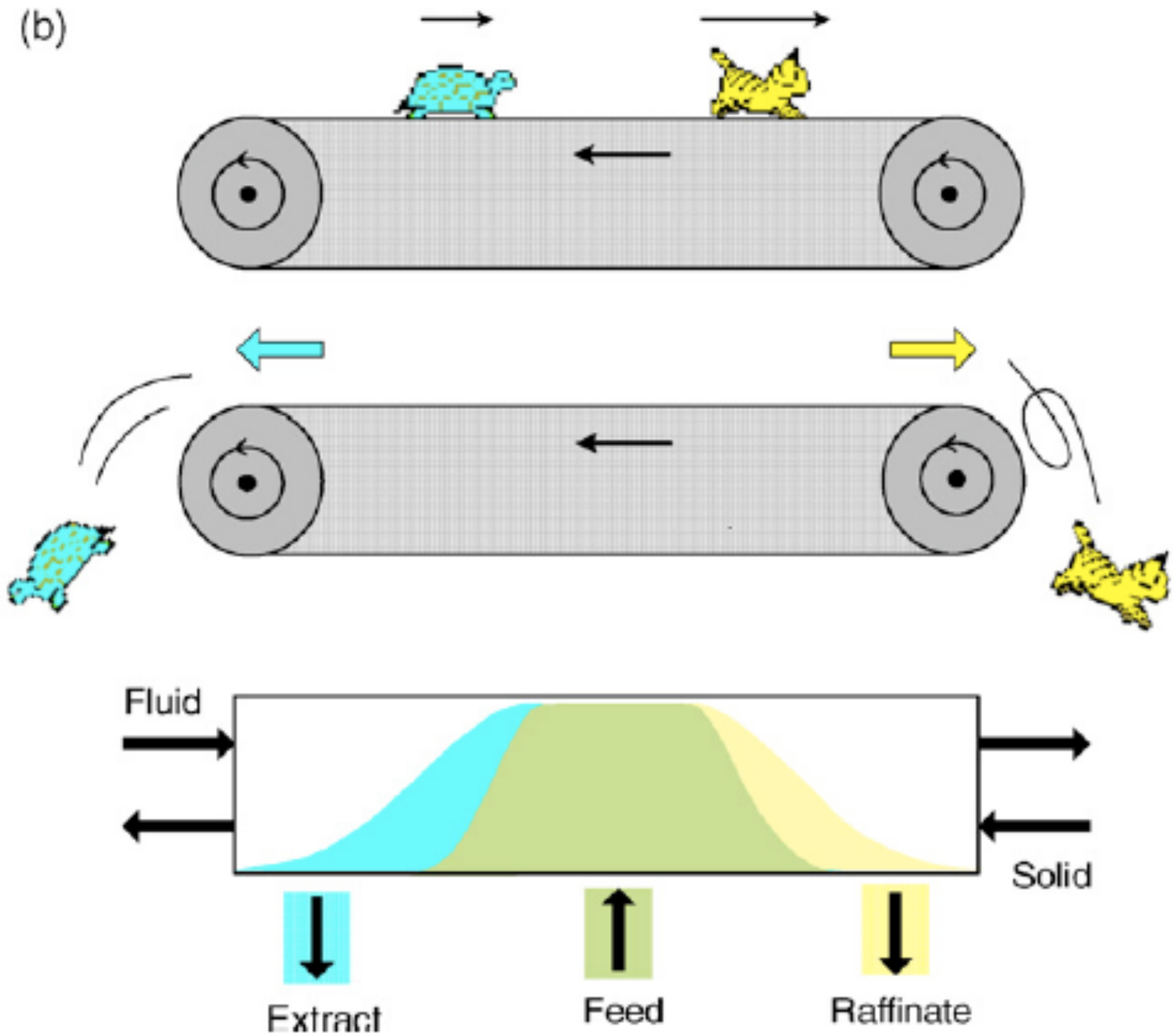
What is Continuous Chromatography (CC)?

- Continuous feed systems vs. multiple recycling batch systems
- Counter-current Chromatography
  - True Moving Bed (TMB)
  - Simulated Moving Bed (SMB)
  - Annular Chromatography (AC, cross current)
- Potential for increased productivity
  - mass of feed processed per unit mass of stationary phase per unit of time

A Summary of Counter-Current Chromatography

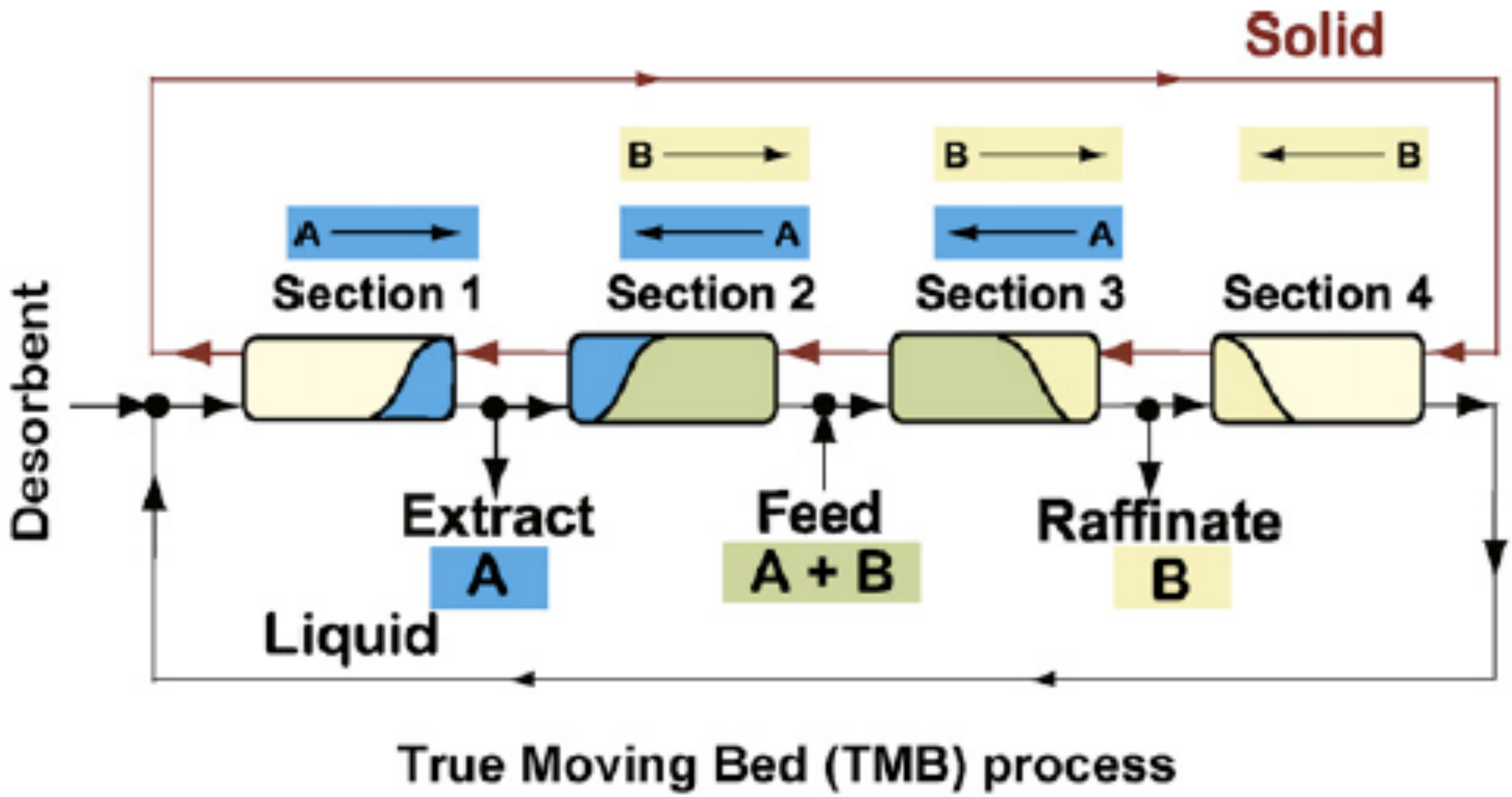
A kitten and a tortoise are placed in the middle of a treadmill

Both animals move against the treadmill in the same direction at different velocities



Mazzotti. et al., *J. Chromatogr. A* **2009**, *1216,* 709-738

True Moving Bed System



Problem with TMB System

How do you move the stationary phase without breaking it?

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Components of an TMB System

- Section 1 – Contains extract component, must be eluted off stationary phase
- Section 2 – Contains both extract and raffinate, raffinate must be removed
- Section 3 – Contains both extract and raffinate, extract must remain adsorped
- Section 4 – Contains raffinate, raffinate must remain adsorped
- Each section may operate and different flow rates
- The ratio of liquid flow rate to solid flow rate in each section is critical for separation

Components of an TMB System

- Feed Stream – Q_F, Typically a binary component mixture dissolved in eluent solution
- Raffinate Stream – Q_R, Contains the less strongly adsorbed component, B, smaller t_r
- Eluent Stream – Q_{el}, Isocratic composition
- Extract Stream – Q_{Ext}, Contains the more strongly adsorbed component, A, larger t_r
- Each stream can operate at different flow rates

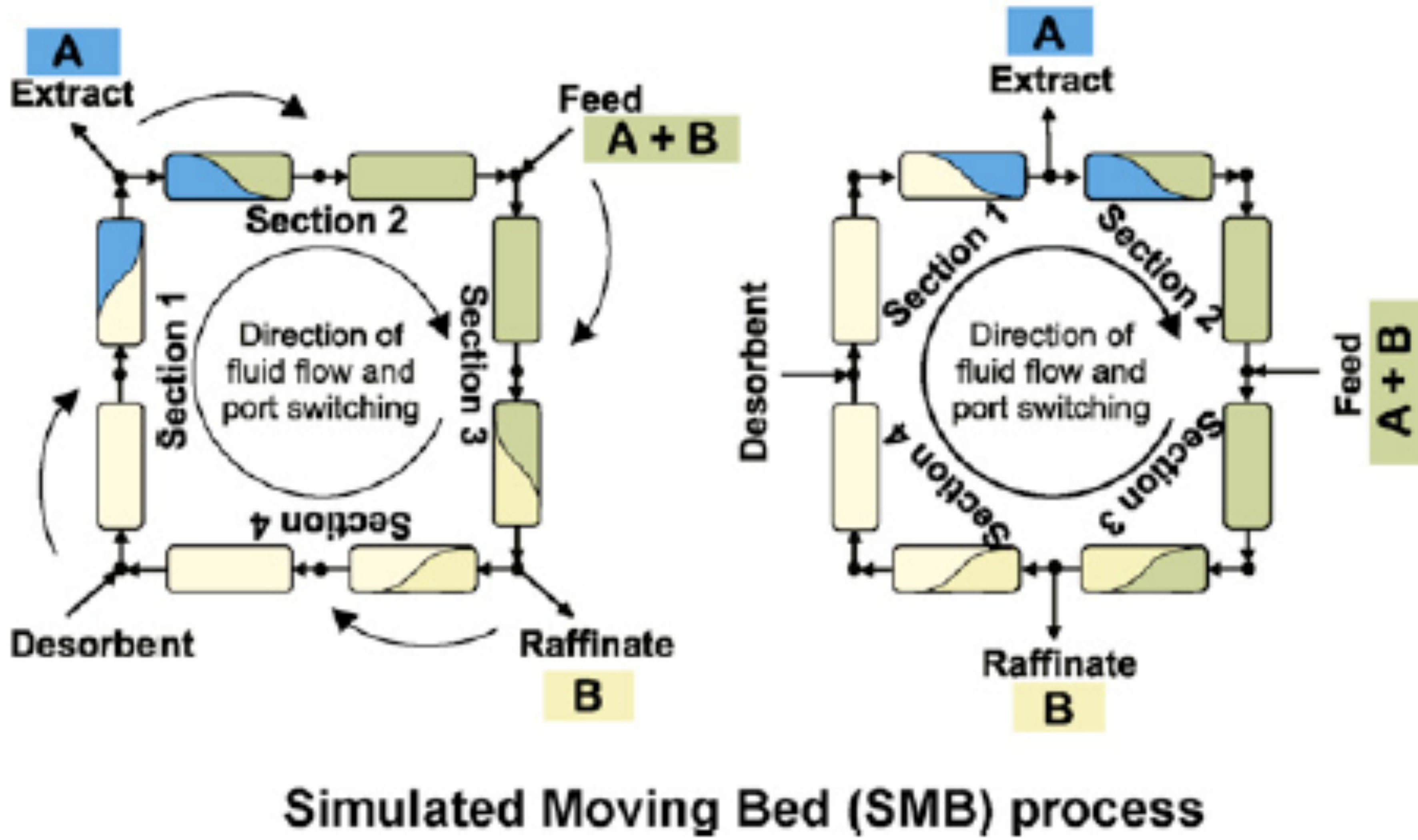
Simulated Moving Bed Chromatography

- Closest approximation to a TMB system
- Like TMB, limited to mainly binary mixtures and isocratic elutions
- First system used for the separation of petrochemicals*. Later applied to saccharide separation

*Broughton, D. B.; Gerhold, C. G. Continuous Sorption Process Employing Fixed Bed of Sorbent and Moving Inlets and Outlets. U.S. Patent 2,985,589, May 23, 1961

SMB System Overview

Ports switch in the same direction synchronously at a predetermined switch time, *t**



Mazzotti. et al., *J. Chromatogr. A* **2009**, *1216*, 709-738

Balance Flow Rates

- $Q_I = Q_{IV} + Q_{El}$
- $Q_{II} = Q_I - Q_{Ext}$
- $Q_{III} = Q_{II} + Q_F$
- $Q_{IV} = Q_{III} – Q_R$
- $Q_{Ext} + Q_R = Q_F + Q_{El}$

$$Q_s = \frac{V(1-\epsilon)}{t^*}$$

solid flow rate, related to switch time, column volume, and the stationary phase void fraction

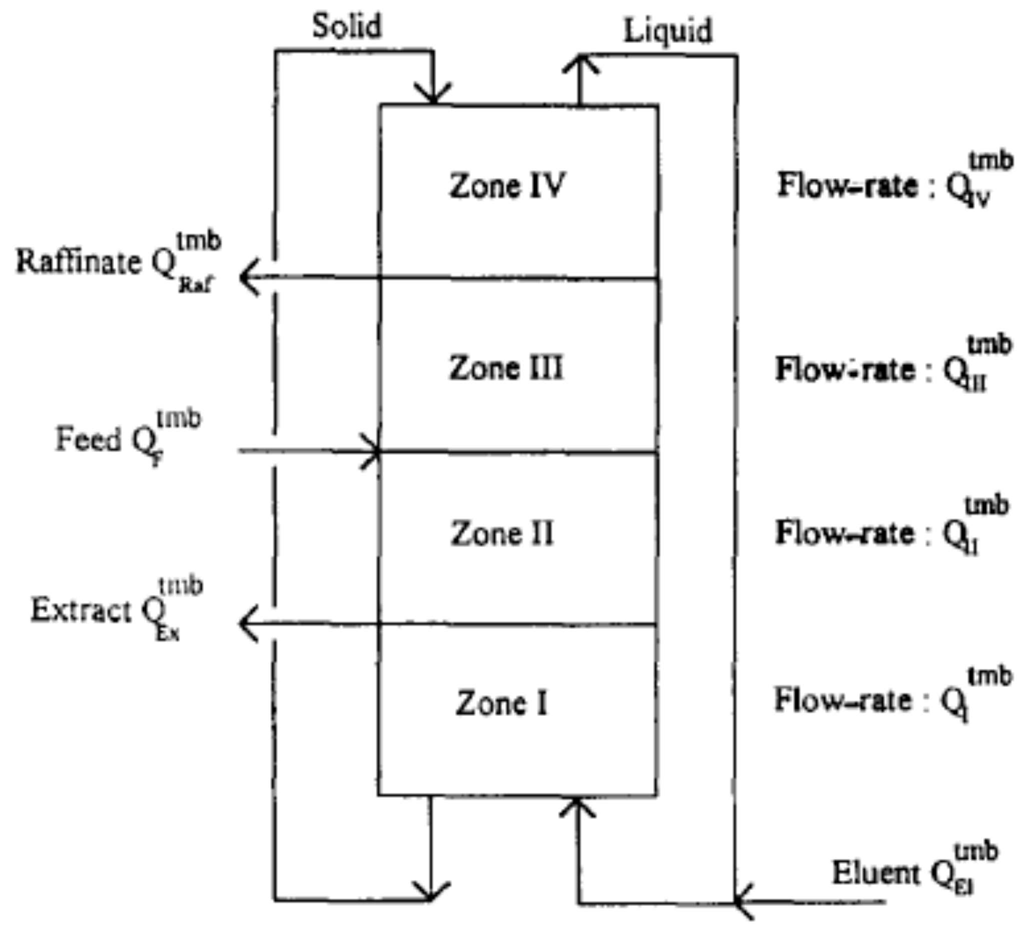


Fig. 1. Schematic representation of a four-zone TMB.

Nicoud, R. M.; Charton, F. *J. Chromatogr. A* **1995**, *702*, 97-112

Determining SMB Operational and Design Parameters

- Constraints set by the desired productivity, purity, and acceptable column pressure drop
- Account for non-linear competitive adsorption profiles. (Determine experimentally)
- Determine feed concentration, number of columns per section, column length and diameter, adsorbent particle size. (Design)
- Determine section flow rates, system pressure, temperature and column switch time. (Operation)

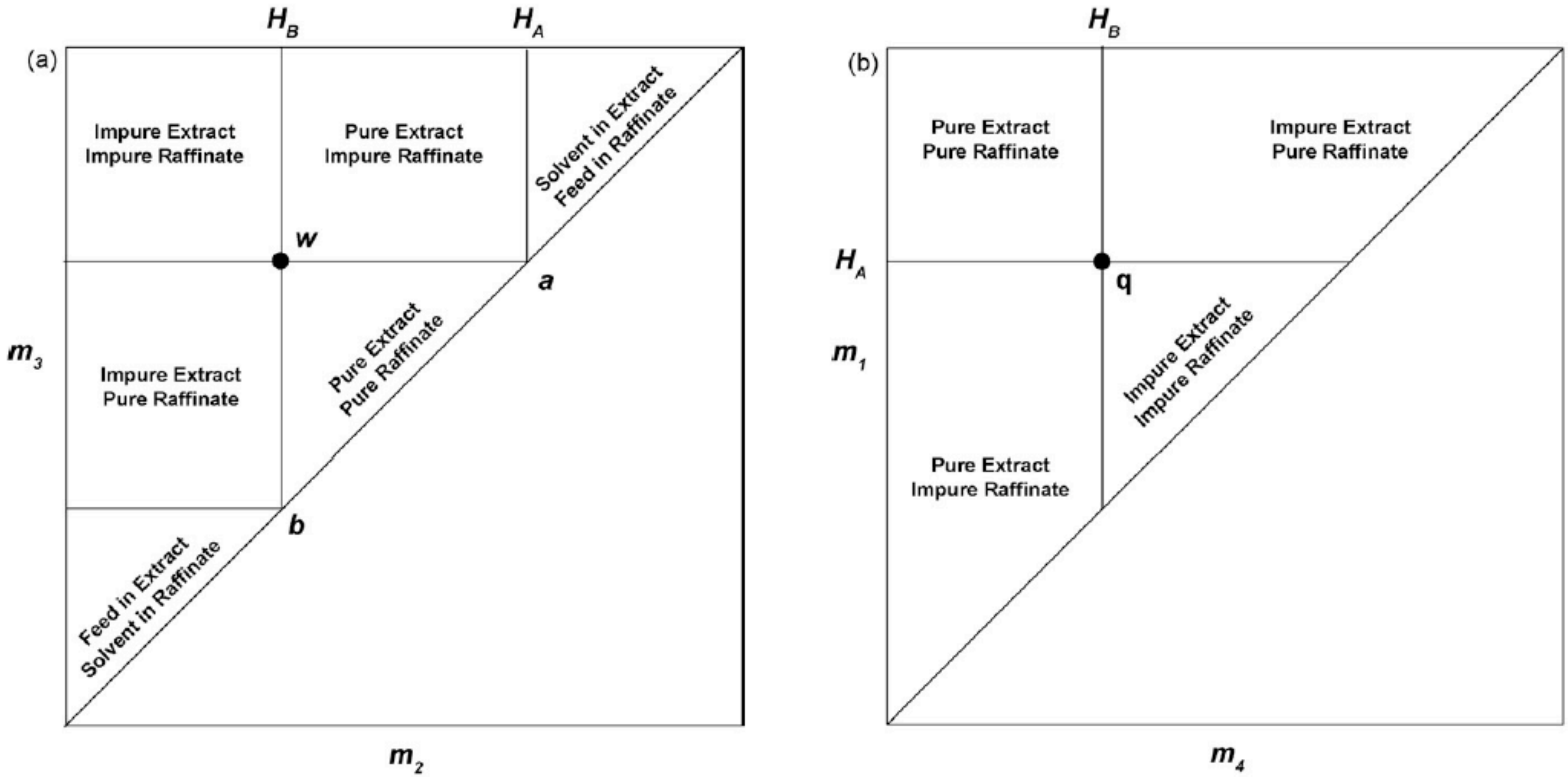
Conditions to Satisfy

$$m_j = \frac{Q_j t^* - V\epsilon^*}{V(1-\epsilon^*)} = \frac{\text{net fluid flow rate}}{\text{net sold flow rate}}$$

- $H_A \leq m_1$
- $H_B < m_2 \leq H_A$
- $H_B \leq m_3 \leq H_A$
- $m_4 \leq H_B$
- Q_j = SMB section flow rate
- ε^* = column void fraction
- V = column volume

- All variables are dimensionless (scale independent)
- Henry constants are determined experimentally (usually from feed solution)

Triangle Theory



These diagrams represent linear adsorption isotherms (very uncommon)
For most binary mixtures the graphical representation of operating conditions can become highly distorted

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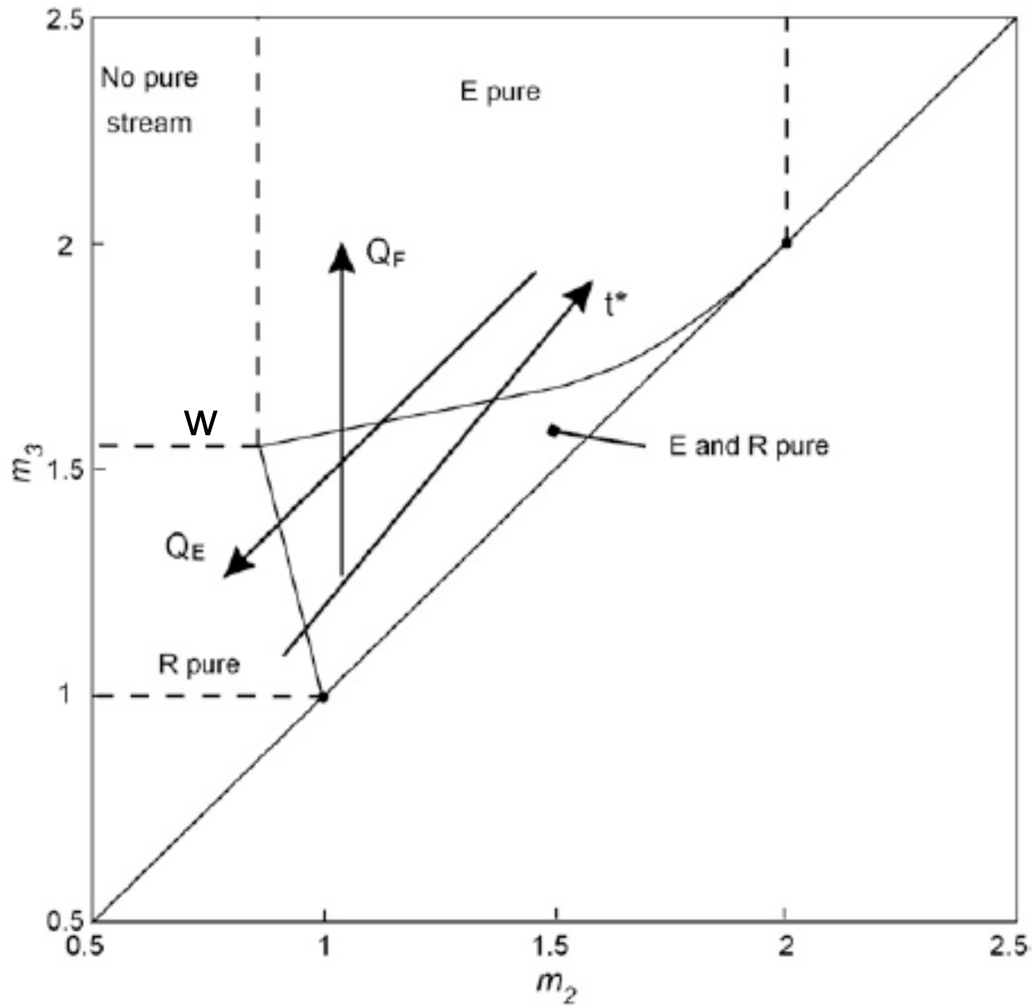
Triangle Theory

- To maintain high productivity, operating conditions should keep (m_2, m_3) coordinates as far as possible from the diagonal (m_2=m_3)
- (m_3-m_2) is related to the feed flow rate, Q_F
- Increasing feed concentration distorts the shape of the optimal separation region (point w migrates towards m_2=m_3)
- The boundaries in the plot (lines shown) represent complex equations derived from determining the specific adsorption isotherm of the mixture.



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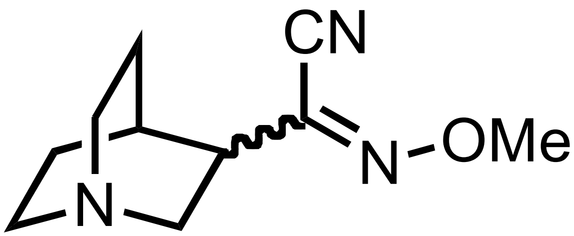
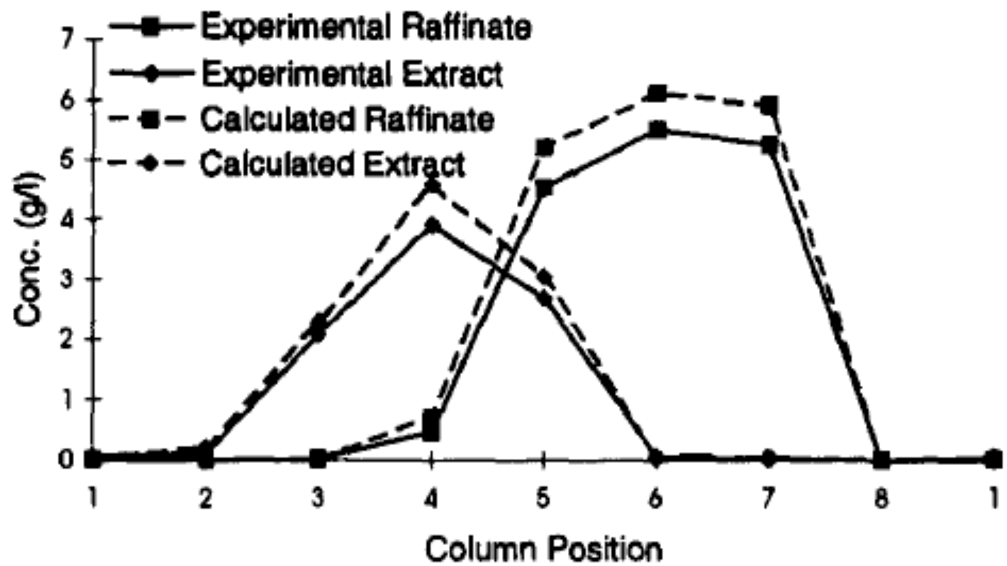
Case Study: Enantioseparation of a Drug Candidate via SMB



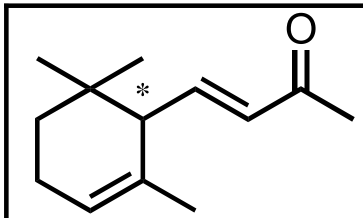
- Partial agonist for muscarinic receptors
- α = 1.8 on ChiralPak AD on analytical scale
- Spare SMB column was used for optimization

- Adsorbtion isotherm determined by measuring enantiomer retention time and the amount of racemic compound loaded on column
- 125 g rac./day
- 8 columns, 2/2/2/2 configuration, 26x105 mm, ChiralPak AD (20 μm)
- Raffinate – 99.5%ee
- Extract – 97.8%ee
- Total Recovery – 98%



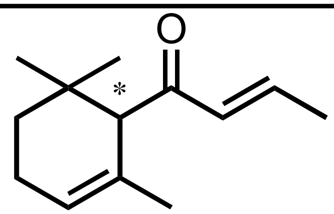
Guest, D. W. *J. Chromatogr. A* **1997**, *760*, 159-162

SMB enantioseparation of α-ionone and α-damascone



α-ionone

- Racemate produced industrially from acetone and citral
- Enantioselective via racemic epoxide precursor
- Threshold concentrations for (R)-α-ionone 0.5-5.0 μg/kg, (S)-α-ionone 20-40 μg/kg



α-damscone

- Racemate produced industrially from allyl Grignard and α-cyclogeranic acid methyl ester
- Enantioselective route via stoichiometric chiral amino alcohol
- (R)-α-damascone 100 μg/kg, (S)-α-damascone 1.5 μg/kg

- Both enantioselective synthesis routes have issues with scale-up
- SMB can provide a convenient alternate for resolution
- α-ionone α = 1.6, α-damascone α = 1.3

Morbidelli et al. *Flavour Fragr. J.* **2002**, 17, 195-202

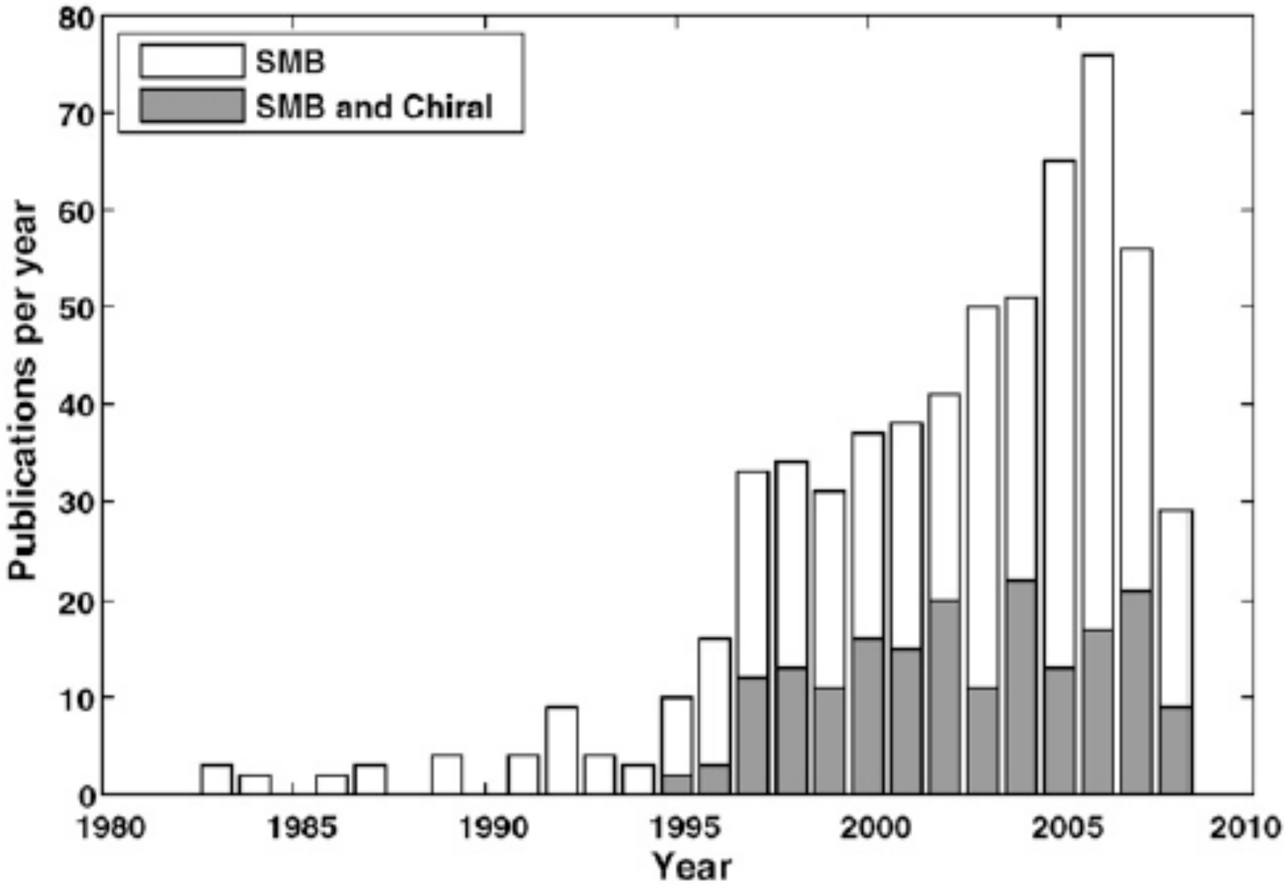
SMB enantioseparation of α-ionone and α-damascone

- 8 columns, Nucleodex-β-PM®, Macherey-Nagel, 12.5 x 1.0 cm, 10 μm, 2/2/2/2 configuration
- Eluent strength 70:30 MeOH:H_2O @ 10°C
- Void fraction determined experimentally by MeOH injection into each SMB column
- Henry constants determined experimentally by the t_r of each enantiomer
- For α-ionone, optimized parameters yield 0.72 g rac./day with 99.9% and 99.2% purity of the S and R enantiomers respectively.
- For α-damascone, optimized parameters yield 0.22 g rac./day with 99.9% and 98.8% purity of the S and R enantiomers respectively
- Parameters optimized only for product purity, productivity remained un-optimized (constant feed concentration)
- The enantioseparation of α-ionone has also been accomplished via GC-SMB and PowerFeed SMB.

Morbidelli et al. *Flavour Fragr. J.* **2002**, 17, 195-202

Prevalence of SMB Separations

Literature References to SMB



- SMB separation has become increasingly prevalent in both commercial and industrial application
- No explanation was given for the decline in SMB reports in 2008.

Mazzotti. et al., *J. Chromatogr. A* **2009**, *1216*, 709-738

Other Modes of SMB Operation

- Several modifications to SMB design and/or operation have been implemented
- All modifications to classical SMB operation have the potential to increase efficiency through increased productivity and/or decreased eluent consumption.
- Useful for reducing the number of columns needed
- Modifications add varying degrees of complexity ($$$) to the SMB system

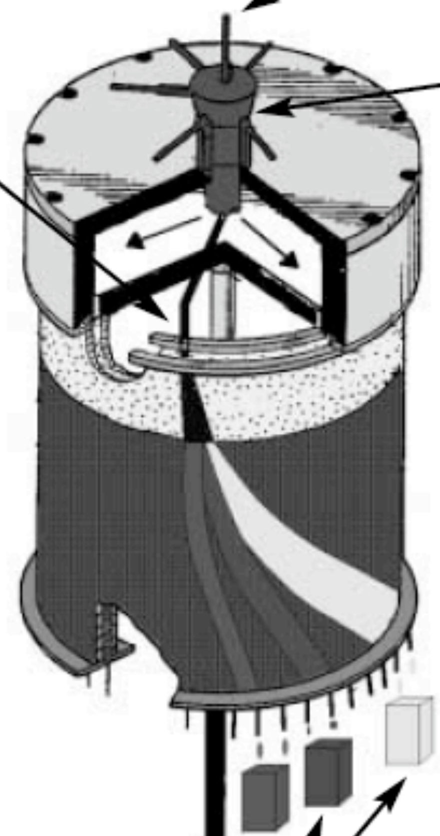
Mazzotti et. al. *Korean J. Chem. Eng.* **2004**, *21(2)*, 454-464

Other Modes of SMB Operation

- **VariCol** – Asynchronous column switching
  - A 1/2/2/1 configuration becomes 1/3/1/1 before going to back to 1/2/2/1
  - Fewer columns, less solvent
- **PowerFeed** – Modulation of flow rates
  - External flow rate changes during operation within a switching interval
- **ModiCon** – Modulation of feed concentration
  - Feed flow rate remains constant, concentration does not.
- **Gradient Elution**
  - Step gradient, high elution strengths in sections I & II.
- **Super-Critical Fluid**
  - Supercritical CO_2 as eluent, elution strength is significantly dependent on system pressure

Seidel-Morgenstern et. al. *Chem. Eng. Technol.* **2008**, 31(6), 826-837

Annular Chromatography

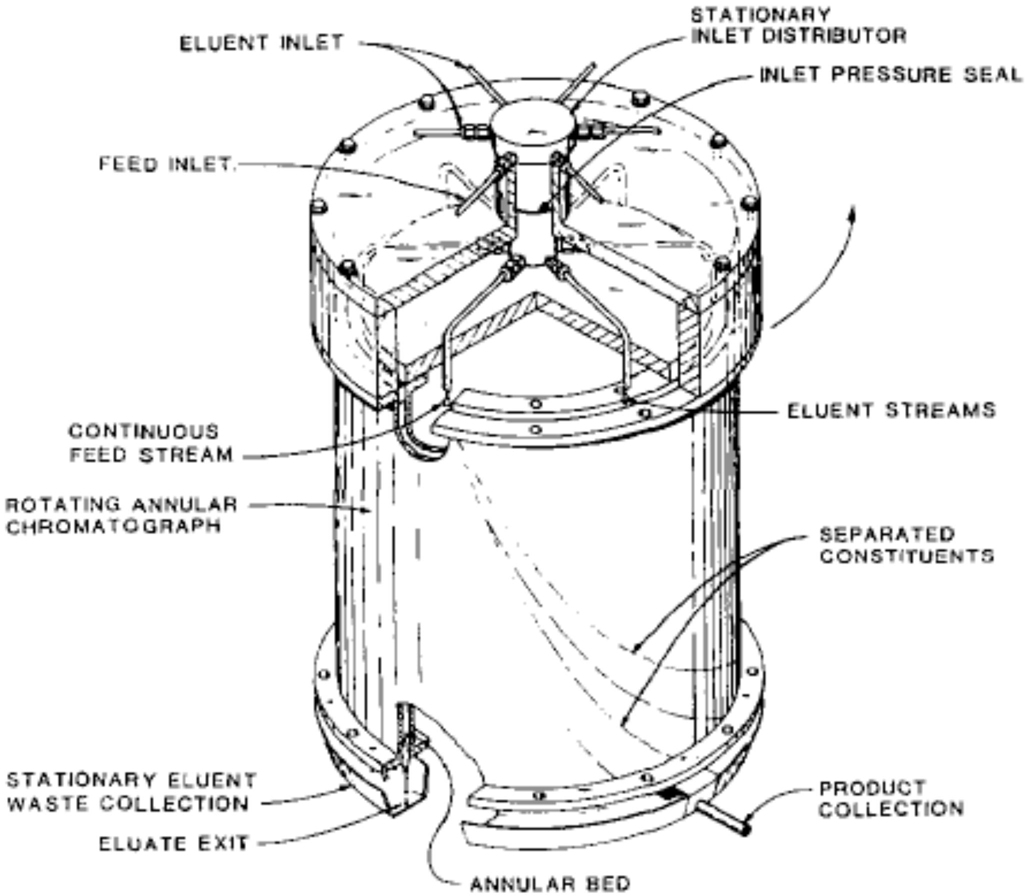


- Operates via cross current of stationary phase with respect to the eluent.
- Advantage of easier operation and less parameter optimization (3) required compared with SMB (5).
- Gradient elution possible as well as multi-component resolutions
- Separation dependent on eluent and feed flow rate, rotation rate, and retention factor
- Disadvantage in the limited selection of stationary phases.

Bench-top Unit

Wolfgang J.; Prior, A. *Adv. Biochem. Eng./Biotech.* **2002**, *76*, 233-255

Desalting of Bovine Serum Albumin via Continuous Annular Chromatography



- Chosen over SMB due to ease of operation
- Feed concentration 10 g/L
- Rotation rate varied between 50° and 150°/hr.
- Feed flow rate 0.3-1.0 mL/min.
- Eluent 4.5 – 23.5 mL/min of aqueous buffer, isocratic
- Stationary phase
  - Toyopearl HW 40F, 30-60 µm, 50Å pore size (size exclusion gel)
  - Length 36 cm, O.D. 12.7 cm, I.D. 11.4 cm
  - Cross-sectional area = 24.6 cm^2
- Rotation rate and eluent rate directly proportional to resolution
- Feed flow rate indirectly proportional to resolution
- BSA collected >98% purity

Bart et. al. *J. Chromatogr. A* **1997**, *763*, 49-56

Conclusions

- SMB & AC systems provide an efficient method for the separation of binary mixtures
- Careful optimization of the design and operational parameters is required for maximum productivity and purity
- When limited to binary mixtures SMB is a superior separation system

Lab-scale SMB systems?

The Semba Octave System for SMB Chromatography. http://sembabio.com/products/octave.html (accessed Jan. 15, 2010)

SMB enantioseparation of α-ionone and α-damascone: Optimized Parameters

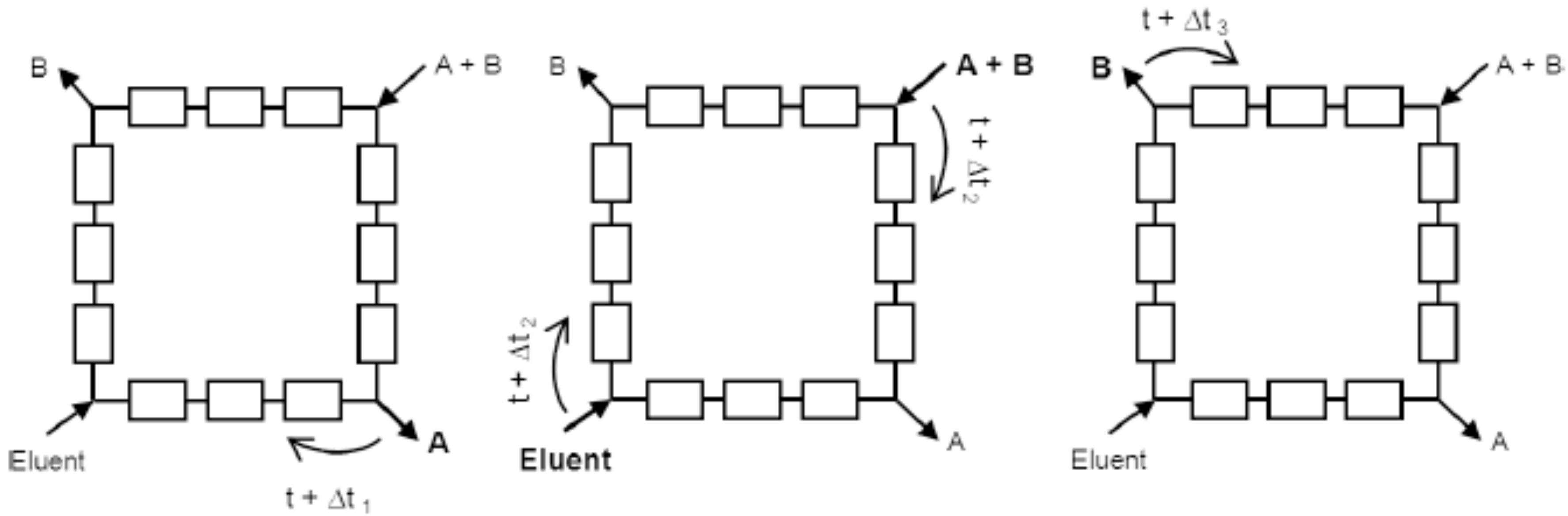
α-ionone: SMB parameters

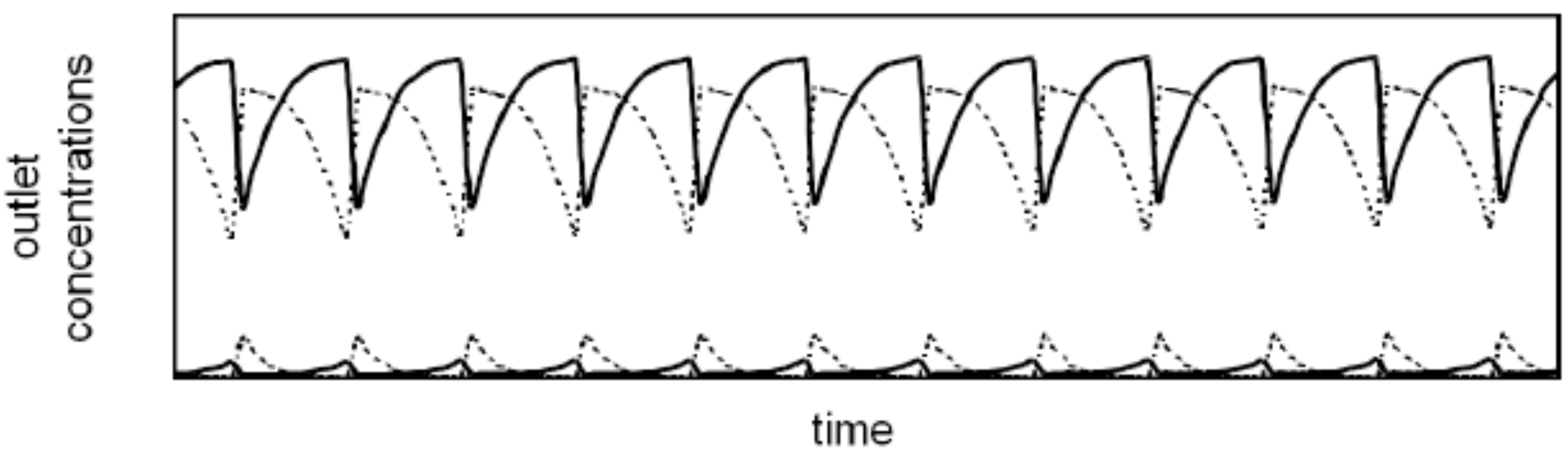
Run	Flow rate (ml/min)				c_T^F	t^*	Operating parameters				Purity		Productivity	P_{max}
	Q_1	Q_2	Q_3	Q_4	(g/l)	(s)	$\overline{m}_1$	$\overline{m}_2$	$\overline{m}_3$	$\overline{m}_4$	P_R	P_E	(g/day)	(bar)
A1	2.00	0.72	0.78	0.12	5.0	1830	14.42	3.72	4.44	−1.10	88.7	99.3	0.43	42
A2	4.00	1.44	1.56	0.24	5.0	930	14.69	3.82	4.55	−1.08	70.0	99.5	0.86	82
A3	4.00	1.45	1.55	0.30	5.0	900	14.15	3.67	4.30	−0.87	75.0	99.3	0.72	83
A4	4.00	1.45	1.55	0.20	5.0	880	13.79	3.54	4.16	−1.29	99.9	99.2	0.72	85
A5	4.00	1.50	1.57	0.25	5.0	860	13.44	3.60	4.10	−1.12	99.9	99.2	0.51	84

α-damascone: SMB parameters

Run	Flow rate (ml/min)				c_T^F	t^*	Operating parameters				Purity		Productivity	P_{max}
	Q_1	Q_2	Q_3	Q_4	(g/l)	(s)	$\overline{m}_1$	$\overline{m}_2$	$\overline{m}_3$	$\overline{m}_4$	P_R	P_E	(g/day)	(bar)
D1	2.00	1.15	1.20	0.20	3.0	840	5.57	2.15	2.57	−1.33	99.9	88.6	0.22	60
D2	2.00	1.15	1.20	0.20	3.0	905	6.15	2.49	2.92	−1.27	99.9	96.0	0.22	60
D3	2.00	1.15	1.20	0.20	3.0	940	6.47	2.67	3.11	−1.24	99.9	98.8	0.22	60
D4	2.00	1.15	1.20	0.20	3.0	965	6.69	2.79	3.24	−1.22	89.2	98.3	0.22	60

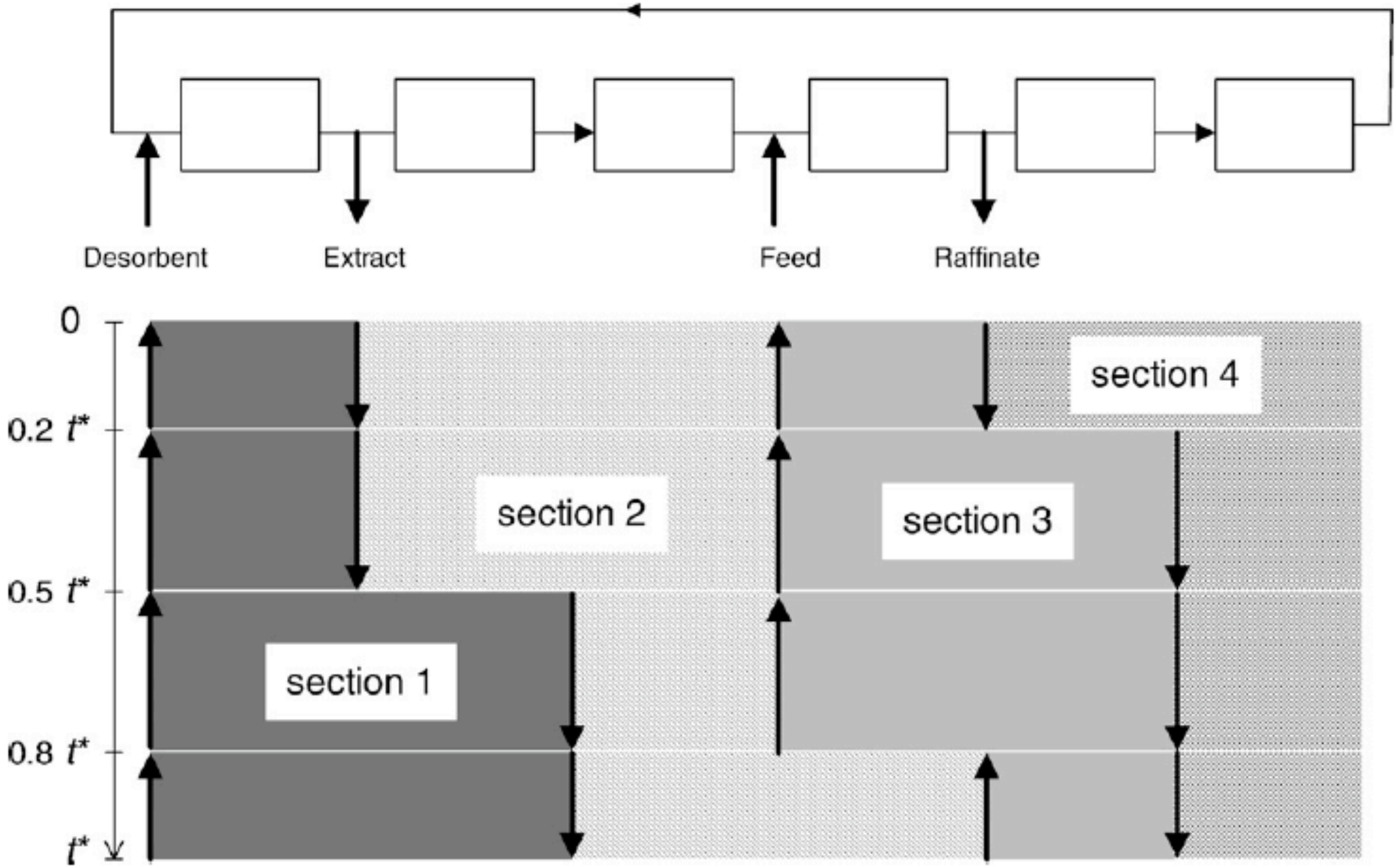
VariCol SMB Process





Seidel-Morgenstern et. al. *Chem. Eng. Technol.* **2008**, *31(6)*, 826-837

VariCol SMB Process



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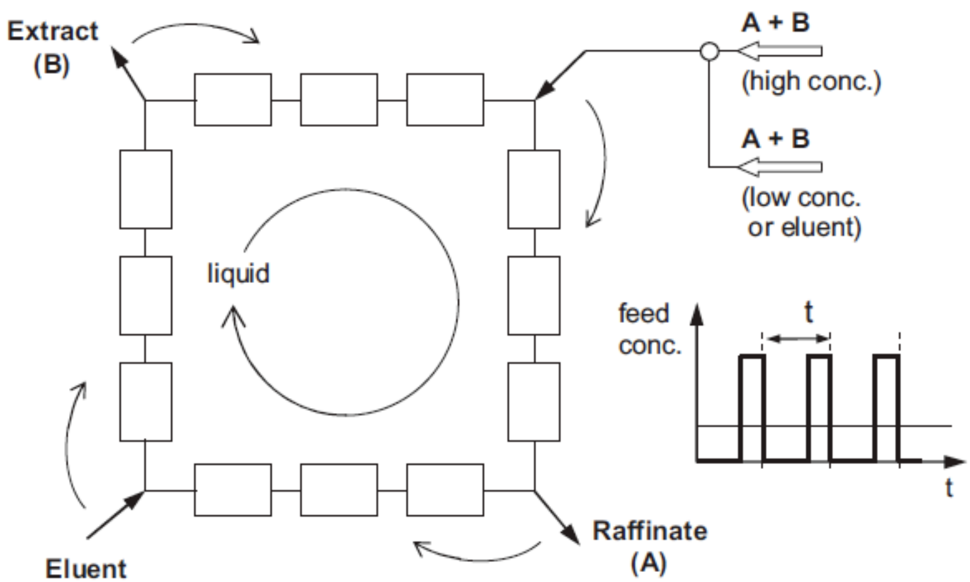
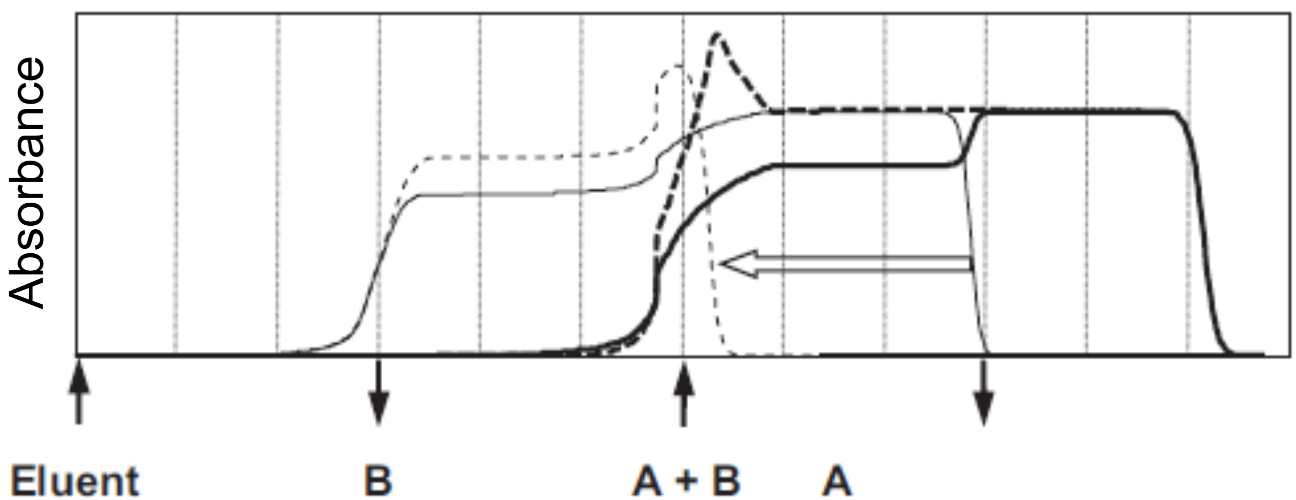
ModiCon SMB Process



Internal concentration profile shows increased resolution by compression of the concentration front



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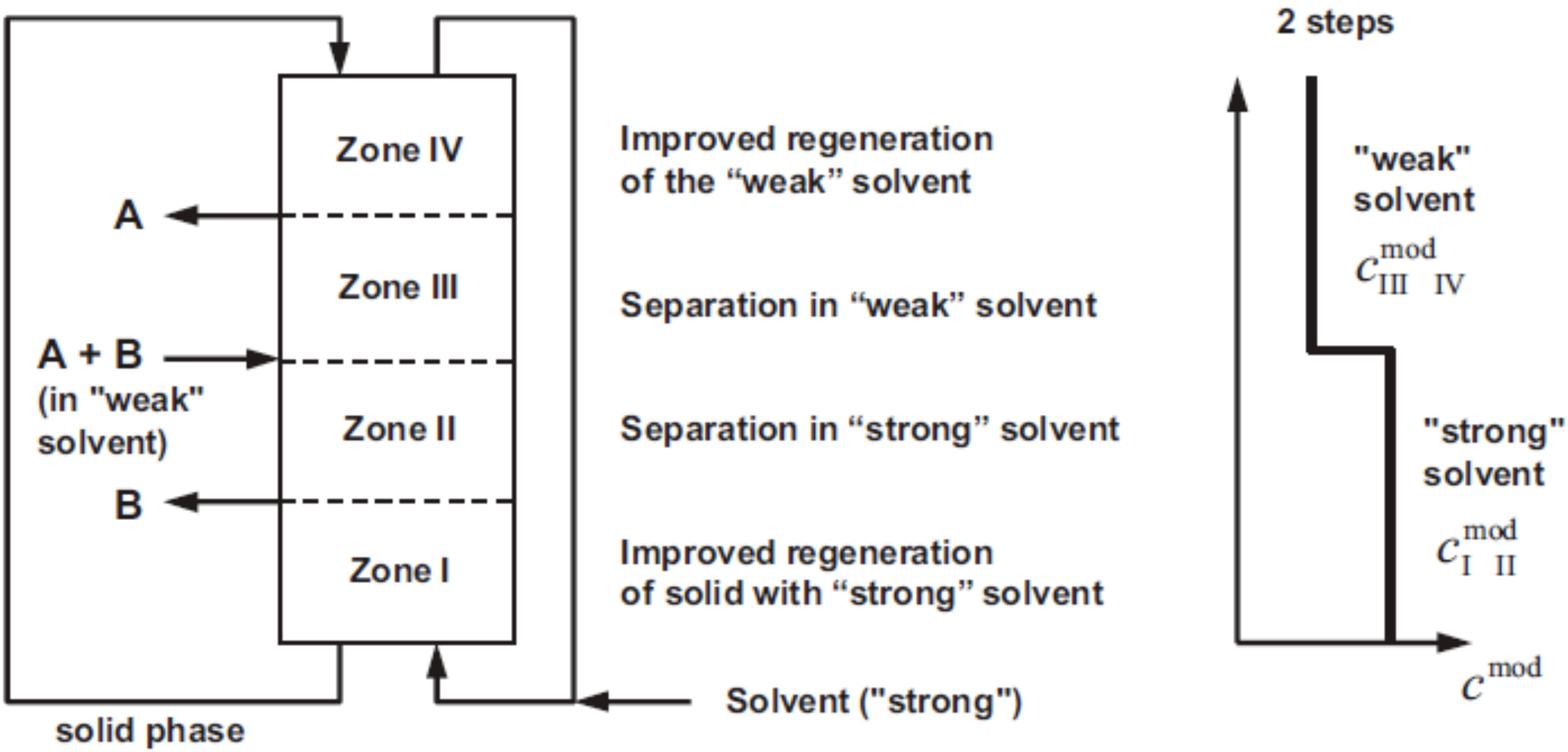
Gradient SMB Process



Gradient can be applied by a change in pressure with supercritical eluents or by the addition of a non-adsorbable modifier to increase elution strength

Seidel-Morgenstern et. al. *Chem. Eng. Technol.* **2008**, *31(6)*, 826-837

Annular Chromatography

Rh, Pd, Pt, & Ir complex ion separation, dual SP, grad. elut.

Wolfgang J.; Prior, A. *Adv. Biochem. Eng./Biotech.* **2002**, *76*, 233-255

Generalized Langmuir Isotherm Equations

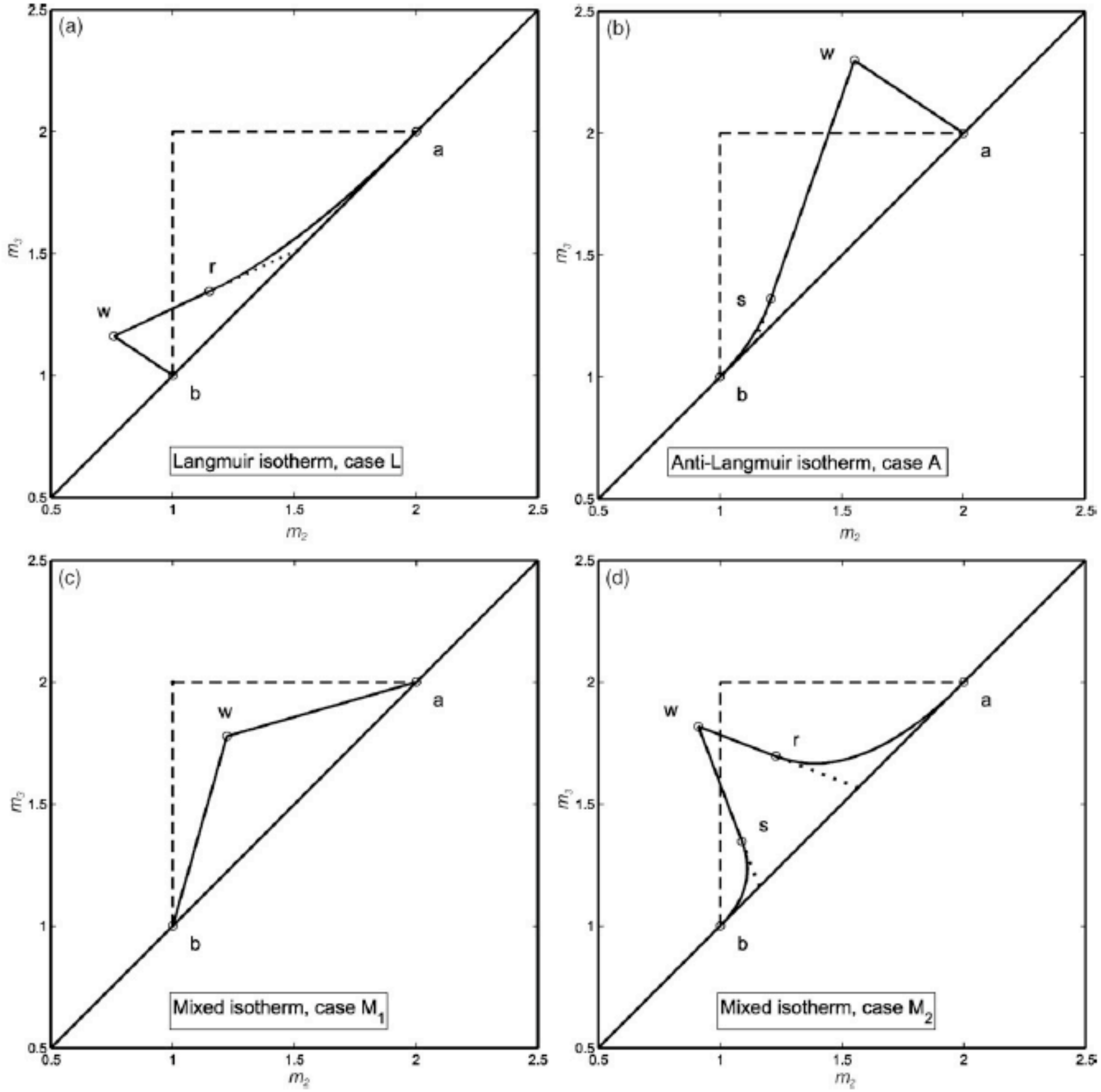
Case	Line or quantity	expression
L, A, M_1, M_2	ab	$m_3 = m_2$
L, M_2	ar	$m_3 = m_2 + \left(\sqrt{m_2} - \sqrt{H_A}\right)^2 / (K_A c_A^F)$
L, M_2	rw	$m_2 H_A(\omega_1^F - H_B) + m_3 H_B(H_A - \omega_1^F) = \omega_1^F \omega_2^F (H_A - H_B)$
A, M_2	bs	$m_2 = m_3 - \left(\sqrt{m_3} - \sqrt{H_B}\right)^2 / (K_B c_B^F)$
A, M_2	sw	$m_2 H_A(\omega_2^F - H_B) + m_3 H_B(H_A - \omega_2^F) = \omega_1^F \omega_2^F (H_A - H_B)$
L, M_1	bw	$p_A K_A c_A^F H_B m_3 + m_2[H_A - H_B(1 + p_A K_A c_A^F)] = H_B(H_A - H_B)$
A, M_1	aw	$m_3[H_A(1 + p_B K_B c_B^F) - H_B] - p_B K_B c_B^F H_A m_2 = H_A(H_A - H_B)$
L, M_2	$m_{1,min}$	H_A
L, M_1	$m_{4,max}$	$\frac{1}{2}\left\{m_3 + H_B + K_B c_B^F(m_3 - m_2) - \sqrt{[m_3 + H_B + K_B c_B^F(m_3 - m_2)]^2 - 4 m_3 H_B}\right\}$
A, M_1	$m_{1,min}$	$\frac{1}{2}\left\{m_2 + H_A + K_A c_A^F(m_3 - m_2) + \sqrt{[m_2 + H_A + K_A c_A^F(m_3 - m_2)]^2 - 4 m_2 H_A}\right\}$
A, M_2	$m_{4,max}$	H_B

A = extract component; B = raffinate component

The coefficients can be determined by a number of different methods

Mazzotti. et al., *J. Chromatogr. A* **2009**, *1216*, 709-738

Generalized Langmuir Isotherm Equations



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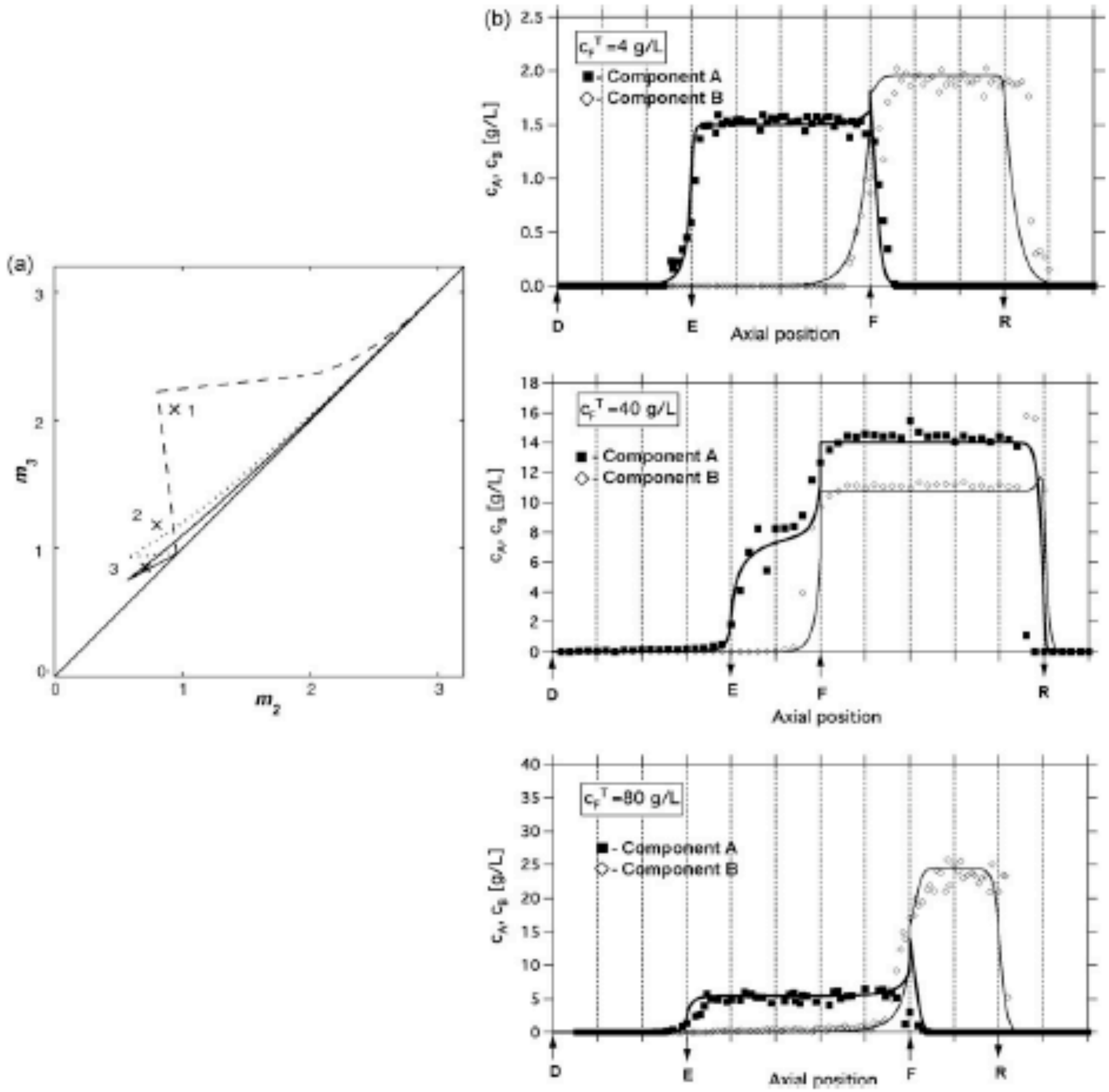
Chiral Separation on Industrial Scale



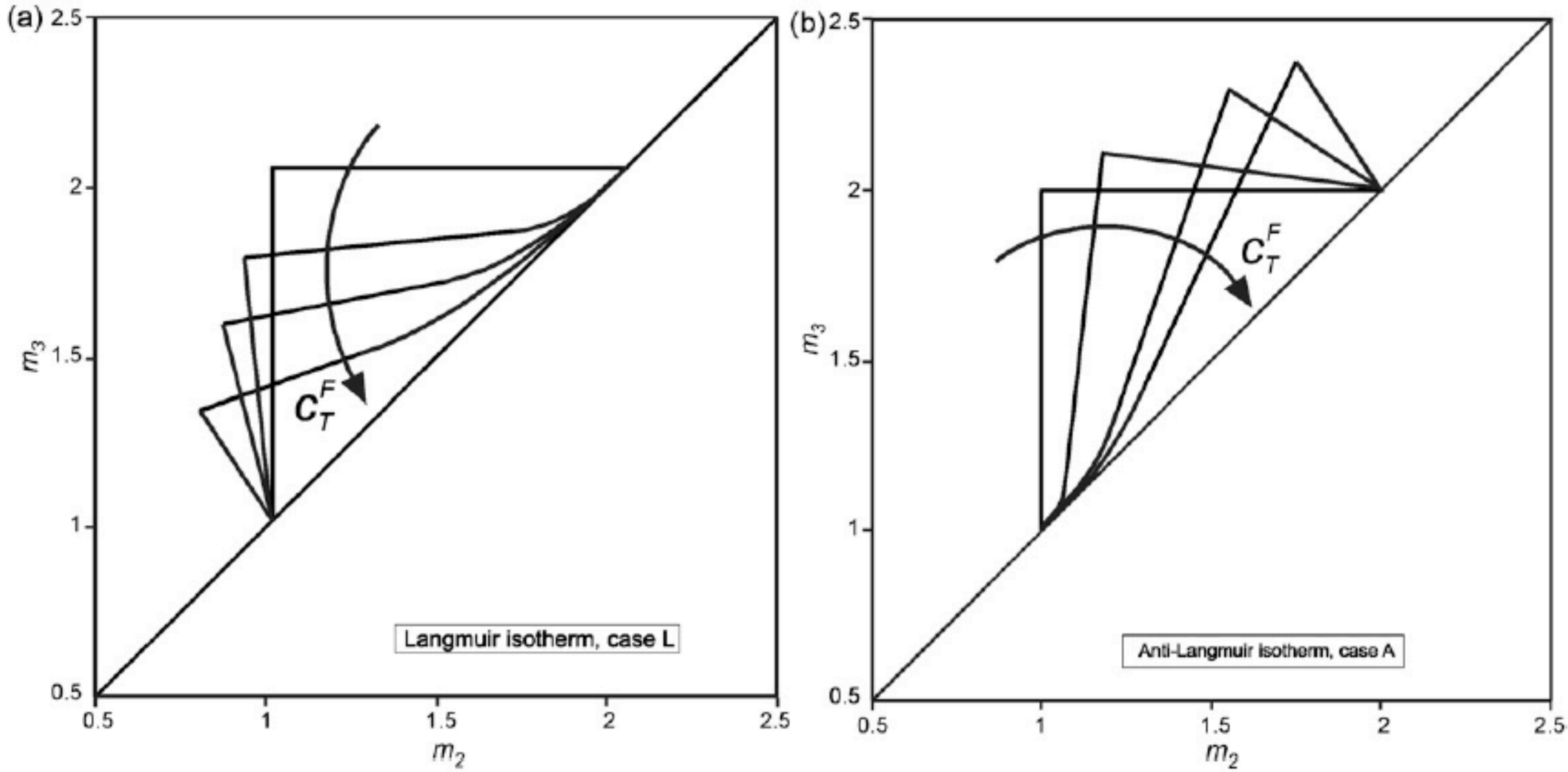
Pure extract, pure raffinate, c_F = 4 g/L

Pure extract, impure raffinate, c_F = 40 g/L

Pure extract, pure raffinate, c_F = 80 g/L

Mazzotti. et al., *J. Chromatogr. A* **2009**, *1216*, 709-738

Effect of Feed Concentration



Mazzotti. et al., *J. Chromatogr. A* **2009**, *1216*, 709-738

Comparison of Chromatographic Methods

<u>Modelling Study of 4 Types of Chromatography Methods</u>

		Elution	Recycling	SMB	AC
$PR_{\alpha} \to Max$	Operating parameters	$V_{inj} = 0.3$ ml $N = 1000$	$V_{inj} = 0.8$ ml $N = 1000$ $n_{cyc} = 2$	$c_{F,A} = c_{F,B} = 200\,\frac{g}{l}$ $\dot{V}_F = 10\,\frac{ml}{min}$ ($\dot{V}_I \ldots \dot{V}_{IV}$ based on [13])	$\varphi_F = 0.0981$ rad $N = 1000$ ($\omega = 16.53$ rad/min)
	$PR_{\alpha}\ \left[\frac{mg}{s\ cm^2}\right]$	7.642	7.637	19.25	7.645
	$EC_{\alpha}\ \left[\frac{l}{g}\right]$	0.328	0.252	0.268	0.328
$EC_{\alpha} \to Min$	Operating parameters	$V_{inj} = 0.5$ ml $N = 7000$	$V_{inj} = 10$ ml $N = 7000$ $n_{cyc} = 3$	$c_{F,A} = c_{F,B} = 200\,\frac{g}{l}$ $\dot{V}_F = 0.25\,\frac{ml}{min}$ ($\dot{V}_I \ldots \dot{V}_{IV}$ based on [13])	$\varphi_F = 0.151$ rad $N = 7000$ ($\omega = 0.906$ rad/min)
	$PR_{\alpha}\ \left[\frac{mg}{s\ cm^2}\right]$	0.686	0.573	4.88	0.686
	$EC_{\alpha}\ \left[\frac{l}{g}\right]$	0.217	0.204	0.264	0.217

Productivity maximized

ΔPR (mg/s•cm^2) = 7.64-19.25

ΔEC (L/g) = 0.25-0.38

Eluent consumption minimized

ΔPR (mg/s•cm^2) = 0.57-4.88

ΔEC (L/g) = 0.20-0.26

When productivity (PR) is maximized, SMB is #1 in PR (19.25) and #2 in EC (0.27)

When eluent consumptions (EC) is minimized SMB is #1 in PR (4.88) and #4 in EC (0.26)

SMB achieved this performance due to short columns used which allowed for higher flow rates

Seidel-Morgenstern et. al. *Chem. Eng. Technol.* **1998**, *21(6)*, 469-477