Speedy Standing Wave Design of Size-Exclusion Simulated Moving Bed: Solvent Consumption and Sorbent Productivity Related to Material Properties and Design Parameters

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Abstract:

Size-exclusion simulated moving beds (SEC-SMB) have been used for large-scale separations of linear alkanes from branched alkanes. While SEC-SMBs are orders of magnitude more efficient than batch chromatography, they are not widely used. One key barrier is the complexity in design and optimization. A four-zone SEC-SMB for a binary separation has seven material properties and 14 design parameters (two yields, five operating parameters, and seven equipment parameters). Previous optimization studies using numerical methods do not guarantee global optima or explicitly express solvent consumption (D/F) or sorbent productivity (P_R) as functions of the material properties and design parameters.

The Standing Wave concept is used to develop analytical expressions for D/F and P_R as functions of 14 dimensionless groups, which consist of 21 material and design parameters. The resulting Speedy Standing Wave Design (SSWD) solutions are simplified for two limiting cases: diffusion or dispersion controlled. An example of SEC-SMB for insulin purification is used to illustrate how D/F and P_R change with the dimensionless groups. The results show that maximum P_R for both diffusion and dispersion controlled systems is mainly determined by yields, equipment parameters, material properties, and two key dimensionless groups: (1) the ratio of step time to diffusion time and (2) the ratio of diffusion time to pressure-limited convection time. A sharp trade off of D/F and P_R occurs when the yield is greater than 99%. The column configuration for maximum P_R is analytically related to the diffusivity ratio and the selectivity. To achieve maximum sorbent productivity, one should match step time, diffusion time, and pressure-limited convection time for diffusion controlled systems. For dispersion controlled systems, the axial dispersion time should be about 10 times the step time and about 50

23 times the pressure-limited convection time. Its value can be estimated from given yields,
24 material properties, and column configuration. Among the material properties, selectivity and
25 particle size have the largest impact on D/F and P_R . Particle size and 14 design parameters can
26 be optimized for minimum D/F , maximum P_R , or minimum cost on a laptop computer.

27 Keywords: Simulated moving bed; Size-exclusion; Standing Wave Design; Solvent
28 consumption; Sorbent productivity; Optimization

30 1.0 Introduction

31 Size-exclusion chromatography (SEC) has many important applications. Examples
32 include gel permeation chromatography (GPC), for analysis of protein mixtures or obtaining
33 molecular weight distributions of polymers [1,2], and purification of proteins, such as human
34 insulin [3]. However, conventional SEC is a batch process and it is less efficient than simulated
35 moving bed (SMB) for large-scale production.

36 In SMB, the columns are connected in a circular configuration (loop). Inlet and outlet
37 ports divide the loop into different sections (zones) with different flowrates. A typical 4-zone
38 SMB with two columns per zone (2-2-2-2 configuration) is shown in Fig. 1. The ports are moved
39 periodically to follow the migrating solute bands. The time between port switches is called the
40 switching time, or step time (t_s). The average port velocity (v) is equal to the column length (L_c)
41 divided by the step time. The separation is achieved by containing the solutes in specific zones.
42 As seen in Fig. 1, the small green component (slow solute) is never present in Zone IV while the
43 large blue component (fast solute) is never present in Zone I. By containing the advancing and
44 trailing concentration waves in their respective zones, pure products can be continuously
45 removed.

46 Size-exclusion simulated moving beds (SEC-SMBs) are more efficient than conventional
47 SEC because only partial separation of solutes in the loop is required to obtain high-purity
48 products with high yield. As a result, a large fraction of the sorbent capacity is utilized and
49 product dilution is reduced. Thus, SMBs consume orders of magnitude less solvent, require an
50 order of magnitude less sorbent, and take up less space than batch operations. Because SMBs are

continuous processes, they also require less manpower. These advantages make SMBs economical for large-scale separations.

The SEC-SMB was first introduced by Universal Oil Products (UOP) in 1961 as the Molex process, which separates linear alkanes from branched alkanes [4,5]. SMBs were later developed for adsorptive systems, such as large-scale hydrocarbon purification and high fructose corn syrup production [6]. SMBs for chiral separations have been developed since the 1990s [7]. Lab-scale SEC-SMB have been developed for insulin purification [8,9], separation of myoglobin from bovine serum albumin (BSA) [10], lactose removal from human milk [11], and polyethylene glycol (PEG) fractionation by molecular weight (MW) [12].

Even though SMBs have many advantages, they have not been widely used for large-scale production. SMBs have complex transient and cyclic steady-state phenomena. Equipment for SMBs is often more complex and expensive than batch equipment and SMB experiments are costly and time-consuming. The most important barrier is the complexity of the design and optimization of SEC-SMB. A four-zone SEC-SMB for a binary separation has 21 variables, which include seven material properties and 14 design parameters, Fig. 2. The 14 design parameters include two yield requirements (Y_i), seven equipment parameters, and five operating parameters. The seven material properties are bed void fraction (ϵ_b), particle porosity (ϵ_p), two apparent retention factors (δ_i), two intraparticle diffusivities ($D_{p,i}$), and particle size (R_p). The two yield requirements can also be specified as two purities or one yield and one purity. The seven equipment parameters are column length (L_c), dead volume (DV), maximum pressure drop (ΔP_{max}), and the column configuration (the number of columns in each zone, N^j). The five operating parameters are the four zone velocities (u_o^j) and port velocity (v). Experimental trial

and error with 14 design parameters would be extremely costly. Additionally, the seven material properties, including particle size, can be optimized.

SEC-SMB systems can be optimized for maximum productivity, minimum solvent consumption, or minimum cost. Cost optimizations need to incorporate three main costs: equipment cost; solvent cost, which is related to solvent consumption; and sorbent cost, which is related to sorbent productivity. These costs are controlled by the equipment, material properties, and operating parameters.

The simplest method for designing the five operating parameters is the local equilibrium theory or “triangle” theory. It is widely used and works well for ideal systems (no mass transfer resistance) [13]. However, for non-ideal systems (with mass transfer resistance), this theory only gives the range of possible operating parameters where separation of the components will occur. It does not guarantee purity or yield and it does not give optimum operating parameters for non-ideal systems (most low pressure systems).

The Standing Wave Design (SWD) was first developed by Ma and Wang in 1997 for binary, linear adsorption systems with mass transfer resistances [14]. For fixed material properties, yields, and equipment parameters, the SWD determines the five optimum operating parameters to maximize productivity and minimize solvent consumption. It was extended to multicomponent linear systems [15] and nonlinear systems [16–18]. Pressure limit considerations were incorporated into the SWD [19] by checking that the resulting operating parameters did not violate the pressure constraint.

The SWD method has been incorporated into various optimization routines, based on grid search [9], genetic algorithms [20], simulated annealing [21,22], or combined simulated annealing and genetic algorithm (SAGA) [23]. Optimization variables include particle size (R_p),

column length (L_c), column configuration (N^f), and yields (Y_i) [24]. These techniques cannot guarantee global optima and they do not provide an overview of how solvent consumption, sorbent productivity, and separation cost are related to material properties and design parameters.

The objective of this work is to find analytical solutions for the solvent consumption and productivity of SEC-SMB systems as functions of the equipment, material, and operating parameters. These analytical solutions can then be used to understand how solvent consumption and sorbent productivity are affected by the material and design parameters. These solutions can also be used to quickly find the optimal designs for maximum productivity, minimum solvent consumption, or lowest separation cost (with given cost functions). This new method is called the Speedy Standing Wave Design (SSWD) method.

To produce the general analytical solutions, the SWD equations are solved in terms of dimensionless groups. For a binary SEC-SMB separation, combining dimensionless groups with the SWD equations reduces the total number of variables from 21 to 14 (Fig. 2). The details are shown in Section 2. The general solutions are simplified for two limiting cases: diffusion or dispersion controlled systems. The solvent consumption and sorbent productivity results from this new method are compared to those from three SEC-SMB systems in the literature. The effects of the dimensionless groups are explored for the diffusion or dispersion controlled cases using an example from insulin purification.

Some highlights of this study are the following. Analytical solutions for solvent consumption and productivity are found in terms of 14 dimensionless groups and they greatly facilitate optimization of SEC-SMBs. With appropriate cost functions, the minimum cost SMB design can quickly be determined. The column configuration for maximum productivity is analytically related to the diffusivity ratio and the selectivity. There is a sharp trade-off for

solvent consumption and sorbent productivity when yields are specified to be greater than 99%. For diffusion controlled systems, matching step time, diffusion time, and pressure-limited convection time gives maximum sorbent productivity. Fifteen decision variables (Y_i , R_p , L_c , DV , N^j , ΔP , u_0^j , and v) can be optimized on a laptop computer.

2.0 Theory

In this section, the basic concept of the Standing Wave Design (SWD) method reported in the literature is briefly reviewed in Section 2.1. The development of new general equations using dimensionless groups is explained in Section 2.2. These new equations are called the Speedy Standing Wave Design (SSWD) because they provide an overview of the solvent consumption, sorbent productivity, and cost over a wide range of design parameters. The SSWD equations are simplified for diffusion- and dispersion-controlled systems in Sections 2.3 and 2.4, respectively. Optimization of decision variables to achieve minimum solvent consumption, maximum productivity, or minimum cost using the SSWD is discussed in Section 2.5.

2.1 Standing Wave Design (SWD)

The SWD for ideal and non-ideal, linear adsorption isotherm systems was first developed by Ma and Wang in 1997. For an ideal system, the SWD matches the port velocity to the velocity of the concentration wave of the “standing” component in each zone in a continuous moving bed. For a non-ideal system, a difference in port velocity and wave velocities is used to confine selected waves in their respective zones. This concept is illustrated for a binary, non-ideal system in Fig. 3. The fast moving solute (insulin, component 1) is removed in the raffinate, while the slow moving solute (ZnCl_2 , component 2) is removed in the extract. The arrows point to the

140 wave which is confined in that zone. The equations for the design of linear systems with mass
 141 transfer effects are presented in Eq. (1) [14],

$$142 \quad uOI = 1 + \phi \delta 2\nu + \beta 2ILIEb, 2I + \phi \delta 2\nu 2K 2I$$

143 (1a)

$$144 \quad uOII = 1 + \phi \delta 1\nu + \beta 1IILIIEb, 1II + \phi \delta 1\nu 2K 1II$$

145 (1b)

$$146 \quad uOIII = 1 + \phi \delta 2\nu - \beta 2IIILIIIEb, 2III + \phi \delta 2\nu 2K 2III$$

147 (1c)

$$148 \quad uOIV = 1 + \phi \delta 1\nu - \beta 1IVLIVEb, 1IV + \phi \delta 1\nu 2K 1IV$$

149 (1d)

$$150 \quad uF = uOIII - uOII \quad (1e)$$

151 where uOj is the interstitial velocity of the fluid in zone j (zone velocity); uF is the feed velocity;
 152 ϕ is the phase ratio which is equal to $(1 - \epsilon_b) / \epsilon_b$; δi is the apparent retention factor for component i;
 153 ν is the port velocity; $\beta i j$ is the natural logarithm of the ratio of the highest concentration to the
 154 lowest concentration of the standing wave of component i in zone j and it is directly related to
 155 the yield, Eq. (A1.1); Lj is the length of zone j and is equal to the product of N^j and L_c ; Eb, ij is
 156 the axial dispersion coefficient for component i in zone j; and Kij is the lumped mass transfer
 157 parameter for component i in zone j.

The overall mass transfer resistance, $1/K_{ij}$, can be written explicitly as mass transfer resistances in series for linear systems, as shown in Eq. (2).

$$\frac{1}{K_{ij}} = R_p \left(\frac{1}{5K_{se,i} \epsilon_p D_{p,i}} + \frac{R_p}{3k_{f,i}} \right) \quad (2)$$

where $K_{se,i}$ is the size-exclusion factor for component i (fraction of the pore volume that can be accessed by the component), $D_{p,i}$ is the pore diffusivity of component i , and $k_{f,i}$ is the film mass transfer coefficient. For most low pressure systems, the film mass transfer resistance is negligible compared to that of intraparticle diffusion or axial dispersion [25].

For linear systems, the apparent retention factor of component i is given by Eq. (3) [8]

$$\delta_i = \epsilon_p K_{se,i} + \frac{1 - \epsilon_p K_{se,i} a_i + DV}{1 - \epsilon b} \quad (3)$$

where a_i in Eq. (3) is the Langmuir “a” value for adsorption and DV is the total dead volume as a fraction of the total sorbent packing volume. For size-exclusion systems, there is no adsorption so the equation for the retention factors is simplified into Eq. (4).

$$\delta_i = \epsilon_p K_{se,i} + \frac{DV}{1 - \epsilon b} \quad (4)$$

Table 1 contains a summary of the definitions and descriptions of the major dimensionless groups which will be derived in the rest of this section.

An often referred to parameter is the selectivity of a system. The definition of selectivity for SEC- SMB is given in Eq. (5).

$$\alpha = \frac{\delta_2}{\delta_1} \quad (5)$$

Given yields, material properties, and column configuration, Eq. (1) is solved to obtain the five operating parameters (u_{Oj} and v). The maximum feed flow rate can be found by increasing the set feed flow rate until the mass transfer limit does not allow further increase.

The SWD equations can be used to determine the five optimum operating parameters for given yields, material properties, and equipment parameters.

2.2 Speedy Standing Wave Design (SSWD)

In this study, solvent consumption and sorbent productivity are expressed in terms of dimensionless groups. Such solutions can be used to elucidate the effects of equipment, material, and operating parameters on solvent consumption and sorbent productivity. Furthermore, designs for minimum cost, maximum productivity, or minimum solvent consumption can be found very quickly. This advanced SWD method is called the Speedy Standing Wave Design (SSWD) method.

Eq. (1) is simplified using the dimensionless groups defined in Table 1. Two key dimensionless groups are used to separate the mass transfer effects due to diffusion from the mass transfer effects due to dispersion. The dimensionless group which is a ratio of diffusion rate to convection rate is $ND_{,i}$ and is defined in Eq. (6).

$$ND_{,i} = \frac{\phi \epsilon_p K_{se,i} D_{p,i} R_p^2 L_{cv}}{t_{st} D_{,i}} = \frac{\text{Diffusion rate}}{\text{Convection rate}} = \frac{\text{Step time}}{\text{Effective diffusion time}} \quad (6)$$

The port velocity is chosen as the characteristic velocity. To separate the influence of the column configuration from that of diffusion, column length, instead of zone length, is chosen as the characteristic length. Particle radius (R_p) is chosen as the characteristic diffusion length. A

characteristic diffusion time ($t_{D,i}$) can be defined as R_p^2 divided by the effective diffusivity ($\phi \epsilon_p K_{se,i} D_{p,i}$), while a characteristic convection time can be defined as L_c divided by v , or the step time (t_s) in SMB. Thus, $N_{D,i}$ can be thought of as the ratio of the step time to the diffusion time. A large $N_{D,i}$ means that in the time between port switches, there is plenty of time for the solute to diffuse through the sorbent particles, which in turn means that the wave spreading due to diffusion is small. A small $N_{D,i}$ means that there is not enough time for the solute to diffuse through the particle within the step time, which in turn means wave spreading due to diffusion is significant.

For a binary separation, there are two $N_{D,i}$ values, one for each component. These two $N_{D,i}$ are related by the definition of the dimensionless group as shown in Eq. (7)

$$N_{D,1} = \lambda \gamma N_{D,2} \quad (7)$$

where λ is the ratio of the size-exclusion factors and γ is the ratio of the intraparticle diffusivities.

The dimensionless group which is a ratio of convection rate to axial dispersion rate is the Peclet number, and is defined in Eq. (8).

$$Pe_{b,i} = \frac{v L_c}{E_{b,i}} = \frac{\text{Convection rate}}{\text{Dispersion rate}} = \frac{t_{Dax}}{t_s} = \text{Axial dispersion time} \quad (8)$$

The characteristic dispersion time (t_{Dax}) can be defined as L_c^2 divided by the dispersion coefficient ($E_{b,i}$), while a characteristic convection time can be defined as L_c divided by v , or the step time (t_s). The Peclet number can also be thought of as the ratio of a characteristic time for dispersion (t_{Dax}) to the step time (t_s). If the Peclet number is very large, then the step time is much smaller than the dispersion time and thus there is a very small effect of dispersion on the

wave spreading. If the Peclet number is small, then the dispersion time is closer to the step time and the effects from dispersion are significant.

For a four-zone SMB, there are four Peclet numbers, but they are related by Eq. (9)

$$P_{ebIV}P_{ebj} = E_{bj}E_{bIV} = \Gamma_j$$

(9)

where Γ^j is the ratio of the axial dispersion coefficient of zone j to the axial dispersion coefficient of Zone IV.

Eqs. (6-9) allow for Eq. (1) to be written using the $N_{D,i}$ of one component and the P_{eb}^j of one zone and are shown in Eq. (10).

$$u_{OI} = v \left(1 + \phi \delta \left(2 + \beta \frac{2 \Gamma I P_{ebIV} N I + \phi 2 \beta 2 I \delta 2 2 1 5 N D, 1 \lambda \gamma N I}{\dots} \right) \right) \quad (10a)$$

$$u_{OII} = v \left(1 + \phi \delta \left(1 + \beta \frac{1 I I I \Gamma I I P_{ebIV} N I I + \phi 2 \beta 1 I I \delta 1 2 1 5 N D, 1 N I I}{\dots} \right) \right) \quad (10b)$$

$$u_{OIII} = v \left(1 + \phi \delta \left(2 - \beta \frac{2 I I I \Gamma I I I P_{ebIV} N I I I - \phi 2 \beta 2 I I I \delta 2 2 1 5 N D, 1 \lambda \gamma N I I I}{\dots} \right) \right) \quad (10c)$$

$$u_{OIV} = v \left(1 + \phi \delta \left(1 - \beta \frac{1 I V P_{ebIV} N I V - \phi 2 \beta 1 I V \delta 1 2 1 5 N D, 1 N I V}{\dots} \right) \right) \quad (10d)$$

For large-scale production, the solvent consumption of the SMB is an important factor for the separation cost. Solvent cost is related to a ratio of the desorbent flow rate (D) and the feed flow rate (F). This ratio (D/F) is also related to the dilution of the products. D and F are determined by Eq. (11) and Eq. (12), respectively where S is the cross-sectional area of a column.

$$D = \epsilon b S (u_{OI} - u_{OIV}) \quad (11)$$

$$F = \epsilon b S (u_{OIII} - u_{OII}) \quad (12)$$

240 Taking the ratio of Eq. (11) to Eq. (12) and substituting the zone velocities with Eq. (10) results
 241 in Eq. (13).

$$\begin{aligned}
 242 \quad D/F = & \phi \delta^2 - \delta + 1 + \frac{P_{eb} IV}{\beta} \frac{2 I \Gamma I N I}{I N I} + \beta \frac{1 I V N I V}{I N I} + \phi \frac{2 \delta 1 2 1 5 N D}{1 2 1 5 N D}, \frac{1 \beta 2 I \alpha 2 \lambda \gamma N I}{2 \lambda \gamma N I} \\
 243 \quad & + \beta \frac{1 I V N I V}{I N I} \phi \delta^2 - \delta + 1 - \frac{1 P_{eb} IV}{\beta} \frac{2 I I I \Gamma I I I N I I I}{I I I \Gamma I I I N I I I} + \beta \frac{1 I I I \Gamma I I N I I}{I I I \Gamma I I N I I} - \\
 244 \quad & \phi \frac{2 \delta 1 2 1 5 N D}{1 2 1 5 N D}, \frac{1 \beta 2 I I I \alpha 2 \lambda \gamma N I I I}{2 \lambda \gamma N I I I} + \beta \frac{1 I I N I I}{I I N I I}
 \end{aligned} \tag{13}$$

245 The v , ε_b , and S all cancelled out in Eq. (13). This solution applies to systems where both
 246 diffusion and dispersion are significant. For an ideal SMB with no mass transfer spreading, the
 247 terms with $N_{D,I}$ or $P_{eb} IV$ are negligible and the value of D/F is 1.

248 Another useful parameter for evaluating SMB designs is productivity. Productivity (P_R)
 249 has dimensions (usually in mass of product per mass of sorbent per time). Eq. (14) defines P_R in
 250 the way that it will be discussed throughout this work.

$$251 \quad P_{R,i} = \varepsilon_b S u \frac{O I I I - u O I I C F, i Y_i S L c N (1 - \varepsilon_b) \rho_p}{C_{F,i}} \tag{14}$$

252 $C_{F,i}$ is the feed concentration of component i (mass solute / volume of feed), N is the total
 253 number of columns in the SMB, and ρ_p is the particle density (mass sorbent / particle volume).
 254 Substituting the zone velocities in Eq. (14) with Eq. (10) results in Eq. (15).

$$\begin{aligned}
 255 \quad P_{R,i} = & Y_i C_{F,i} N t_s \phi \rho_p \phi \delta^2 - \delta + 1 - \frac{1 P_{eb} IV}{\beta} \frac{2 I I I \Gamma I I I N I I I}{I I I \Gamma I I I N I I I} + \beta \frac{1 I I I \Gamma I I N I I}{I I I \Gamma I I N I I} - \phi \frac{2 \delta 1 2}{1 2} \\
 256 \quad & \frac{1 5 N D}{1 5 N D}, \frac{1 \beta 2 I I I \alpha 2 \lambda \gamma N I I I}{2 \lambda \gamma N I I I} + \beta \frac{1 I I N I I}{I I N I I}
 \end{aligned} \tag{15}$$

257 For an ideal system, the terms with $N_{D,I}$ and P_{eb}^{IV} are negligible and the productivity is the first
 258 term on the right-hand side of Eq. (15).

259 One can define component independent N_D and zone independent P_{eb} by Eq. (16) and
 260 (17), respectively.

$$261 \quad ND^* = \delta 2^{-\delta} ND, \quad 1\phi\delta 12 = ND, \quad 2\delta 2^{-\delta} 1\lambda\gamma\phi\delta 12$$

$$262 \quad (16)$$

$$263 \quad Peb^* = \phi\delta 2^{-\delta} 1PebIV = \phi\delta 2^{-\delta} 1Pebj\Gamma_j \quad (17)$$

264 After substituting Eqs. (16-17) into Eqs. (10,13), the resulting uOj equations are presented in the
 265 first column of Table 2 and are given by Eq. (18), Table 2. The D/F and P_R expressions resulting
 266 from using Eq. (18) for the zone velocities are shown in Table 2, Eqs. (19) and (20), respectively.

267 The column configuration which achieves the highest P_R can be obtained from Eq. (20).

268 For a fixed total number of columns (N), the question is how to distribute the columns between

269 the zones. Since N^I and N^{IV} do not appear in Eq. (20), columns placed in these zones do not

270 affect P_R with the same operating conditions. This means Zones I and IV should have the

271 minimum number of columns (i.e. one). Increasing N^{II} or N^{III} will increase P_R . The column

272 configuration that yields the maximum productivity can be obtained by taking the partial

273 derivative of Eq. (20) with respect to N^{II} , or N^{III} , and setting the resulting equation equal to zero.

274 The fractional column configuration for maximum P_R is given by Eq. (21).

$$275 \quad NIN = 1N \quad (21a)$$

$$276 \quad NIIN = NIIN\beta 1II\Gamma IIPeb^* + 115ND^*\beta 2II\Gamma IIIIIPeb^* + \alpha 215ND^*\lambda\gamma \quad (21b)$$

$$277 \quad NIIN = 1 - NIN - NIVN1 + \beta 1II\Gamma IIPeb^* + 115ND^*\beta 2II\Gamma IIIIIPeb^* +$$

$$278 \quad \alpha 215ND^*\lambda\gamma \quad (21c)$$

$$N_{IVN} = 1N \quad (21d)$$

For systems where diffusion and dispersion are significant, the column configuration that results in the highest P_R is dependent on both N_D^* and P_{eb}^* . Once these two dimensionless groups, the material properties, yields, and the total number of columns are fixed, the optimum configuration can easily be calculated.

Previous studies have shown that the true moving bed assumption holds for SMBs with two or more columns per zone [14]. Having only one column in a zone may violate the true moving bed assumption of the SWD. If this assumption is violated, the purities and yields can be lower than those specified by SWD. Column configurations that have a zone with one column should be simulated to ensure that the waves are actually confined [9]. To avoid the need for simulations, the minimum number of columns per zone is set to be two in this study.

A major factor for equipment cost and sorbent cost is a pressure limitation. Systems may be limited by pressure if the sorbent is very soft. In this case, the pressure drop per packing length is limited [9]. Other systems may be limited by the maximum pressure allowed by pumps, valves, or columns. The pressure drop across a uniformly packed bed of monodisperse, spherical particles can be estimated using the simplified Ergun equation [26].

$$\Delta P = 37.5 \mu L c u_0 I \phi^2 R_p^2 \quad (22)$$

ΔP is the pressure drop and μ is the viscosity of the fluid. Because the velocity in Zone I is always the largest in SEC-SMB, it is used to calculate the maximum pressure drop (ΔP_{max}) across a column in the SMB. Substitution of Eq. (18a) into Eq. (22) and rearranging results in Eq. (23).

300 ΔP

301 $R_p 237.5 \phi \mu L_{cv} = \phi 1 + \phi \delta 2 + \beta 2 I \Gamma I \phi \delta 2 - \delta 1 P e b * N I + \phi \beta 2 I \alpha 2 \delta 2 - \delta 1 1 5 N D * \lambda \gamma$

302 $N I = N \Delta P = t_{stc} I$ (23)

303 This dimensionless group, $N_{\Delta P}$, can be considered as a dimensionless pressure drop, which is
304 equal to the ratio of step time to the pressure-limited convection time through a column in Zone I
305 (t_c'). It is analogous to the Bejan number, which was developed for the pressure drop across a
306 channel [27].

307 **2.3 Diffusion Controlled**

308 Equations (18-21) and (23) can be simplified for diffusion controlled systems. The results
309 are summarized in the middle column of Table 2. If the Peclet number is very large, dispersion
310 effects are negligible. The zone velocities are controlled by Eq. (24). The resulting equation for
311 D/F is presented in Eq. (25).

312 Equation (25) indicates that increasing the zone length ($N' L_c$) in any zone will decrease
313 D/F by decreasing the effects from diffusion. The optimum column configuration is controlled
314 by the selectivity (α), diffusivity ratio (γ), and size-exclusion factor ratio (λ). For SEC-SMBs
315 with small dead volumes (DV), λ is approximately equal to α . If γ is much larger than α , Zone
316 IV should have more columns than Zone I, and Zone II should have more columns than Zone III.
317 A large value of γ indicates that the fast solute has a lower diffusivity than the slow solute,
318 resulting in broader waves of the fast solute. This column configuration uses the extra columns in
319 Zones II and IV to better confine the trailing wave and advancing wave of the fast solute
320 (insulin), respectively. However, when γ is large, the column configuration does not have a large

impact on D/F because the terms inside the parentheses in Eq. (25) are already relatively small.

The column configuration will have a larger impact on systems where α is larger than γ .

The denominator of Eq. (25) must be positive for SEC-SMB. Therefore there is a minimum value of N_D^* for the operation to be feasible, which is shown in Eq. (26).

$$N_{D, \min} = \frac{1}{1 + 5\beta} \frac{2 \min(N_D^* \alpha, 2\lambda\gamma N)}{1 + \beta} \frac{1}{1 + \beta} \quad (26)$$

For Eq. (20), the terms with Peclet numbers are negligible and the step time can be replaced by the definition of N_D^* , resulting in Eq. (27)

$$P_{R,i} = \phi \delta \frac{1}{Y_i} C_{F,i} \epsilon_p K_{se} \frac{1}{D_p} \frac{1}{N \rho_p R_p} \frac{2 N_D}{1 + \alpha - 1 - \phi \delta} \frac{1}{1 + 5 N_D} \frac{1}{\beta} \frac{2 \min(N_D^* \alpha, 2\lambda\gamma N)}{1 + \beta} \frac{1}{1 + \beta} \quad (27a)$$

The second term in the brackets of Eq. (27b), Table 2, represents the loss of productivity due to diffusion effects compared to the productivity of an ideal system. For the productivity to be positive, the value of the second term in the in the bracket,

$$\frac{1}{1 + 5 N_D} \frac{1}{\beta} \frac{2 \min(N_D^* \alpha, 2\lambda\gamma N)}{1 + \beta} \frac{1}{1 + \beta},$$

must be less than one. When the other parameters are fixed, there is a minimum γ , for the productivity to be positive.

For diffusion controlled systems, the step time is proportional to N_D^* . As N_D^* increases, the loss of productivity due to diffusion effects decrease, but the step time increases. These competing effects result in a maximum in the productivity. Taking the partial derivative of Eq. (27b) with respect to N_D^* and setting the resulting equation equal to zero can solve for the N_D^* which achieves the maximum P_R . The result is shown in Eq. (28).

$$ND, \max PR^* = 215\beta^2, \max Pr III \alpha 2\lambda\gamma N III + \beta 1, \max Pr I IN II$$

$$(28a)$$

$$PR, i, \max = 15\epsilon b Y_i C F, i \alpha - 12\epsilon p K s e, 1 D p, 14 N \rho p R p 2 \beta^2, \max Pr III \alpha 2\lambda\gamma N III$$

$$+ \beta 1, \max Pr I IN II \quad (28b)$$

Eq. (26) and Eq. (28) indicate that the N_D^* to achieve maximum productivity ($ND, \max PR^*$) is about twice the value of the minimum N_D^* for the SEC-SMB to be feasible ($ND, \min^*$). The maximum productivity, given by Eq. (28b), is inversely proportional to R_p^2 . Larger productivity can be achieved with smaller particles, longer fractional zone length (N^j/N) for Zones II and III, or larger feed concentration, selectivity, size-exclusion factor, and diffusivity.

The optimum column configuration for maximum P_R for diffusion controlled systems is shown in Eq. (29).

$$N IN = 1 N \quad (29a)$$

$$N I I N = N I I I N \beta 1 I I I \lambda \gamma \beta 2 I I I \alpha 2 \quad (29b)$$

$$N I I I N = 1 - N IN - N I V N 1 + \beta 1 I I I \lambda \gamma \beta 2 I I I \alpha 2 \quad (29c)$$

$$N I V N = 1 N \quad (29d)$$

The maximum productivity configuration for diffusion controlled systems is not a function of N_D^* . As such, there is one column configuration which will have a larger productivity than other configurations at every N_D^* . Once α , λ , γ , Y_i , and N are specified, the maximum productivity configuration can be determined from Eq. (29).

The values of β 's for Zones II and III are often similar, so the maximum productivity column configuration mainly depends on γ/α , for small DV (< 0.02). A large γ/α indicates that more columns should be placed in Zone II than Zone III to contain the wave of the fast solute. The sharp wave of the slow solute in Zone III does not need as many columns when the diffusivity of the slow solute is very large. A small γ/α means the reverse. More columns are needed in Zone III to confine the spreading wave of the slow solute and Zone II does not need as many columns because there is enough difference in the wave velocities to keep the trailing wave of the fast solute confined in Zone II.

Equation (23) can be simplified since the term with the Peclet number is negligible. Additionally, the port velocity can be replaced with a function of N_D^* . Rearrangement results in Eq. (30a).

This group can be considered as a ratio of the diffusion time ($t_{D,I}$) to pressure-limited convection time through a column in Zone I (t_c^I). Eq. (30a) indicates that $N\Delta P_{\text{diff}}$ decreases with increasing N_D^* . For fixed material properties, yields, and equipment parameters, Eq. (30a) can be used to find the minimum N_D^* to satisfy the pressure limit. For a fixed diffusion time, a large value of $N\Delta P_{\text{diff}}$ corresponds to a small pressure-limited convection time, or higher zone velocities.

The N_D^* for maximum sorbent productivity can be found from Eq. (28). This value can be used in Eq. (30a) to determine $N\Delta P_{\text{diff,maxPR}}$, which is the combination of $\Delta P_{\text{max}} R_p^4 / L_c^2$ necessary to achieve the maximum sorbent productivity, Eq. (30b).

$$N\Delta P_{\text{diff,maxPR}} = \Delta P_{\text{max}} R_p^4 / L_c^2 = 15 \phi^2 \alpha - 12 \epsilon_p K_{se} / 2 \beta^2, \text{maxPrIII} \alpha^2 \lambda \gamma N_{\text{III}} + \beta^2, \text{maxPrIINII} 1 + \phi \delta^2 \phi \delta^2 - \delta^2 1 + \beta^2 I \alpha^2 2 \lambda \gamma N_{\text{I}} \beta^2, \text{maxPrIII} \alpha^2 \lambda \gamma N_{\text{III}} + \beta^2, \text{maxPrI}$$

382 $rIINII$

383 (30b)

384 For fixed material properties, yields, and column configuration, the right hand side of Eq. (30b)
385 is fixed. Thus, the value of $\Delta P_{max} R_p^4 / L_c^2$ for maximum productivity is fixed. For fixed particle
386 size and operating pressure (limited by equipment or resin material), there is only one column
387 length that can achieve the maximum productivity.

388 **2.4 Dispersion Controlled**

389 For axial dispersion controlled systems, N_D^* is very large and diffusion effects become
390 negligible. The dispersion controlled versions of Eqs. (18-21) and (23) are shown in the last
391 column of Table 2. The zone velocities for dispersion controlled systems are shown in Eq. (31).
392 The resulting equation for D/F is presented in Eq. (32). For low Reynolds numbers, P_{eb}^* is
393 independent of port velocity. When P_{eb}^* is 50 or larger, the effects of dispersion on D/F and P_R
394 become negligible.

395 Similar to the diffusion controlled case, there is a minimum Peclet number for the SEC-
396 SMB operation to be feasible and it is given by Eq. (33).

$$397 \quad P_{eb,min} = \beta 2, \min P_{eb} \quad IIII \Gamma \min P_{eb} IIII N IIII + \beta 1, \min P_{eb} III \Gamma \min P_{eb} I I N I I$$

398 (33)

399 Equation (20) shows that P_R depends on L_c and P_{eb}^* . However, L_c can be expressed as a
400 function P_{eb}^* using the Chung and Wen correlation for low Reynolds numbers ($Re < 10$), for
401 which Ebj is related to ε_b , R_p , and uOj as follows. [28].

$$402 \quad Ebj = 10 \varepsilon_b R_p uOj \quad (34)$$

403 Since $P_{eb}^{IV} = L_c v / E b j$, Table 1, one can obtain Eq. (35).

$$404 \quad P_{eb}^{IV} = L_c v \frac{1}{O_{\epsilon} b R p u} O_{IV}$$

$$405 \quad (35a)$$

$$406 \quad P_{eb}^* = \phi (\delta^2 - \delta) \frac{1}{L_c v} \frac{1}{O_{\epsilon} b R p u} O_{IV}$$

$$407 \quad (35b)$$

408 The $u O_{IV}$ in Eq. (35) can be replaced by Eq. (31d) to obtain Eq. (36a) and rearranged to solve

409 for column length, Eq. (36b).

$$410 \quad P_{eb}^* = \phi \delta^2 - \delta \frac{1}{1 + \phi \delta} \frac{1}{L_c} \frac{1}{O_{\epsilon} b R p} + \beta \frac{1}{IV N_{IV}}$$

$$411 \quad (36a)$$

$$412 \quad L_c = \frac{1}{O_{\epsilon} b R p} P_{eb}^* \frac{1}{1 + \phi \delta} \frac{1}{\phi \delta^2 - \delta} \frac{1}{1 - \beta} \frac{1}{IV N_{IV}}$$

$$413 \quad (36b)$$

414 Equation (36b) can be substituted for the column length in Eq. (20), where the terms with

415 N_D^* are negligible, to obtain Eq. (37).

$$416 \quad P_{R,i} = v Y_i C F_i \frac{1}{O_{\epsilon} b R p} P_{eb}^{IV} \frac{1}{1 + \phi \delta} -$$

$$417 \quad \beta \frac{1}{IV N_{IV}} \phi \rho p \phi \delta \frac{1}{\alpha - 1} - \frac{1}{P_{eb}^{IV}} \beta \frac{2 III \Gamma III N III}{1 + \beta} \frac{1}{III \Gamma II N II} \quad (37a)$$

418 The P_{eb}^* for maximum $P_R (P_{eb}, \max P_R^*)$ can be found by taking the partial derivative of

419 Eq. (36b) with respect to P_{eb}^* and setting the resulting equation to zero. The value of

420 $P_{eb}, \max P_R^*$ can be determined from yields, material properties, and column configuration, see

Appendix A3. The optimum column configuration for maximum P_R for dispersion controlled systems is shown in Eq. (38).

$$N_{IN} = 1N \quad (38a)$$

$$N_{IIN} = N_{IIIN} \beta^1 \Gamma_{II} \beta^2 \Gamma_{III} \quad (38b)$$

$$N_{IIIN} = 1 - N_{IN} - N_{IVN}^1 + \beta^1 \Gamma_{II} \beta^2 \Gamma_{III} \quad (38c)$$

$$N_{IVN} = 1N \quad (38d)$$

Equation (23) can be simplified into Eq. (39) because the term with N_D^* is negligible. This group can be considered as a ratio of step time to pressure-limited convection time through a column in Zone I. The column length in Eq. (39) can be replaced by Eq. (36b). Thus, for fixed material properties and maximum pressure, the maximum port velocity at every P_{eb}^* can be found. The value of $P_{eb, \max PR^*}$ (Appendix A3) can be substituted into Eq. (39) and rearranged to find the port velocity for maximum P_R , Eq. (40).

$$v_{\max PR} = \frac{\Delta P_{\max} R_p}{375 \phi^2 \mu_{eb} P_{eb}^*} \frac{1 + \phi \delta^1 \phi \delta^2 - \delta^1 - \beta^1 IV N_{IV}^1 + \phi \delta^2 + \beta^2 \Gamma_I \phi \delta^2 - \delta^1 P_{eb, \max PR^*} N_I}{(40)}$$

The port velocity in Eq. (40) will achieve the maximum productivity when yields, material properties, column configuration, viscosity, and maximum operating pressure are specified. If R_p is fixed, there is only one L_c that can satisfy $P_{eb, \max PR^*}$, as expected from Eq. (36b). Using this port velocity to achieve maximum P_R , ensures that the minimum cost design will not be pressure limited, as discussed in Section 3.6.1.

2.5 Optimization Using SSWD

The values of the 15 decision variables (Y_i , R_p , L_c , DV , N^j , ΔP_{max} , u_0^j , and ν), which will achieve minimum solvent, maximum productivity, or minimum cost can be found using the SSWD. Overviews of D/F and P_R as functions of N_D^* and P_{eb}^* can be generated using Eq. (19) and Eq. (20), respectively, for given input parameters (material properties, yields, column configuration, dead volume, and maximum operating pressure). Minimum solvent consumption and maximum productivity can easily be identified from these overviews. With given cost functions (Appendix A4), the total cost surface can also be generated as a function of N_D^* and P_{eb}^* . By varying the input parameters of interest, the surfaces can be used to determine optimum input parameters for minimum solvent consumption, maximum productivity, or minimum cost.

Optimization of the decision variables for maximum productivity becomes simpler for the limiting cases already discussed in Sections 2.3 and 2.4. For diffusion controlled systems, the value of N_D^* and the column configuration can be analytically determined using Eq. (28a) and Eq. (29), respectively. For dispersion controlled systems, the value of P_{eb}^* and the column configuration can be analytically determined using Eq. (A3.1a) and Eq. (38), respectively. However, the values of N_D^* and P_{eb}^* for maximum productivity may not be achievable because not all combinations of port velocity and column length can satisfy a given pressure limit, Eq. (23).

For cost optimizations in this study, the costs are based on \$/kg of product. Detailed cost functions are given in Appendix A4. The overall separation cost (total cost) consists of equipment cost, sorbent (or resin) cost, and solvent cost. Equipment cost is mainly controlled by the maximum allowable pressure and total number of columns, Eq. (A4.2). Resin cost can be

calculated from the sorbent productivity, Eq. (A4.3). Solvent cost can be calculated from solvent consumption, Eq. (A4.4).

Optimization of decision variables for minimum cost can be achieved by evaluating the total cost using the zone velocities and port velocity determined from the SSWD equations. For the insulin example discussed in Section 3, four of the decision variables (Y_i , R_p , and DV) are fixed and the remaining 11 are optimized. The algorithm used to optimize the 11 decision variables (column configuration, column length, operating pressure, zone velocities, and port velocity) to achieve minimum cost is shown in Appendix A5, Fig. A5.1. The example algorithm can easily be extended to optimize the remaining decision variables.

3.0 Results

The experimental D/F and P_R from three literature cases are compared to those of the SSWD. Additionally, D/F and P_R are examined when one dimensionless group is varied at a time. All other variables are held constant. The SEC-SMB for separating insulin from zinc chloride was chosen as the example because the intrinsic parameters for the specific sorbent / buffer system were verified experimentally [8]. The tandem SEC-SMB for insulin purification is then optimized for minimum cost while satisfying an imposed maximum pressure drop per column.

3.1 Comparisons of D/F and P_R of Literature Designs with Those of SSWD

The three literature SEC-SMB separations analyzed in this study are polyethylene glycol fractionation by molecular weight (Case 1, Fig. 4) [12], myoglobin separated from bovine serum albumin (BSA) (Case 2, Fig. 5) [29], and insulin separated from zinc chloride (Case 3, Fig. 6) [8]. A brief summary of the three cases is presented in Table 3 with the complete set of material

properties and design parameters in Appendix B. The operating parameters of Cases 1 and 2 reported in the literature were obtained using the Triangle theory. The operating parameters of Case 3 were designed using the SWD method at the specific N_D^* of 8.9 (Table 3).

The material properties, equipment parameters, and yields for each case reported in the literature were used in the SSWD equations to generate D/F and P_R for a wide range of operating parameters. For Case 1, both N_D^* and P_{eb}^* are very large, making it a nearly ideal system. For Case 2, both N_D^* and P_{eb}^* are relatively small, so both diffusion and dispersion effects are important. For Case 3, N_D^* is relatively small while P_{eb}^* is relatively large, making it a diffusion controlled system.

Figure 4a shows the D/F results from SSWD for Case 1, which is a three-zone open-loop SMB. The minimum D/F from SSWD is about 6.5 because there is no recirculation of the solvent. The difference between the three curves is due to the yield requirements, Table 3. Because the N_D^* value for each of the three runs (1A-1C) is over 4,000, diffusion effects in Case 1 are negligible. The solvent consumption for the Case 1 experiments could have been reduced by about 50% if the operating parameters had been obtained from the SSWD method, Figs. 4a, 7a.

Figure 4b shows the P_R results from SSWD for Case 1. Because the N_D^* values are so large, the P_R^* is very low. The results from SSWD show that P_R could increase over 100 fold if the operating parameters were designed based on $N_D^* \sim 4,600$.

Figure 5 compares the SSWD results with the literature results for Case 2. The experiments in the literature were operated at a relatively low N_D^* (~ 0.4). The curves generated by the SSWD do not extend to lower N_D^* values because assumptions used to obtain Eq. (1) do not hold in the low yield and low N_D^* regime [14]. In Fig. 5a, the D/F curve for 2E is

significantly higher than the other curves because the yield for component 1 (BSA) is very large (99.8%) and the yield for component 2 (Myoglobin) is very low (40.5%) compared to the other experiments. The solvent consumption for these experiments could have been reduced 2-9 fold if the operating parameters were designed using SSWD at the same N_D^* , Fig. 7a.

Figure 5b shows the P_R results from SSWD for Case 2. The P_R curves generated by the SSWD do not extend to low N_D^* (< 0.3) because of the low yield specifications. Because the N_D^* values for the literature are lower than those of Case 1, the productivities are much larger. The productivity values for Case 2A-2E are in the same order of magnitude as that of the SSWD at the same N_D^* . However, the P_R for Case 2A-2E could have been increased 4-6 fold if the operating parameters were designed using SSWD at the same N_D^* , Fig. 7b.

Since the operating parameters for Case 3 were designed using SWD, D/F and P_R of are the same as those from SSWD at the same N_D^* , column configuration (2-3-3-2), and yields (99.7%) Figs. 6-7.

The SSWD works for ideal systems, diffusion controlled systems, or systems where both diffusion and dispersion are significant. For given material properties, yields, and equipment parameters, SSWD can quickly generate an overview of D/F and P_R over a wide range of operating parameters. The conditions for maximum P_R or small D/F can be easily identified from such figures. The comparisons with literature results show that all three cases could have been improved by orders of magnitude using the SSWD method to reduce D/F and/or increase P_R . Without the overview provided by the SSWD, it would be challenging to explore the multi-dimensional SEC-SMB design space with simulations or experiments.

3.2 Example System Based on Insulin Purification for Parametric Studies

In the production of insulin, many purification steps are needed [3]. Before crystallization, SEC is used to separate high molecular weight proteins (HMWP) and zinc chloride (ZnCl_2) from insulin [8]. This batch chromatography produces 99% pure insulin with 89% yield. In 2002, Xie et al. designed and experimentally verified a tandem SEC-SMB system (two SMBs in series) to obtain 99% pure insulin with 99% yield.

The first ring of the tandem SMB (Ring A) separates the HMWP (fast solute) from insulin (slow solute). No constraints are placed on the zinc chloride, which means that zinc chloride is distributed throughout the entire SMB to reduce the impurity to be removed in Ring B. There is significant insulin fronting due to dimerization reactions that occur in Zone III of Ring A. This fronting can be accounted for by assuming that the axial dispersion coefficient in Zone III is 40 times the value predicted by the Chung and Wen correlation [8]. Because of this large axial dispersion, both diffusion and dispersion effects are important for Ring A. The extract from Ring A is then sent to the second SMB (Ring B) to remove the zinc chloride.

Ring B separates zinc chloride (slow solute) from insulin (fast solute). Because of dilution from Ring A, the insulin fronting is insignificant in Ring B. Thus, Ring B is a diffusion controlled system. The solutions for D/F and P_R are calculated according to Table 2. The intrinsic material properties and yields were obtained from Xie et al., 2002, Table 4. The dimensionless parameters in Table 4 are fixed for all figures unless specified otherwise. Ring A will later be used as a cost optimization example (Section 3.6), where both diffusion and dispersion are significant. Ring B is used for the parametric studies in the following sections. The tandem SMB requires significantly less solvent and less sorbent than the batch SEC, Table 5.

3.3 Parametric Studies – Diffusion Controlled

For D/F , P_R , and pressure limit curves in this section, the values for α , λ , γ , δ , ϕ , and yields are reported in Table 4 and are fixed unless noted otherwise. For D/F curves, t_s , R_p , and $D_{p,i}$, are allowed to vary with changing N_D^* . For P_R and pressure limit curves, ε_p , ε_b , $K_{se,i}$, $D_{p,i}$, N , feed concentration ($C_{F,i}$), packing density (ρ_b), and R_p , are fixed at the values reported in Table 4, unless noted otherwise. For P_R curves, t_s is allowed to vary with changing N_D^* . For the pressure limit curves, viscosity (μ) and maximum pressure (ΔP_{max}) are fixed at the values reported in Table 4 and L_c is fixed at 13.5 cm.

3.3.1 N_D^* and Column Configuration

Figure 6 also shows how column configuration affects solvent consumption and sorbent productivity for diffusion controlled systems. Since most industrial applications have a fixed number of columns or valves, it is more useful to determine the optimum distribution of columns, or column configuration, for a given total number of columns. Three column configurations with 12 columns total are plotted for comparison purposes: minimum D/F (2-4-2-4), maximum productivity (2-6-2-2), and an equal distribution (3-3-3-3).

Figure 6a illustrates the relation between N_D^* and D/F for the three column configurations. As N_D^* increases, the step time increases relative to the diffusion time, which means that diffusion becomes less controlling and the system approaches an ideal system with D/F equal to one. Solvent consumption decreases slowly after N_D^* increases beyond 2 for this system. As N_D^* decreases, the denominator of Eq. (25) approaches zero, resulting in a sharp rise in D/F near $N_{D, min}$, which corresponds to the minimum relative diffusion time required for any separation to occur. The vertical line is based on the pressure limits of the system (1.5 psi) [9], and the column length of 13.5 cm, which is the optimal column length to achieve the lowest

total cost Ring B (Section 3.6). This line can be found by solving Eq. (30) for N_D^* because $N_{aP,diff}$ is fixed for fixed material properties, yields, and equipment parameters. N_D^* values to the right of this will give port velocities, or interstitial velocities, which do not exceed the pressure limit.

In this example, diffusivity ratio ($\gamma = 7.21$) is much larger than the selectivity ($\alpha = 1.34$). Because the terms inside the parentheses in Eq. (25) are already relatively small, the column configuration does not have a large impact on D/F .

The effect of N_D^* on P_R is presented in Fig. 6b. There is a minimum N_D^* for P_R to be positive, $N_{D,min}^*$ (~ 0.1), which is the same $N_{D,min}^*$ for D/F . Increasing N_D^* from $N_{D,min}^*$ to $N_{D,max}^*$ will increase P_R , as expected from Eq. (27b). Increasing N_D^* means sharper concentration waves, which mean more effective utilization of the sorbent, or higher sorbent productivity. The P_R curve peaks near $N_D^* = 0.2$, Eq. (28). This N_D^* corresponds to $N_{D,I} \sim 1$, Eq. (16), where the step time is approximately equal to the diffusion time. Increasing N_D^* after this point reduces P_R because the increase in step time is more significant than the reduced wave spreading. In general, the maximum P_R for SEC-SMBs occurs at $N_{D,I} \sim 1$, as evidenced by all three literature cases.

Figure 6b also shows how column configuration significantly affects the maximum P_R . Because γ/α is about 5.4, Eq. (29) gives 2-6-2-2 as the column configuration for maximum productivity. For N_D^* larger than 2, the column configuration does not significantly affect the productivity.

The pressure limit for a column length of 13.5 cm is again shown by the vertical line, indicating that the theoretical maximum productivity is not achieved since the pressure limit, column length, particle size, and column configuration are fixed. The productivity for the lowest

cost system is less than 15% of the theoretical maximum productivity for the 2-6-2-2 column configuration.

3.3.2 Particle Size and Pressure Limit

P_R is strongly affected by particle size, as seen in Fig. 8a. From Eq. (27b), it is obvious that P_R is inversely proportional to R_p^2 for a fixed N_D^* . However, reducing R_p also increases the pressure drop across a column (ΔP). As discussed in Section 2.3, Eq. (28) and Eq. (30) can be used to determine the combination of pressure limit, column length, and particle size ($\Delta P_{max} R_p^4 / L_c^2$), which is needed to achieve the maximum productivity.

In Fig. 8b, $\Delta P / L_c^2$ is plotted for a wide range of R_p (5-500 μm) for fixed column configuration (3-3-3-3) and other material properties (Table 4). The yield for each solute is varied from 90% to 99.9%. This result shows that the pressure drop rapidly increases when R_p is below 50 μm . For a 10 cm column packed with $R_p = 50 \mu\text{m}$, the pressure drop required to realize the maximum productivity is 10 psi. For $R_p = 25 \mu\text{m}$, the productivity can be four times higher (Fig. 8a), but the pressure drop will be about 1,000 psi, which requires high pressure equipment. Conversely, for high pressure SMB equipment with a maximum operating pressure of 1,500 psi, one can find the combination of particle size and column length to maximize productivity. The trade-off between pressure and productivity can be optimized if appropriate cost functions are known.

3.3.3 Yield

The effect of yield on solvent consumption is examined in Fig. 9a. Increasing the yield requirement increases the values of the four β terms in Eq. (25), resulting in the increase of the numerator and the decrease of the denominator. Thus, increasing yield results in increasing D/F . However, the increase in D/F is not very significant until yield is larger than 99%. The increase

after 99% is more significant for small N_D^* (< 1). Increasing N_D^* reduces the dependence of D/F on yield. There is a sharp increase near 100% yield because significantly more solvent is required to confine the very low concentration portions of the waves in their respective zones.

The effect of yield on P_R is presented in Fig. 9b. Increasing yield from 90% does not significantly change P_R until after yield exceeds 99%. From Eq. (27), it can be seen that increasing the values of the β 's in the denominator decreases P_R , but the yield outside the brackets in the numerator mitigates this effect until the yields are very high. Increasing yield requirement means more separation between the solute bands, resulting in less column utilization or lower P_R . The productivity approaches zero near 100% yield because a very small feed flow rate is required for the separation. Increasing N_D^* decreases the dependence of P_R on yield.

3.3.4 Retention Factors and Selectivity

Because N_D^* is dependent on selectivity and retention factors, $N_{D,I}$ was fixed at 6.5, which corresponds to the lowest cost design for Ring B (see Section 3.6.1). Solvent consumption is plotted against α in Fig. 10a. Increasing α always decreases D/F because there is an increasing difference in wave velocities but there is little gain when α is larger than 1.5. There is a vertical asymptote at α equal to one because there would be no difference in the wave velocities of the two species and no separation could occur. The effect of the retention factors (δ) can also be seen in Fig. 10a. The lines for δ_I stop at different α 's because there is a maximum δ_2 in SEC. When a solute accesses all the pore space, the maximum size-exclusion factor is one and the maximum δ is equal to the particle porosity if DV is negligible, Eq. (4). The D/F values are higher for larger δ 's because more solvent is needed for the solutes to diffuse out of the particles at the same α .

Increasing α always increases the P_R , as shown in Fig. 10b. Increasing α is shown as increasing δ_2 for a fixed δ_I . The more the slow solute can access the pore volume, the more

efficiently the sorbent particles are used. Therefore, a larger retention factor for the slow solute provides a higher productivity at the same selectivity. The P_R linearly increases with selectivity because the P_R for an ideal system is linearly dependent on selectivity, as are the correction terms for non-ideal SEC systems with negligible DV , Eq. (27a).

3.3.5 Dead Volume Effect on Retention Factors and Selectivity

Extra-column DV increases the retention factors and introduces dispersion effects. The dispersion can be plug flow (no dispersion), Taylor dispersion, or that of a completely stirred tank. Since they are equipment dependent, they are not considered in this study. Only the effect of DV on the retention factors, and subsequently selectivity, is discussed below.

Increasing DV increases the values of the retention factors (δ), Eq. (4). Since N_D^* is dependent on δ , Eq. (16), constant $N_{D,I}$ curves are shown in Fig. 11. Dead volume can significantly increase D/F , Fig. 11a. From Eq. (25), it is clear that increasing δ values increases D/F for diffusion controlled systems. However, the effect of DV can be significantly reduced at larger $N_{D,I}$. Because the difference in the retention factors is unaffected by DV , D/F is unaffected by DV at large $N_{D,I}$, Eq. (13). Dead volumes less than 2% ($DV < 0.02$) do not significantly increase D/F for this system.

Increasing the DV of the system reduces the selectivity, which in turn reduces the productivity, Fig. 11b. It can be seen from Eq. (14) that increasing $N_{D,I}$ can reduce the impact of DV because the difference in retention factors is not affected by DV . However, the productivity also decreases with increasing $N_{D,I}$. Dead volumes less than 2% do not significantly affect the productivity of the SEC-SMB.

3.3.6 Diffusivity Ratio

The effect of diffusivity ratio (γ) on D/F is explored in Fig. 12a. As γ increases, D/F decreases when N_D^* is a fixed parameter (i.e. $N_{D,I}$ is fixed). Increasing γ with a fixed $N_{D,I}$ is equivalent to increasing $D_{p,2}$. By increasing the diffusivity of the slow solute, the concentration waves become sharper and thus require less solvent to prevent the waves from spreading into different zones. There is a minimum value of γ for the system to be feasible, as discussed in Section 2.3. For γ greater than three, D/F does not change significantly. The D/F dependence on γ is larger at low N_D^* , where diffusion effects are more significant.

The P_R curves always increase with increasing γ , until P_R reaches a plateau. The waves become sharper, resulting in increased column utilization or sorbent productivity, Fig. 12b. As discussed in Section 2.3, there is a minimum γ for P_R to be positive. The P_R does not change significantly after γ exceeds 3. Increasing N_D^* reduces P_R , and also reduces the dependence of P_R on γ .

Figures 10 and 12 show that large α and large γ both decrease D/F and increase P_R . A large ratio of γ/α can also decrease D/F and increase P_R , as shown in Eqs. (25) and (27a). If γ/α is small, increasing the length of Zones I and III can have a similar effect on D/F as increasing γ/α , Eq. (25). Increasing the length of Zone III also increases P_R , Eq. (27a).

3.3.7 Phase Ratio

For diffusion controlled systems, D/F is independent of the phase ratio (ϕ), Eq. (25), because N_D^* is independent of ϕ , Table 1. The P_R is also independent of ϕ , Eq. (27).

3.4 Parametric Studies – Dispersion Controlled

As shown in Table 2, D/F , P_R , and N_{AP} are functions of Γ . To obtain values for Γ , axial dispersion coefficients were estimated using the Chung and Wen correlation for low Re , Eq. (34). For D/F , P_R , and pressure limit curves in this section, the values for α , δ , ϕ , and yields are reported in Table 4 and are fixed unless noted otherwise. For D/F curves, L_c and R_p are allowed to vary with changing P_{eb}^* . For P_R and pressure curves, the values of ε_b , N , $C_{F,i}$, ρ_p , and R_p , are given in Table 4, unless noted otherwise. The port velocity for P_R and pressure curves is fixed at 1 cm/min. For P_R curves, L_c varies with changing P_{eb}^* . For the pressure curves, μ and ΔP_{max} are fixed at the values reported in Table 4 and L_c is fixed at 13.5 cm.

3.4.1 P_{eb}^* and Column Configuration

The effect of P_{eb}^* on D/F is illustrated in Fig. 13a. There is a minimum P_{eb}^* for the system to be feasible, as predicted by Eq. (33). The D/F decreases with increasing P_{eb}^* because axial dispersion effects decrease. These trends are supported by Eq. (32). The D/F does not change much after a P_{eb}^* of 50 ($L_c/R_p \sim 900$ for the given ϕ and δ , Eq. (35a)), when the dispersion effects start becoming negligible.

Figure 13a also shows the effect of column configuration on D/F . From Eq. (32), it is apparent that increasing the zone length of any zone will decrease D/F . Since the Γ values for the four zones are not very different from each other, the column configuration for minimum D/F is an equal distribution (3-3-3-3). However, the D/F curve for the minimum D/F configuration is only slightly better than the D/F curve for the maximum P_R configuration (2-4-4-2).

For a fixed particle size, increasing P_{eb}^* is equivalent to increasing the column length. Because maximum pressure drop and port velocity are fixed, the maximum column length can be

illustrated in Fig. 13 as a vertical line. The vertical line represents the maximum P_{eb}^* allowed by the pressure limit. Values to the left of the line will satisfy the pressure limit.

The effect of P_{eb}^* on P_R is illustrated in Fig. 13b and can be seen from Eq. (35). There is a minimum P_{eb}^* for the SMB to have a positive P_R , which is the same minimum P_{eb}^* for D/F . P_R increases with increasing P_{eb}^* rapidly at first, then peaks, and then slowly decreases. Increasing P_{eb}^* decreases the effects from axial dispersion. The maximum P_R occurs around a P_{eb}^* of 6. The effects of column configuration can also be seen in Fig. 13b. Longer Zones II and III can increase P_R significantly, as expected from Eq. (37), but there is no effect at large P_{eb}^* (>50) because the dispersion effects become negligible.

3.4.2 Yield

The effect of yield requirement on D/F for dispersion controlled systems is shown in Fig. 14a. Increasing yield requirement always increases D/F because of the extra solvent needed to confine the low concentration portions of the waves. This trend is similar to that for diffusion controlled systems. D/F does not change much until after yield exceeds 99%. There is a sharp increase near 100% yield because significantly more solvent is required to confine the very low concentration portions of the waves in their respective zones. Increasing P_{eb}^* decreases the effect of yield on D/F because dispersion effects decrease.

The effect of yield on P_R is shown in Fig. 14b. Productivity does not significantly change with yield until it exceeds 99%. Increasing P_{eb}^* decreases the effect of yield on P_R , but also decreases P_R . To approach 100% yield, the feed flowrate must be significantly reduced, resulting in very small P_R .

3.4.3 Retention Factors and Selectivity

Because P_{eb}^* is a function of retention factors and selectivity (Table 1), Fig. 15 is generated using a constant Peclet number in Zone IV ($P_{eb}^{IV} = 50$). At very low selectivities ($\alpha \sim 1$), very large amounts of solvent are required to achieve separation, Fig. 15a. Increasing α decreases the amount of solvent required for the separation because less solvent is needed to confine the concentration waves in their respective zones. Larger values of retention factors at the same α result in lower D/F . This result can be explained by Eq. (17) and Eq. (32) because increasing the retention factors increases P_{eb}^* , which decreases D/F . The lines for different retention factors end at different α 's because of the limit on the maximum value of a retention factor in SEC.

The impact of α on P_R can be seen in Fig. 15b. Productivity increases linearly with increasing α , Eq. (36a). Increasing δ_1 , while maintaining the same α , results in a larger P_R because a larger amount of the pore phase of the sorbent particles is being accessed by the solutes, increasing the column utilization and productivity.

3.4.4 Phase Ratio

The solvent consumption (D/F) as a function of P_{eb}^* is given in Eq. (32). For constant P_{eb}^* , D/F has only a weak dependence on ϕ because the axial dispersion coefficient ratios (F') are weak functions of ϕ , Eq. (A2.1). The phase ratio only affects D/F for low P_{eb}^* (<20), figure not shown. Increasing ϕ increases P_R for dispersion controlled systems, according to Eq. (36b). The term $(1 + \phi\delta_I)/\phi$ does not change significantly with increasing ϕ , but decreasing the ε_b in the denominator outside the brackets increases P_R , figure not shown.

3.5 Comparison of Diffusion Controlled and Dispersion Controlled Systems

Diffusion controlled systems and dispersion controlled systems are very similar in how D/F and P_R vary with the dimensionless groups. Increasing N_D^* (or P_{eb}^*) decreases D/F while P_R increases to a maximum and then decreases. Increasing α decreases D/F and increases P_R while increasing yield increases D/F and decreases P_R . Small retention factors favor low D/F and high P_R for diffusion controlled systems, whereas large retention factors are better for dispersion controlled systems. Increasing γ decreases D/F and increases P_R for diffusion controlled systems, but has no effect on dispersion controlled systems. Increasing ϕ increases P_R for dispersion controlled systems, but has no effect on D/F or P_R for diffusion controlled systems. Maximum P_R for diffusion controlled systems can be achieved when the diffusion time, step time, and pressure-limited convection time are matched. For dispersion controlled systems, the maximum P_R occurs when the axial dispersion time is about 10 times the step time and 50 times the convection time.

3.6 Cost Optimization of SEC-SMB for Insulin Purification

The production scale was chosen to be 5,000 kg insulin / year and the optimization results are reported in Table 5. Low pressure SMB (< 150 psi per zone) equipment was chosen because at this production scale, the equipment cost is dominating and high pressure equipment would be even more expensive. The sorbent was chosen to be the same as the sorbent used in the batch purification of insulin because the material properties are known and the performance of optimized SEC-SMB can be compared with that of batch SEC. For this particular sorbent, Sephadex G50, the maximum pressure drop per column is limited to 1.5 psi. The total dead volume was kept at 1.9% of the total packing volume because DV less than 2% does not significantly affect D/F or P_R , Fig. 11. The yield specifications for both rings were set at 99%

because Fig. 9 shows that the yields do not significantly affect D/F or P_R unless they are specified over 99%. The potential impact of optimizing particle size on total cost is small ($< 2\%$) for this sorbent, and will be discussed in the following section. For these reasons, four decision variables (Y_i, R_p, DV) were fixed, while the remaining 11 decision variables ($L_c, N^j, \Delta P_{max}, u_0^j$, and v) were optimized for minimum cost. Optimization of the 11 decision variables for one ring takes less than one minute on a laptop.

3.6.1 Ring B Cost Optimization

Ring B is diffusion controlled whereas both diffusion and dispersion effects are important in Ring A. For this reason, the optimization of Ring B is discussed first. Because the material properties are fixed, the total cost for Ring B can be plotted versus N_D^* as a single 2-D curve, Fig. 16. Cost functions for solvent, sorbent, and equipment are presented in Appendix A4. Unit equipment cost does not vary with N_D^* for fixed N^j and ΔP_{max} . At low N_D^* ($< 0.2, ND, \max PR^*$), sorbent and solvent costs are high because D/F is large and productivity is low, Fig. 6. The costs decrease with increasing N_D^* as D/F decreases and productivity increases. When N_D^* is larger than $ND, \max PR^*$, the sorbent cost increases with N_D^* because the productivity decreases. This increase in the sorbent cost causes a minimum in the total cost curve. This minimum, however, does not satisfy the pressure limit for this system. As a result, the lowest cost design allowed by the pressure is at $N_D^* \sim 2$. At this N_D^* , column configuration has little effect on D/F or productivity, Fig. 6. However, the equipment cost can be lowered by using fewer columns. Thus, the optimum column configuration is 2-2-2-2 if a minimum of two columns per zone is required.

If production scales are much larger than that of insulin, the unit equipment cost can be a small fraction of the total separation cost. In these cases, optimization of the material properties (especially R_p) and equipment parameters (L_c , ΔP_{max}) can significantly reduce the separation cost. For diffusion controlled systems, one can find the optimal combination of $(\Delta P_{max} R_p^4 / L_c^2)$, using Eq. (30a), such that the minimum cost design is feasible. One can use ND , $\max PR^*$, Eq. (28a), in Eq. (30a) to obtain $N\Delta P_{diff, \max PR}$. With ϕ and viscosity (μ), the value of $(\Delta P_{max} R_p^4 / L_c^2)$ can be calculated. Because the value of N_D^* corresponding to the minimum cost design is always greater than, or equal to, ND , $\max PR^*$, designing $\Delta P_{max} R_p^4 / L_c^2$ for maximum P_R will always satisfy the pressure limit at the minimum cost design.

For dispersion controlled systems, Eq. (39) can be used to find the minimum N_{aP} at the P_{eb}^* value corresponding to the minimum cost design. The value of N_{aP} can then be used to find a value of $(\Delta P_{max} R_p^2 / L_c \nu)$, which ensures that the minimum cost design satisfies the pressure limit. For systems in which both diffusion and dispersion effects are significant, Eq. (23) can be used in a similar manner.

The calculated cost of Ring B based on the experimental design reported by Xie et al., 2002 is about \$6 higher than the minimum cost found in this study. Their operating conditions were based on SWD for a fixed column length, 13.7 cm, and 10 columns were used instead eight columns, the optimum number of columns obtained from SSWD. The switching time was also longer than the optimum switching time, resulting in $N_D^* = 8.9$. The calculated cost falls close to the SSWD prediction for $N_D^* = 8.9$, Fig. 16. The difference in total cost is mainly due to the difference in the total number of columns.

3.6.2 Ring A Cost Optimization

Because both diffusion and dispersion effects are important for Ring A, the total cost should be plotted against N_D^* and P_{eb}^* as a 3D surface. However, the total cost surface is concave up and cannot be easily viewed. As such, the inverse of the total cost is plotted against N_D^* and P_{eb}^* in Fig. 17a. Since the z-axis is the inverse of total cost, the maximum point of the surface corresponds to the minimum cost design.

The grey surface represents the pressure limit and divides the cost surface into feasible and infeasible regions. N_D^* lower than the pressure surface and P_{eb}^* larger than the surface would violate the maximum pressure constraint. Because the system is limited by pressure, the achievable minimum cost point is $N_D^* = 14.9$ and $P_{eb}^* = 560$, which is marked on a contour plot of the surface, Fig. 17b. The lines in Fig. 17b represent constant total cost values projected onto the N_D^* and P_{eb}^* plane. The black dashed line is the pressure limit. The region below the black line is infeasible. A summary of the optimized costs and equipment parameters are shown in Table 5.

Table 5 compares batch SEC production of insulin and two different SEC-SMB systems based on the same sorbent. The SMB design of Xie in 2002 was based on the operating parameters from the SWD method for a fixed column length of 13.7 cm. A cost optimized SMB design for both Ring A and Ring B was found using the SSWD equations, Table 5. The cost optimized design reduced the overall separation cost by 16% from the design of Xie et al. Both SMBs are significantly lower in cost than the batch method. The optimized SMB reduces the solvent consumption from batch SEC by 66%, increases the productivity by 34 times, and reduces the cost by 62%.

3.6.3 Ring B Material Property and DV Sensitivity

The cost optimization shown in Table 5 is based on the material properties, pressure limit, and dead volume of the experimental system of Xie et al. Column length and configuration are optimized to reduce the unit separation cost. If the material properties, pressure limit, and dead volume are allowed to vary, the SSWD can further reduce the separation cost. The effects of changing each of the equipment parameters and material properties on solvent cost and sorbent cost are shown in Table 6.

Increasing the pressure limit from 1.5 to 50 psi per column moves the pressure limit line in Fig. 16 to a lower N_D^* , allowing the system to be designed at the N_D^* corresponding to the global minimum cost. As a result, D/F decreases by 5% and P_R increases by 16%. The separation cost only reduces by 1% because the equipment cost is dominating at 83% of the total cost. Because the minimum cost N_D^* was already accessible at 50 psi per column, increasing the pressure limit to 75 psi per column does not change the value of N_D^* for minimum cost. Only the aspect ratio of the column increases (L_c increases, ID decreases). This change can be explained by the left-hand side of Eq. 30a.

As expected from Fig. 11, decreasing the dead volume from 1.9% CV in the base case to zero has little effect on D/F or P_R , while increasing the dead volume to 10% CV increases D/F by 5% and decreases P_R by 16%.

The bed void fraction can only be varied from 0.3 to 0.4, and does not directly affect D/F (Eq. 19) or P_R for diffusion controlled systems (Eq. 27b), as expected. However, it indirectly affects P_R because larger ε_b values result in longer columns for the same pressure drop, Eq. (22), which allows for a smaller N_D^* value, which results in slightly higher P_R (2%). However, the overall impact on D/F or P_R is relatively small for this system.

The particle porosity does not typically exceed 0.95. Increasing ε_p from 0.89 to 0.95 does not have much of an effect on D/F or P_R . However, decreasing ε_p to 0.5 reduces both the dimensionless diffusion rate, N_D^* , and the δ 's, resulting in increasing D/F by 10%, Eq. (25), and decreasing P_R by 65%, Eq. (27b).

Increasing the diffusivity ratio from 7.2 to 100 does not significantly reduce D/F , Eq. (25), but increases P_R by 11%, Eq. (27b). Decreasing the diffusivity ratio to 1 increases D/F by 8% and decreases P_R by 34%, as expected from the trends shown in Fig. 12.

Reducing the size-exclusion coefficient of insulin from 0.74 to 0.1 increases selectivity from 1.3 to 7.7, which reduces D/F by 23% and increases P_R by 676%, Eq. (25) and Eq. (27b), respectively. Further reduction of the size-exclusion coefficient of insulin to 0.01 increases the selectivity to ~ 23 , does not further reduce D/F and further increases P_R by 9%.

Low pressure sorbents do not typically have radii much smaller than 25 microns, because smaller particles will require a packing length much shorter than 10 cm, as expected from Fig. 8b. Decreasing the particle radius from 54 to 25 μm reduces D/F by 9% and increases P_R by 110%, Eqs. (13, 15). However, L_c is impractically small because of the limited pressure drop of 1.5 psi per column. Increasing R_p to 100 μm increases D/F by 16% and decreases P_R by 53%, Eq. (13) and Eq. (15), respectively.

The result of combining all the hypothetical changes in the material properties and equipment parameters is shown in the last row of Table 6. The D/F approaches that of an ideal system, as a result of the high selectivity and zero DV . The P_R increases by 66 fold mainly because of the synergistic effects of reducing particle size, increasing selectivity, and increasing the pressure limit. The total cost approaches the lowest possible total cost for the given feed concentration, because the sorbent cost becomes negligible and the solvent cost approaches that

of an ideal system. Further decrease in unit solvent cost is only possible if the feed concentration can be increased. Increasing feed concentration would also reduce the unit equipment cost because the production rate is increased using the same equipment. The results in Table 6 indicate that the factors with the largest impact on solvent and sorbent costs are particle size, selectivity, and pressure limit.

In this example, equipment cost is dominating (81-90%) because of the small production scale (5,000 kg/year). Optimization of the material properties and equipment parameters has limited impact on the total separation cost (8%). However, for other applications with much larger production scales, optimization of the material properties and equipment parameters can significantly reduce the total separation cost.

4.0 Conclusions

By solving the SWD equations with dimensionless groups, analytical expressions for solvent consumption (D/F) and sorbent productivity (P_R) were obtained for SEC-SMBs. Solvent consumption and sorbent productivity are clearly related to the material properties, equipment parameters, and operating parameters. The sensitivity of solvent cost, sorbent cost, and total cost with respect to the material, equipment, and operating parameters was also elucidated.

The results of the parametric studies show that for diffusion controlled systems, one can reduce D/F and increase P_R by increasing selectivity (α), diffusivity ratio (γ), or γ/α . Decreasing retention factors (δ_i) reduces D/F , but also decreases P_R . The phase ratio (ϕ) does not affect D/F or P_R . When the yield specification is larger than 99%, D/F significantly increases and P_R significantly decreases. The key dimensionless group governing the operating parameters is N_D^* . There is a minimum value (N_D, min^*) required for the operation to be feasible. Increasing N_D^*

will always reduce D/F , but the P_R peaks at about twice ND , min^* , after which P_R decreases with increasing N_D^* . The column configuration (N^j) does not significantly affect D/F , but can significantly increase the peak P_R . Dead volume (DV) should be reduced to less than 2% of the total packing volume to minimize its impact on D/F and P_R . The competing effects of solvent consumption and P_R result in a cost minimum because solvent cost always decreases with N_D^* and sorbent cost increases when $N_D^* > ND$, $maxPR^*$. However, the cost minimum may not be achievable if the system has a pressure limit. The combination of $(\Delta PR_p^4/L_c^2)$ which allows access to the cost minimum can be calculated from ND , $maxPR^*$, material properties (other than R_p), yields, column configuration, and viscosity, Eq. (30a). The corresponding $N_{AP,diff}$ for maximum P_R is about 1 for the example system. Thus, the diffusion time, step time, and pressure-limited convection time are approximately equal at the maximum P_R .

For dispersion controlled systems, D/F can be reduced and P_R can be increased by increasing α and increasing retention factors. The dependence of D/F on retention factors is opposite to that of diffusion controlled systems. Increasing phase ratio does not significantly reduce D/F , but does increase P_R . The effects of yield specification on D/F and P_R are similar to those for diffusion controlled systems. The key dimensionless group controlling the operating parameters is P_{eb}^* . The effects of P_{eb}^* on D/F and P_R are also similar to those of N_D^* for diffusion controlled systems. The column configuration and DV have similar effects on D/F and P_R as those of diffusion controlled systems. The value of $(\Delta P_{max} R_p^2/L_c)$ can be found at the value of P_{eb}^* for minimum cost from Eq. (39), such that the minimum cost design satisfies the pressure limit. The value of $P_{eb,maxPR^*}$ can be calculated from yields, material properties, and column

configuration. The maximum P_R occurs when the axial dispersion time is about 10 times the step time and about 50 times the pressure-limited convection time.

The recast SWD solutions of D/F and productivity can be used to optimize SMB designs. This method was demonstrated using insulin purification as an example and the optimal SMB design was compared to the industrial batch process. Optimization of 11 parameters (column length, column configuration, operating pressure, and operating parameters) reduces the solvent consumption from batch SEC by 66%, increases the sorbent productivity by 34 times, and reduces the total cost by 62%. If the material properties, pressure limit, and dead volume are allowed to change, solvent consumption can be further reduced by 28% and productivity can be further increased by 67 times. Since the equipment cost dominates (81% of total cost) at this relatively small production scale, optimization of the material properties and pressure limit only reduces the separation cost by 8%, Table 6. Among the material properties, selectivity and particle size have the largest impact on solvent consumption and sorbent productivity. For applications with large production scales, the unit equipment cost is expected to be a small fraction of the total cost, and this general optimization method is expected to significantly reduce solvent consumption, increase sorbent productivity, and reduce separation cost.

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1030 **Appendices**

1031 *Appendix A – Additional Equations and Cost Optimization*

1032

1033 *Appendix A1 – Equations Relating β_{ij} to Yields and Zone Velocities*

1034 The equations for the β terms are given by Eq. (A1.1), which were derived from
1035 equations presented in Hritzko et al. [15].

$$1036 \beta_{2I} = \ln \frac{Y_{2I} - Y_{2u} O_{III} I_{uOIV}}{1 - u O_{II} I_{uOI}}$$

$$1037 \quad (A1.1a)$$

$$1038 \beta_{1II} = \ln \frac{u O_{IuOII} - 1}{1 - Y_{1Y} 1 - u O_{IV} u O_{III} - 1}$$

$$1039 \quad (A1.1b)$$

$$1040 \beta_{2III} = \ln \frac{1 - u O_{IV} u O_{III} 1 - Y_{2Y} 2u O_{IuOII} - 1}{1 + 1}$$

$$1041 \quad (A1.1c)$$

$$1042 \beta_{1IV} = \ln \frac{Y_{1I} 1 - Y_{1I} 1 - u O_{II} I_{uOI} O_{III} I_{uOIV} - 1}{1}$$

$$1043 \quad (A1.1d)$$

1044 *Appendix A2 – Expression of Γ_j Using the Chung and Wen Correlation for Low Re*

1045 The Chung and Wen correlation for low Re ($Re < 10$) (Eq. 34) was used to evaluate the
1046 ratios of axial dispersion coefficients (Γ^j) from Eq. (9). The resulting equations are rearranged to
1047 solve for Γ^j , Eq. (A2.1).

$$1048 \Gamma I = 1 + \phi \delta 2 I + \phi \delta 1 - \phi \delta 2 - \delta 1 P e b * \beta 1 I V N I V + \beta 2 I N I$$

$$1049 \quad (A2.1a)$$

$$\Gamma_{II} = 1 + \phi\delta 11 + \phi\delta 1 - \phi\delta 2 - \delta 1 P_{eb} \star \beta 1 IVNIV + \beta 1 IINII$$

$$(A2.1b)$$

$$\Gamma_{III} = 1 + \phi\delta 21 + \phi\delta 1 - \phi\delta 2 - \delta 1 P_{eb} \star \beta 1 IVNIV - \beta 2 IIINIII$$

$$(A2.1c)$$

Appendix A3 – Expression for P_{eb}^* for Maximum Productivity in Dispersion Controlled Systems

The Peclet number for maximum productivity, $P_{eb, \max PR}^*$, at a constant port velocity can be found by taking the partial derivative of Eq. (37b) with respect to P_{eb}^* and setting the resulting equation equal to zero. The expression that $P_{eb, \max PR}^*$ must satisfy is given by Eq. (A3.1).

$$\begin{aligned} & 1 + \phi\delta 1\phi\delta 2 - \delta 1\beta 1 IINII + 1 + \phi\delta 1\phi\delta 2 - \delta 1 P_{eb} \star - \beta 1 IVNIV + 1 + \phi\delta 1\phi\delta 2 - \delta 1 P_{eb} \star - \beta 1 IINII - \beta 1 IV \\ & NIV + 2 + 1 + \phi\delta 2\phi\delta 2 - \delta 1\beta 2 IIINIII + 1 + \phi\delta 1\phi\delta 2 - \delta 1 P_{eb} \star - \beta 1 IVNIV + 1 + \phi\delta 1\phi\delta 2 - \delta 1 P_{eb} \star + \beta 2 III \\ & NIII - \beta 1 IVNIV + 2 + 1 + \phi\delta 1\phi\delta 2 - \delta 1\beta 1 IINII + 1 + \phi\delta 1\phi\delta 2 - \delta 1 P_{eb} \star - \beta 1 IINII - \beta 1 IVNIV + 1 + \phi\delta 2 \\ & \phi\delta 2 - \delta 1\beta 2 IIINIII + 1 + \phi\delta 1\phi\delta 2 - \delta 1 P_{eb} \star + \beta 2 IIINIII - \beta 1 IVNIV = 1 \end{aligned}$$

$$(A3.1a)$$

At a large P_{eb}^* , or a large number of columns in all zones, Eq. (A3.1a) simplifies to Eq. (A3.1b).

$$P_{eb, \max PR}^* = 2\beta 1 IINII + 2 + 1 + \phi\delta 21 + \phi\delta 1\beta 2 IIINIII$$

$$(A3.1b)$$

Appendix A4 – Cost Functions

The total cost (TC) is defined as the sum of the Equipment Cost (EC), Resin Cost (RC), and Solvent Cost (SC), Eq. (A4.1).

$$TC = EC + RC + SC \quad (A4.1)$$

The purchase cost of the equipment is assumed to be \$400,000 plus \$10,000 per column with a depreciation time of seven years and 4% downtime for a production scale of 5,000 kg insulin per year. The unit equipment cost is given by Eq. (A4.2)

$$EC \text{ \$kginsulin} = 400,000\$ + 10,000\$ \text{column} N \text{columns} 7 \text{ years} 0.965,000 \text{ kginsulinyear} \quad (A4.2)$$

The purchase cost for the sorbent is assumed to be \$150 per liter. The usable life of the sorbent is assumed to four years. The diameter of the columns is determined by the production rate and the zone velocities. The unit sorbent cost is given by Eq. (A4.3).

$$RC \text{ \$kginsulin} = \text{Bed} \text{Vol} (1 - \epsilon b) (\rho_{\text{particle}}) \text{Resin price} \text{Resin Life} \text{Production} = N L c \pi D^2 4 L 1 - \epsilon b 0.12 \text{ kgL} 3086.5 \text{ \$kg} 4 \text{ years} 5,000 \text{ kginsulinyear} \quad (A4.3)$$

The purchase price of solvent is assumed to be \$0.10 per liter. Assuming no recycle of the recycle, the unit solvent cost is given by Eq. (A4.4).

$$SC \text{ \$kginsulin} = 1 + DF \text{Solvent price} \text{Feed Conc.} \text{Yield} = 1 + DF 0.1 \text{ \$ / L } 1,000 \text{ ginsulin kginsulin} \text{Feed conc. ginsulinLYield} \quad (A4.4)$$

Batch SEC equipment cost is assumed to be \$100,000 per unit of 12 columns with the same depreciation rate, resin life, and utilization factor as that of the SEC-SMB.

Appendix A5 – Cost Optimization Algorithm

The algorithm that was used to determine the optimum column configuration, column length, zone velocities, and port velocity for minimum cost is shown in Fig. A5.1. Material properties, yields, dead volume, pressure limit, feed concentration, packing density, fluid viscosity, and production scale were held constant. The total number of columns was varied from eight to twelve and each zone was constrained to have at least two columns. The number of columns in Zone IV was calculated from the column balance of the other zones and the total number of columns. N_D^* ranged from 0.02 to 100 and P_{eb}^* ranged from 5 to 1,000. The initial values of the variables were sent to the SSWD algorithm, Fig. A5.1b. This algorithm used an initial guess for β_i^j and Γ^j and then evaluated u_0^j/v . The SSWD algorithm then calculated β_i^j and Γ^j from u_0^j/v using Eq. (A1.1) and Eq. (A2.1), respectively. If the calculated values were not within a tolerance of 0.001 of the guessed values, then the u_0^j/v calculations were repeated with the new values of β_i^j and Γ^j . Once the values were within the tolerance, L_c was calculated from P_{eb}^* using Eq. (36b) and v was calculated from N_D^* using Eq. (6) and Eq. (16). After v was calculated, the zone velocities could be calculated using Eq. (18). The solvent consumption and sorbent productivity were then calculated using Eq. (19) and Eq. (20), respectively. The total cost of the separation was then calculated using Eqs. (A4.1-A4.4). The pressure drop of the system was calculated from Eq. (22) and compared to the set pressure limit of 1.5 psi per column. If the calculated pressure exceeded the pressure limit, then the design was not considered feasible. After the pressure check, the Peclet number was incremented and the process repeated until it reached 1,000. Then N_D^* was incremented and the P_{eb}^* cycle was repeated. Once N_D^* reached a value of 100, the column configuration would change, and the N_D^* and P_{eb}^* cycles would repeat. After all the cycles were completed, the minimum cost was found from all the stored values and

1112 the associated cost, L_c , N^j , u_{θ}^j , and ν were determined. This algorithm was implemented using
1113 MATLAB R2014a on a laptop computer with a total run time of less than one minute.

1114 ***Appendix B – Parameters from Literature Cases***

1115 The expanded sets of parameters are shown in tables for Case 1 (Table B.1), Case 2
1116 (Table B.2), and Case 3 (Table B.3).

1117

Figure Captions

Figure 1. Diagram of a four-zone SMB. (a) Step N ; (b) step $N + 1$.

Figure 2. Design overview.

Figure 3. Standing Wave Design mid-step concentration profiles for a binary, non-ideal separation.

Figure 4. Comparison of (a) D/F and (b) productivity for Case 1.

Figure 5. Comparison of (a) D/F and (b) productivity for Case 2.

Figure 6. (a) D/F and (b) P_R for three column configurations with varying N_D^* - diffusion controlled. Vertical line represents the minimum N_D^* allowed by the pressure limitation (designs to the left of the line are not feasible). D/F and P_R curves for $N^j = 2-3-3-2$ are at 99.9% yield to match data point from Xie et al.

Figure 7. Comparison of (a) D/F and (b) productivity for literature designs and SSWD of SEC-SMB at the same N_D^* .

Figure 8. (a) Productivity at varying R_p and (b) pressure drop per length² vs. R_p at varying yields (fixed $N_D^* = ND, \max PR^* \sim 0.2$) – diffusion controlled.

Figure 9. (a) D/F and (b) P_R vs. yield at various N_D^* - diffusion controlled, 3-3-3-3 configuration.

Figure 10. (a) D/F and (b) P_R vs. selectivity at a fixed N_D^* and various δ_I – diffusion controlled, 3-3-3-3 configuration. Fixed $N_{D,I} = 6.5$.

Figure 11. (a) D/F and (b) P_R vs. DV for various $N_{D,I}$ - diffusion controlled, 3-3-3-3 configuration.

Figure 12. (a) D/F and (b) P_R vs. γ at various N_D^* - diffusion controlled, 3-3-3-3 configuration.

Figure 13. (a) D/F and (b) P_R vs. P_{eb}^* for multiple column configurations at constant port velocity = 1 cm/min – dispersion controlled. Vertical line represents the maximum P_{eb}^* allowed by the pressure limitation (designs to the right of the line are not feasible).

Figure 14. (a) D/F and (b) P_R vs. yield at varying P_{eb}^* . Constant port velocity = 1 cm/min – dispersion controlled.

Figure 15. (a) D/F and (b) P_R vs. selectivity at various values for δ_I . P_{eb}^{IV} fixed at 50 and port velocity fixed at 1 cm/min – dispersion controlled, 3-3-3-3 configuration.

Figure 16. Estimates of total, resin, and solvent costs vs. N_D^* – diffusion controlled, 2-2-2-2 configuration. Black star indicates minimum achievable cost at pressure limit.

1160
1161 Figure 17. (a) Inverse of total cost curve vs. P_{eb}^* and N_D^* for Ring A. Pressure limit is indicated
1162 by the black surface and indicates the minimum N_D^* at each P_{eb}^* for the system to not exceed the
1163 maximum pressure. (b) Contour plot of (a). Black dashed line represents the maximum pressure
1164 limit. Regions below the black line are infeasible.

1165
1166 Figure A5.1. (a) algorithm for optimizing 11 decision variables (column configuration, column
1167 length, zone velocities, and port velocity) for minimum cost and (b) algorithm used by SSWD to
1168 determine column length, β_i^j , Γ^j , zone velocities, and port velocity from given dimensionless
1169 groups.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

(a)

(b)

Figure 6

(a)

(b)

Figure 7

(a)

(b)

Figure 8

(a)

(b)

Figure 9

(a)

(b)

Figure 10

(a)

(b)

Figure 11

(a)

(b)

Figure 12

(a)

(b)

Figure 13

(a)

(b)

Figure 14

(a)

(b)

Figure 15

(a)

(b)

Figure 16

Figure 17

(a)

(b)

Figure A5.1

Table 1. Dimensionless variables and groups for binary, SEC-SMB

Symbol	Name	Definition	Description
δ_i	Retention factor	$\delta_i = \varepsilon_p K_{se,i} + \frac{DV}{(1 - \varepsilon_b)}$	Measure of how much each component is retained by the sorbent
α	Selectivity	$\alpha = \frac{\delta_2}{\delta_1}$	Ratio of retention factors: greater than one for separation
β_i^j	-	$\beta_i^j = \ln \left(\frac{C_{max,i}^j}{C_{min,i}^j} \right)$	Natural log of ratio of max. conc. to min. conc. of standing component i in zone j
γ	Diffusivity ratio	$\gamma = \frac{D_{p,2}}{D_{p,1}}$	Ratio of intraparticle diffusivities
λ	Size-exclusion ratio	$\lambda = \frac{K_{se,2}}{K_{se,1}}$	Ratio of size-exclusion factors; equal to α if there is no dead volume
ϕ	Phase ratio	$\phi = \frac{1 - \varepsilon_b}{\varepsilon_b}$	Particle phase relative to bed void
$N_{D,i}$	-	$N_{D,i} = \frac{\phi \varepsilon_p K_{se,i} D_{p,i} L_c}{R_p^2 \nu} = \frac{t_s}{t_{D,i}}$	Step time relative to diffusion time
N_D^*	-	$N_D^* = \frac{N_{D,1}(\alpha - 1)}{\phi \delta_1} = \frac{N_{D,2}(\alpha - 1)}{\lambda \gamma \phi \delta_1}$	Component-independent N_D ; $N_{D,i}$ as base
$N_{\Delta P}$	-	$N_{\Delta P} = \frac{\Delta P_{max} R_p^2}{37.5 \phi \mu L_c \nu} = \frac{t_s}{t_c^I}$	Step time relative to pressure-limited convection time
$N_{\Delta P,diff}$	-	$N_{\Delta P,diff} = \frac{\Delta P_{max} R_p^4}{37.5 \phi \mu D_{p,1} L_c^2} = \frac{t_{D,1}}{t_c^I}$	Diffusion time relative to pressure-limited convection time
P_{eb}^j	Peclet number	$P_{eb}^j = \frac{\nu L_c}{E_b^j} = \frac{t_{Dax}}{t_s}$	Axial dispersion time relative to step time
Γ^j	Axial dispersion ratio	$\Gamma^j = \frac{E_b^j}{E_b^{IV}}$	Ratio of axial dispersion coefficients of zone j and zone IV
P_{eb}^*	-	$P_{eb}^* = \phi(\delta_2 - \delta_1) P_{eb}^j \Gamma^j$	Zone-independent Peclet number, Zone IV as base

Table 2. SSWD equations for binary SEC-SMB.

General		Diffusion controlled		Dispersion controlled		
u_0^I	$\nu \left(1 + \phi \delta_2 + \frac{\beta_2^I \Gamma^I \phi(\delta_2 - \delta_1)}{P_{eb}^* N^I} + \frac{\phi \beta_2^I \alpha^2 (\delta_2 - \delta_1)}{15 N_D^* \lambda \gamma N^I} \right)$	(18a)	$\nu \left(1 + \phi \delta_2 + \frac{\phi \beta_2^I \alpha^2 (\delta_2 - \delta_1)}{15 N_D^* \lambda \gamma N^I} \right)$	(24a)	$\nu \left(1 + \phi \delta_2 + \frac{\beta_2^I \Gamma^I \phi(\delta_2 - \delta_1)}{P_{eb}^* N^I} \right)$	(31a)
u_0^{II}	$\nu \left(1 + \phi \delta_1 + \frac{\beta_1^{II} \Gamma^{II} \phi(\delta_2 - \delta_1)}{P_{eb}^* N^{II}} + \frac{\phi \beta_1^{II} (\delta_2 - \delta_1)}{15 N_D^* N^{II}} \right)$	(18b)	$\nu \left(1 + \phi \delta_1 + \frac{\phi \beta_1^{II} (\delta_2 - \delta_1)}{15 N_D^* N^{II}} \right)$	(24b)	$\nu \left(1 + \phi \delta_1 + \frac{\beta_1^{II} \Gamma^{II} \phi(\delta_2 - \delta_1)}{P_{eb}^* N^{II}} \right)$	(31b)
u_0^{III}	$\nu \left(1 + \phi \delta_2 - \frac{\beta_2^{III} \Gamma^{III} \phi(\delta_2 - \delta_1)}{P_{eb}^* N^{III}} - \frac{\phi \beta_2^{III} \alpha^2 (\delta_2 - \delta_1)}{15 N_D^* \lambda \gamma N^{III}} \right)$	(18c)	$\nu \left(1 + \phi \delta_2 - \frac{\phi \beta_2^{III} \alpha^2 (\delta_2 - \delta_1)}{15 N_D^* \lambda \gamma N^{III}} \right)$	(24c)	$\nu \left(1 + \phi \delta_2 - \frac{\beta_2^{III} \Gamma^{III} \phi(\delta_2 - \delta_1)}{P_{eb}^* N^{III}} \right)$	(31c)
u_0^{IV}	$\nu \left(1 + \phi \delta_1 - \frac{\beta_1^{IV} \phi(\delta_2 - \delta_1)}{P_{eb}^* N^{IV}} - \frac{\phi \beta_1^{IV} (\delta_2 - \delta_1)}{15 N_D^* N^{IV}} \right)$	(18d)	$\nu \left(1 + \phi \delta_1 - \frac{\phi \beta_1^{IV} (\delta_2 - \delta_1)}{15 N_D^* N^{IV}} \right)$	(24d)	$\nu \left(1 + \phi \delta_1 - \frac{\beta_1^{IV} \phi(\delta_2 - \delta_1)}{P_{eb}^* N^{IV}} \right)$	(31d)
$\frac{D}{F}$	$\frac{1 + \frac{1}{P_{eb}^*} \left(\frac{\beta_2^I \Gamma^I}{N^I} + \frac{\beta_1^{IV}}{N^{IV}} \right) + \frac{1}{15 N_D^*} \left(\frac{\beta_2^I \alpha^2}{\lambda \gamma N^I} + \frac{\beta_1^{IV}}{N^{IV}} \right)}{1 - \frac{1}{P_{eb}^*} \left(\frac{\beta_2^{III} \Gamma^{III}}{N^{III}} + \frac{\beta_1^{II} \Gamma^{II}}{N^{II}} \right) - \frac{1}{15 N_D^*} \left(\frac{\beta_2^{III} \alpha^2}{\lambda \gamma N^{III}} + \frac{\beta_1^{II}}{N^{II}} \right)}$	(19)	$\frac{1 + \frac{1}{15 N_D^*} \left(\frac{\beta_2^I \alpha^2}{\lambda \gamma N^I} + \frac{\beta_1^{IV}}{N^{IV}} \right)}{1 - \frac{1}{15 N_D^*} \left(\frac{\beta_2^{III} \alpha^2}{\lambda \gamma N^{III}} + \frac{\beta_1^{II}}{N^{II}} \right)}$	(25)	$\frac{1 + \frac{1}{P_{eb}^*} \left(\frac{\beta_2^I \Gamma^I}{N^I} + \frac{\beta_1^{IV}}{N^{IV}} \right)}{1 - \frac{1}{P_{eb}^*} \left(\frac{\beta_2^{III} \Gamma^{III}}{N^{III}} + \frac{\beta_1^{II} \Gamma^{II}}{N^{II}} \right)}$	(32)
$P_{R,i}$	$\frac{\nu Y_i C_{F,i} (\delta_2 - \delta_1)}{N L_c \rho_p} \left[1 - \frac{1}{P_{eb}^*} \left(\frac{\beta_2^{III} \Gamma^{III}}{N^{III}} + \frac{\beta_1^{II} \Gamma^{II}}{N^{II}} \right) - \frac{1}{15 N_D^*} \left(\frac{\beta_2^{III} \alpha^2}{\lambda \gamma N^{III}} + \frac{\beta_1^{II}}{N^{II}} \right) \right]$	(20)	$\frac{Y_i C_{F,i} (\alpha - 1)^2 \varepsilon_p K_{se,1} D_{p,1}}{N \rho_p R_p^2 N_D^*} \left[1 - \frac{1}{15 N_D^*} \left(\frac{\beta_2^{III} \alpha^2}{\lambda \gamma N^{III}} + \frac{\beta_1^{II}}{N^{II}} \right) \right]$	(27b)	$\frac{\nu Y_i C_{F,i} (\delta_2 - \delta_1)}{10 N \varepsilon_b R_p \rho_p \left[P_{eb}^* \frac{(1 + \phi \delta_1)}{\phi (\delta_2 - \delta_1)} - \frac{\beta_1^{IV}}{N^{IV}} \right]} \left[1 - \frac{1}{P_{eb}^*} \left(\frac{\beta_2^{III} \Gamma^{III}}{N^{III}} + \frac{\beta_1^{II} \Gamma^{II}}{N^{II}} \right) \right]$	(37b)
N_{AP}	$\frac{\Delta P_{max} R_p^2}{37.5 \phi \mu L_c \nu} = \phi \left(1 + \phi \delta_2 + \frac{\beta_2^I \Gamma^I \phi(\delta_2 - \delta_1)}{P_{eb}^* N^I} + \frac{\phi \beta_2^I \alpha^2 (\delta_2 - \delta_1)}{15 N_D^* \lambda \gamma N^I} \right)$	(23)	$\frac{\Delta P_{max} R_p^4}{37.5 \phi \mu D_{p,1} L_c^2} = \frac{\phi^2 (\alpha - 1)^2 \varepsilon_p K_{se,1}}{N_D^*} \left(\frac{1 + \phi \delta_2}{\phi (\delta_2 - \delta_1)} + \frac{\beta_2^I \alpha^2}{15 N_D^* \lambda \gamma N^I} \right)$	(30a)	$\frac{\Delta P_{max} R_p^2}{37.5 \phi \mu L_c \nu} = \phi \left[1 + \phi \delta_2 + \frac{\beta_2^I \Gamma^I \phi(\delta_2 - \delta_1)}{P_{eb}^* N^I} \right]$	(39)

Table 3. Table of parameters for three literature cases. Complete lists of parameters in Tables B.1-B.3.

	Case 1	Case 2	Case 3 *
Authors	Liang and Liang	Houwing et al.	Xie et al.
Year	2012	2003	2002
Component 1	20,000 MW PEG	BSA	Insulin
Component 2	1,500 MW PEG	Myoglobin	ZnCl ₂
Design	Triangle	Triangle	SWD
Yield (%)	1A: 65.5, 99.9	2A: 46.2, 90.0	
(Comp. 1, Comp. 2)	1B: 99.9, 99.9	2B: 60.5, 90.0	
	1C: 99.9, 70.7	2C: 71.3, 82.5	99.0, 99.0
		2D: 86.7, 60.0	
		2E: 99.8, 40.5	
Configuration	2-2-2	2-2-2-2	2-3-3-2
L_c (cm)	30	8.9	13.7
ID (cm)	0.75	1.0	5.1
R_p (μm)	8.5	100	54
N_D^*	$\sim 4,600$	0.36	8.9
$P_{eb}^* (L_c/10\epsilon_b R_p)$	1,751 (9,688)	35.8 (228)	145 (725)

* Ring B of two ring tandem SMB

Table 4. Fixed parameters for insulin parametric study unless otherwise specified.

R_p^* (μm)	ε_b	ε_p	ϕ	DV (%)	Y (%)	$E_{b,i}^j$
54	0.35	0.89	1.86	1.9	99	Chung and Wen Correlation
Component				D_p (cm^2/min)	K_{se}	δ
High Molecular Weight Proteins (HMWP)				2.00×10^{-5}	0.19	0.198
Insulin				2.29×10^{-5}	0.74	0.688
Zinc Chloride				1.65×10^{-4}	0.99	0.910
SMB Ring			α	γ	γ/α	
A (Insulin / HMWP)			3.47	1.15	0.33	
B (ZnCl_2 / Insulin)			1.32	7.21	5.46	
C_{Ei} (g/L)	ρ_p (kg sorbent/L particle volume)			μ (cP)	ΔP_{max}^* (psi)	
54	0.12			2.5	1.5	

*Sephadex G50

Table 5. Comparison of batch, SMB, and cost optimized SMB

Parameter (5,000 kg insulin / year)	Batch ^b	Xie (2002) ^b	Optimized SMB ^a		
			Ring A ^b	Ring B ^c	Overall ^b
Overall Yield (%)	89	99	99	99	98
Product Concentration (g/L)	45.0	59.0	61.9	47.8	47.8
Column Configuration	12 in series	A: 2-2-4-2 B: 2-3-3-2	2-2-2-2	2-2-2-2	A: 2-2-2-2 B: 2-2-2-2
Feed Flowrate (mL/min)	119 (each)	109	109	-	109
Column Length (cm)	15	A: 13.7 B: 13.7	15.9	11.2	A: 15.9 B: 11.2
Diameter (cm)	45 (12 units)	A: 47.9 B: 58.6	20.4	29.8	A: 20.4 B: 29.8
N_D^*	-	A: 6.0 B: 8.9	14.9	1.48	A: 14.9 B: 1.48
P_{eb}^*	-	A: 145 B: 145	560	108	A: 560 B: 108
Solvent consumption (L/kg insulin)	150.0	42.0	28.0	22.8	50.8
Productivity (kg /kg sorbent /day)	0.05	0.14	4.47	2.80	1.69
Equip. Cost (\$/kg insulin)	35.71 (39%)	29.76 (72%)	14.29	14.29	28.58 (81%)
Solv. Cost (\$/kg insulin)	15.00 (17%)	3.96 (10%)	2.80	2.28 ^d	5.08 (15%)
Resin Cost (\$/kg insulin)	40.07 (44%)	7.41 (18%)	0.43	0.79	1.22 (4%)
Total Cost (\$/kg insulin)	90.78	41.43	17.58	17.36	34.94

^aUnder constraint that there is a minimum of two columns per zone^bFeed concentration of insulin is 88.5 g/L.^cFeed concentration of insulin for Ring B is product concentration from Ring A^dRing B solvent cost only includes desorbent cost because feed solvent was already accounted for in Ring A

Table 6. Effects of material properties, pressure limit, and dead volume on Ring B optimization.

Parameter Changed	New Parameter Values	D/F	Solvent Cost (\$/kg insulin)	L_c (cm)	ID (cm)	P_R (kg insulin/kg resin/day)	Sorbent Cost (\$/kg insulin)	Total Cost ^e (\$/kg insulin)
Base Case (Table 5)		1.39	2.27	11.4	29.6	2.79	0.79	17.35
ΔP_{max} (psi)	50	1.32	2.16	61.5	11.9	3.23	0.68	17.13
	75	1.32	2.15	75.3	10.7	3.23	0.68	17.12
DV (% CV)	0	1.38	2.25	11.2	29.0	2.96	0.74	17.28
	10	1.46	2.38	11.9	31.9	2.33	0.95	17.62
ε_b	0.3	1.40	2.29	8.4	33.3	2.79	0.79	17.37
	0.4	1.40	2.28	14.8	26.8	2.85	0.77	17.34
ε_p	0.50	1.53	2.49	12.2	35.7	1.80	1.22	18.00
	0.95	1.38	2.25	11.4	29.1	2.91	0.76	17.30
γ	1	1.50	2.46	13.7	33.5	1.83	1.21	17.96
	100	1.37	2.24	10.9	28.8	3.11	0.71	17.24
$K_{se,l}$	0.010	1.07	1.74	8.3	12.0	23.33	0.09	16.12
	0.100	1.07	1.75	8.2	12.6	21.36	0.10	16.14
R_p (μm)	25	1.26	2.06	3.7	35.9	5.85	0.38	16.73
	100	1.61	2.63	29.9	26.8	1.31	1.68	18.61
$\Delta P_{max}, DV, \varepsilon_b, \varepsilon_p, \gamma, K_{se,l}, R_p$	150, 0.0, 0.3, 0.95, 100, 0.01, 25	1.01	1.65	10.4	3.7	187.49	0.01	15.95

^eThe equipment cost does not change between cases.

Table B.1. Extended table of parameters for Case 1.

	1A	1B	1C
Authors		Liang and Liang	
Year		2012	
Component 1		20,000 MW PEG	
Component 2		1,500 MW PEG	
Design		Triangle	
ε_p		0.80	
ε_b		0.364	
$K_{se,1}, K_{se,2}$		0.38, 0.57	
δ_1, δ_2		0.30, 0.46	
$D_{p,1}, D_{p,2}$ (cm ² /min)		$2.9 \times 10^{-4}, 2.9 \times 10^{-4}$	
γ/α		0.66	
ϕ		1.74	
Configuration		2-2-2	
L_c (cm)		30	
Diameter (cm)		0.75	
DV		~ 0.00	
R_p (μm)		8.5	
$C_{F,1}, C_{F,2}$ (g/L)		1.9, 1.7	
Y_1, Y_2 (%)	65.5, 99.9	99.9, 99.9	99.9, 70.7
t_s (min)	20.5	21.5	22.5
Flowrates (mL/min)			
Desorbent		0.5	
Feed		0.045	
Extract		0.15	
Raffinate		0.395	
N_D^*	4,447	4,664	4,881
$P_{eb}^* (L_c/10\varepsilon_b R_p)$		1,751 (9,696)	

Table B.2. Extended table of parameters for Case 2.

	2A	2B	2C	2D	2E
Authors			Houwing et al.		
Year			2003		
Component 1			BSA		
Component 2			Myoglobin		
Design			Triangle		
ε_p			0.98		
ε_b			0.39		
$K_{se,1}, K_{se,2}$			0.65, 0.88		
δ_1, δ_2			0.73, 0.95		
$D_{p,1}, D_{p,2}$ (cm ² /min)			3.66 x 10 ⁻⁵ , 7.2 x 10 ⁻⁵		
γ/α			1.50		
ϕ			1.56		
Configuration			2-2-2-2		
L_c (cm)			8.9		
Diameter (cm)			1.0		
DV			0.06		
R_p (μm)			100		
$C_{F,1}, C_{F,2}$ (g/L)			1.9, 1.7		
Y_1, Y_2 (%)	46.2, 90.0	60.5, 90.0	71.3, 82.5	86.7, 60.0	99.8, 40.5
t_s (min)	1.14	1.14	1.14	1.14	1.14
Flowrates (mL/min)					
Desorbent	2.58	2.65	2.69	2.65	2.65
Feed	0.15	0.15	0.15	0.15	0.15
Extract	1.49	1.35	1.12	0.90	0.67
Raffinate	1.23	1.46	1.72	1.91	2.13
N_D^*	0.11	0.11	0.11	0.11	0.11
$Pe_b^* (L_c/10\varepsilon_b R_p)$			38.0 (228)		

Table B.3. Extended table of parameters for Case 3.

	Case 3*
Authors	Xie et al.
Year	2002
Component 1	Insulin
Component 2	ZnCl ₂
Design	SWD
ε_p	0.89
ε_b	0.35
$K_{se,1}, K_{se,2}$	0.74, 0.99
δ_1, δ_2	0.69, 0.91
$D_{p,1}, D_{p,2}$ (cm ² /min)	2.29×10^{-5} , 1.65×10^{-4}
γ/α	5.46
ϕ	1.86
Configuration	2-3-3-2
L_c (cm)	13.7
Diameter (cm)	5.1
DV	0.02
R_p (μm)	54
$C_{F,1}, C_{F,2}$ (g/L)	69.5, 0.303
Y_1, Y_2 (%)	99.7, 99.0
t_s (min)	33.7
Flowrates (mL/min)	
Desorbent	1.35
Feed	1.10
Extract	1.17
Raffinate	1.29
N_D^*	8.9
$P_{eb}^* (L_c/10\varepsilon_b R_p)$	145 (725)