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Design of Membrane Cascades

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Abstract: Suggestions are made for the practical implementation of membrane cascades using diafiltration for the fractionation of solute pairs. Experiments are described that demonstrate the desirability of replacing solvent during the course of each diafiltration, and a parallel modeling development suggests an attractive means for accomplishing this replacement. A batch process is described to achieve such separations by simple assemblies of existing equipment, and suggestions are made for designing continuous processors. Such cascades are attractive for a wide variety of solutes including native proteins, as well as commodity chemicals, and they can be applied to the resolution of enantiomers through simple modifications already described in the public literature. The same techniques can be applied to multicomponent systems using the concept of key components as has long been done in distillation.

The low inherent capital costs and high throughput rates of such membrane cascades strongly suggest that they should compete successfully against a significant number of presently used chromatographic processes, and their simplicity should make then formidable competitors to simulated moving beds as well.

Keywords: Cascades, diafiltration, downstream processing, membrane filtration, proteins, steady counterflow

INTRODUCTION

It was suggested in a recent paper (8) that efficient counterflow cascades of simple diafilter based modules, as described in Fig. 1, could substantially

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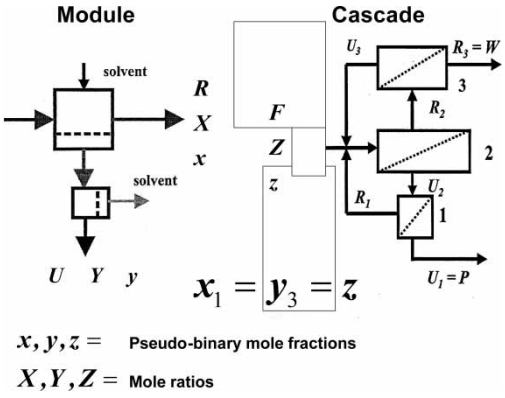

Figure 1. Introduction to membrane cascades.

increase the effectiveness of selective membranes for a wide variety of separations. The impetus for this suggestion was the rapid increase of membrane selectivity, reported by several groups of researchers (2, 10, 11, 16, 17, 18, 20). It was shown in this paper how even very simple cascades would greatly increase the degree of separation obtained. Individual modules of such cascades, shown in Fig. 1, consist of a combination of a diafiltration system, selectively permeable to one solute of a binary mixture, or one key component of a multicomponent one, coupled with another filter permeable only to the solvent. It was shown that a modified ideal cascade, defined as one in which streams to be mixed have the same proportion of key solutes (8), is particularly effective. This constraint is also illustrated in Fig. 1. Here mole fractions and mole ratios are pseudo-binary: based only upon the two solutes or two key components of the solution. For the three-stage system shown this means that the retentate from stage 1, the permeate from stage 3, and the feed have the same proportion of the two solutes.

It was further shown that the design of a suitable apparatus and procedure could be facilitated by breaking the overall problem down into two simpler ones:

(1) specification of solvent-free separations using ideal cascade theory, and
(2) design of a solvent management system to minimize solvent related costs.

The first of these two sub-problems is very simple and will not be considered further here. For the second there is no such simple algorithm, and one must develop heuristic approaches that depend upon available technology and the nature of the larger process within which this fractionation is to be implemented. Solvent related costs can be quite significant.

The discussion below is primarily concerned with these solvent related problems, and it will be based upon the simple definitions of separability illustrated in Fig. 2. Here N_i is the rate at which moles of solute "i" pass through the

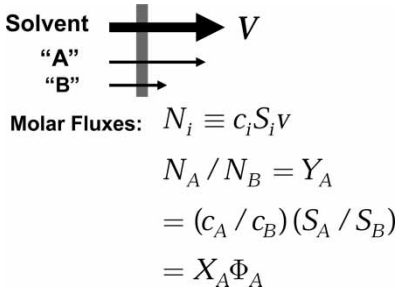

Figure 2. Definitions and the basis of separability.

membrane per unit exposed area, c_i is the observable molar concentration of species "i", and v is the observable velocity at which solvent leaves the solution to cross the membrane. The two solutes of interest are designated "A" and "B", and X_A is the observable molar ratio in the retentate compartment. The corresponding ratio in the permeate is Y_A, and S_A is the local sieving coefficient. However, the sieving coefficients defined in this figure are not physical properties: like mass transfer coefficients they are process dependent, and observable, local or global. Values for the filter as a whole can be different from the local values illustrated here. In particular they depend upon the flow conditions upstream from and within the retetentate compartment, and the way in which the solvent driving the solutes across the membrane is distributed. Two quite different filter designs are sketched in Fig. 3, and the comparison of their behavior will be an important aspect of the following discussion. Most diafilters add solvent only into the feed as indicated in the upper example of the figure, and it will be shown that continuing the input to the retentate, as suggested in the lower example, offers major advantages. This claim will be investigated both experimentally and via model calculations, and its practical significance will be shown by way of specific examples. The filtration unit at the top of the figure is not per se a diafilter, but the one at the bottom is.

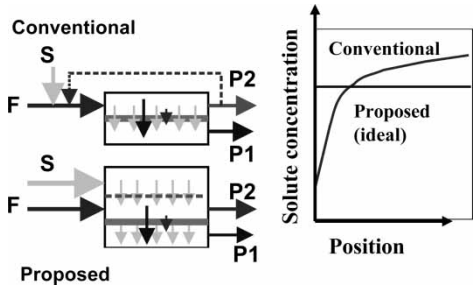

Figure 3. Solvent distribution.

Diafiltration, the primary basis upon which cascade modules are built, is fundamentally a two-step process: dilution of a feed stream followed by membrane filtration to produce a permeate and a retentate stream. It is a mature and widely used process that has been described in the reviewed literature since at least 1967 (4). Early work is reviewed by Ho and Sirkar (5) and by Noble and Stern (11).

Most existing process configurations had developed by 1992, and the governing mathematics were also established by that time. Two examples are of interest here:

(1) pre-dilution and continuous filtration through a simple filter, and
(2) batch filtration through a simple filter from a tank with continuing solvent replacement.

It should be noted that dilution can take place at the entrance to the filter in example (1), and this would often be the case in a continuous operation. This is the situation illustrated in the upper module of Fig. 3. A recycle is sometimes used to decrease the boundary layer resistance, but this feature will not be discussed here. The lower unit sketched in Fig. 3 combines both dilution and filtration, and it may be considered as a true diafilter.

Much of this early work has been repeated, apparently independently (19), because of the recent utility for downstream processing of biologicals. Interest has apparently centered on example (2).

PROCEDURE

The filtration unit consisted of a Millipore Pellicon XL 30 kDa membrane module. The fluid was pumped by a Cole-Parmer MasterFlex L/S variable speed pump. The total flow was controlled by pump rpm and the fine control of the permeate/retentate ratio by pinch clamps. The permeate and retentate flows were measured by weight over short measured time intervals. In the batch filtration experiments, the protein feed solution was filtered as shown in Fig. 4, with the retentate returned to the feed container and the permeate collected in a separate container. In the solvent replacement experiments, the same setup was used with the continuous addition of the

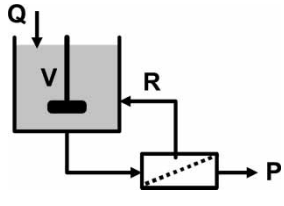

Figure 4. Schematic description of the experimental System.

solvent to the feed container at the same volumetric rate as that of permeate removal. In both cases, the feed container was stirred with a magnetic spin bar.

The proteins were β-lactoglobulin (SigmaAldrich catalog no. L3908), and α-lactalbumin (SigmaAldrich catalog number. L5385). The proteins were 85–90% pure. The filtration buffer (solvent) was 1 mM Na_2HPO_4, adjusted to pH 7 and 1700 mS conductivity. The initial flow rate was set using the buffer, and the actual flow rate for the protein solution was measured during the run at each sample collection. Where whey protein isolate was used, it was Bi-Pro whey protein isolate (Davisco Foods, Eden Prairie, MN).

Permeate and retentate samples were analyzed using a Waters Alliance HPLC with a Hamilton PRP-Infinity 4.1 × 50 mm column. Proteins were separated on the 47 μm non-porous reverse phase styrene-divinyl benzene column packing by gradient elution starting at initial conditions 70% H_2O 30% acetonitrile(ACN) 0.1% trifluoroacetic acid(TFA), with a linear gradient to 45% H_2O, 55% ACN 0.1% TFA over 5 minutes. There was a 2 minute hold at the end gradient composition and 5 minutes at the initial conditions before the injection of the next sample. All solvents were HPLC grade, obtained from Sigma-Aldrich; water was prepared by Milli-Q filtration system to 18 MΩ conductivity. The protein concentration was measured by integration of the absorption peaks at 280 nm, calibrated to known standards of the mixed proteins run the same day.

THEORY

Here we provide some simple models of filtration behavior to guide both interpretation of existing data and ultimately the design of devices. We begin with stirred tanks from which the solution is removed directly through a permselective membrane over the surface of which both the solute composition and the permeation velocity are uniform. We then suggest how these simple models can be used to approximate the performance of more complex devices.

Stirred Tanks

We begin by looking at simple stirred tanks as shown in Fig. 5, widely used for laboratory studies, and we review the macroscopic material balances governing them for the specific case of filtering aqueous solutions of solute pairs. We begin with the limiting case in which no replacement solvent is fed to the tank. This corresponds to dilution before the start of filtration, but it is more useful as a model for the course of filtration within a conventional filter. Here it will be contrasted with solvent replacement within the filter itself as shown in Fig. 3.

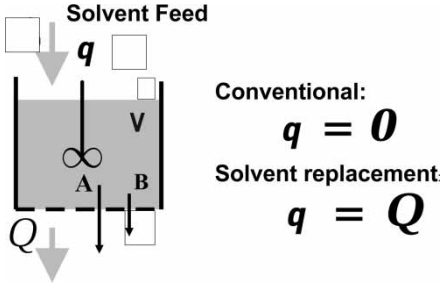

Figure 5. Batch diafiltration from a well-mixed reservoir.

No Solvent Replacement

We consider an initial volume F, corresponding to the feed in a filter, from which the solution is removed by filtration at a volumetric rate Q. The initial solute concentration is c_{i0}, and the sieving coefficient is constant at S_i. The remaining volume at any time is designated as R, and it is given simply by

$$R = F - \int_0^t Q(\tau)d\tau \tag{1}$$

The initial solute mass is m_{i0}.

We may now construct a solute mass balance as follows:

$$\begin{aligned} dm_i &= -QS_ic_i = \frac{d}{dt}Rc_i = c_i\frac{dR}{dt} + R\frac{dc_i}{dt} \\ &= -Qc_i + \left[F - \int_0^t Q(\tau)d\tau\right]\frac{dc_i}{dt} \end{aligned} \tag{2}$$

where c_i is solute concentration. This may be rearranged to

$$\frac{1}{c_i}dc_i = -Q(1 - S_i)\frac{dt}{[F - \int_0^t Q(\tau)d\tau]} \tag{3}$$

or

$$d\ln c_i = -(1 - S_i)d\ln[F - \int_0^t Q(\tau)d\tau] \tag{4}$$

$$\ln\frac{c_i}{c_{i0}} = (1 - S_i)\ln\left(\frac{F}{F - \int_0^t Q(\tau)d\tau}\right) \tag{5}$$

We now write more explicitly $c_i = c_i(R)$ and therefore that

$$c_i(R) = c_0\left[\frac{F}{F - \int_0^t Q(\tau)d\tau}\right]^{(1-S_i)} = c_{i0}(F/R)^{(1-S_i)} \tag{6}$$

It may now be noted that the integral in the above equations need not be evaluated: one only needs to know, the instantaneous retentate volume R. We are however, assuming the sieving coefficient S_i to be time independent

It follows from the above that the mass of solute "*i*" in the retentate

$$m_i(R) = Rc_iR = Rc_{i0}(F/R)^{(1-S_i)} \tag{7}$$

Then the mass and concentration in the permeate P respectively

$$\begin{aligned} m_iP &= Fc_{i0} - Rc_{i0}(F/R)^{(1-S_i)} \\ c_iP &= (F/P)c_{i0} - (R/P)c_{i0}(F/R)^{(1-S_i)} \end{aligned} \tag{8, 9}$$

Then the observed or global sieving coefficient is

$$\bar{S}_i = c_i(P)/c_i(R) = \frac{(F/P) - (R/P)(F/R)^{(1-S_i)}}{(F/R)^{S_i}} \tag{10}$$

The system behavior described by these equations is shown graphically in Fig. 6. The most important aspect of this behavior from our present standpoint is that both individual sieving coefficients and their ratio, the stage separation factor, are very insensitive to the fraction of initial volume removed even up to

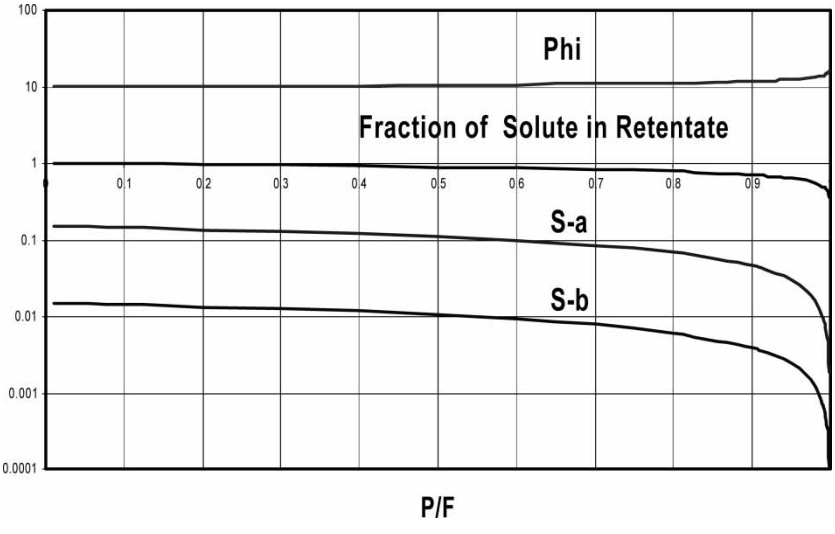

Figure 6. Diafiltration without solvent feed.

ratios P/F of 0.7. We shall use this insensitivity to advantage in our discussion below.

Note also that the abscissa in this figure is the total solute yield: both the feed mass "F" and product mass "P" are for the combined solutes and on a solvent-free basis.

Complete Solvent Replacement

We now consider the case of complete solvent replacement so that reservoir volume remains constant at V, or equivalently, that the volumetric replacement rate, q, is equal to the withdrawal rate Q. The mass balance now takes the form

$$\begin{aligned} -Vdc_i/dt &= vAS_ic_i = QS_ic_i \\ -dc_i/dt &= S_ic_i;\ t = tQ/V \end{aligned} \tag{11, 12}$$

with

$$c_i = c_{i0} \quad at \quad t = 0$$

Then

$$c_i/c(0) = e^{-S_it} \tag{13}$$

It follows that the molar mass of "i" remaining in the volume element (retentate) at any time is

$$M/M(0) = e^{-S_it} \tag{14}$$

and that in the accumulated permeate is

$$\mathcal{M}_i = M_i(0) - M_i = M_i(0)[1 - e^{-S_it}] \tag{15}$$

The ratio of "i" in permeate to retentate is then

$$\mathcal{M}_i/M_i = \frac{1 - e^{-S_it}}{e^{-S_it}} = e^{-S_it} - 1 \tag{16}$$

Now the solvent-free mole ratios of species "A" in an "A"-"B" mixture for permeate and retentate are respectively

$$X_A = M_A/M_B;\ Y_A = \mathcal{M}_A/\mathcal{M}_B \tag{17}$$

and the global separation factor

$$\Phi_{\mathrm{A,glob}} Y_A/X_A = (e^{S_At} - 1)/(e^{S_Bt} - 1) \tag{18}$$

We may now look at limiting behavior:

$$1)\ \tau, t \to 0:$$

$$\text{Here } e^{S\tau} 1 + S\tau \text{ and } \Phi_{A,glob} = \Phi_{A,loc} = S_A/S_B \tag{19}$$

This is the value implicit in much of the literature.

$$2)\ \tau, t \gg 1:$$

$$\text{Here } \Phi_{A,glob} = e^{S_A\tau}/e^{S_B\tau} = e^{(S_A - S_B)\tau} \tag{20}$$

As shown in Fig. 7 the increase of global separation factors predicted by this equation can be very large. Note here that the abscissa of the inset graph here is the yield of solute "A".

We thus find that both global sieving coefficients and separation factors are predicted to increase strongly with fractional cut, and it is possible to use this variation to advantage in module design. This behavior is widely used. A primary purpose of this discussion is to demonstrate the validity of this prediction in a real system. This result also means that for ideal cascades the proper criterion, mixing only streams of identical solvent-free composition, becomes a bit more complicated: one must know tQ/V.

Data Analysis

We are now faced with the problem of determining sieving coefficients from measurements of solute concentration as functions of time, and we begin with local values. This may be done several different ways:

(1) Basic definition:

$$S_i = c_{iP}/c_{iR} \tag{21}$$

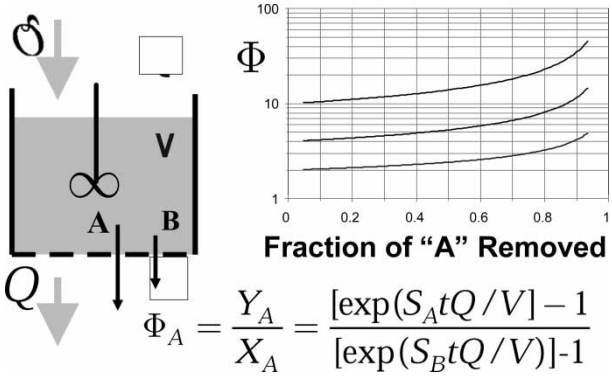

Figure 7. Effects of solvent replacement.

(2) Macroscopic mass balance on feed reservoir:

$$Vdc_{iF}/dt = -QS_ic_{iF} \tag{22}$$

$$\begin{aligned} c_{iF}/c_{iF}(0) &= \exp[-(S_i/V_{res})\int_0^t Qdt] \\ &= \exp[(S_i/V_{res})\cdot 60\,ml\cdot I] \\ &= \exp[Arg\cdot I] \end{aligned} \tag{23}$$

Here Arg is the quantity provided in Table 1. The identity:

(3) The identify:

$$c_{iP} = S_ic_{iF} \tag{24}$$

permits replacing c_{iF} by c_{iP} in the above exponential. Approach (1) is the most obvious, but it is also the most sensitive to error since it does not depend upon averaging individual values. This problem is immediately apparent on examination of the data presented.

EXPERIMENTAL

Two kinds of data will be provided here: batch operations using the Pellicon units in conventional filtration mode ($q = 0$) and the more complex operation in the apparatus sketched in Fig. 5 with "q" equal to "Q". The second set is made as a test of the solvent replacement model of Fig. 7.

Values of the sieving coefficients will be obtained directly from (1) as the ratio of permeate and feed species concentrations, and via methods (2) and (3) as well.

Batch Experiments

Two preliminary investigations of batch filtration behavior were made as background for the simulations of solvent replacement discussed in the next section.

The first investigation was performed to determine the effects of transmembrane solvent flux on local sieving coefficients for α-lactalbumin ("A") and β-lactoglobulin ("B"). This series covered almost four orders of magnitude of solvent flux, and, although the coefficients did increase, the extent was found to be quite small. The results are summarized in Fig. 8. The most likely cause of the increase is concentration polarization at the upstream membrane surface, and the very small effect observed suggests that there is excellent lateral mixing. Note that the dispersion of the data is significant compared to the small slope of the trend line. The second investigation was made to determine the effects of fractional cut, and the results are illustrated in Fig. 9. Again the effect is small relative to the dispersion of the

Table 1. Summary of α-lactalbumin correlations

		Reservoir			Permeate		
Run	Identification	Coeff.	Arg min^{-1}	R^ 2 dmls	Coeff.	Arg min^{-1}	R^ 2 dmls
1	25 Oct	—	—	0.373	−0.1271	0.9452	
2	Bill 1	0.561	−0.036	0.461	0.128	−0.0942	0.961
3	Bill 11/1	—	—	—	0.0551	−0.1248	0.9705
4	Nov 3	0.472	−0.0494	0.9683	0.0438	−0.154	0.982
5	8 Nov	0.5104	−0.1326	0.9876	0.1447	−0.2091	0.9961
6	10 Nov	0.4677	−0.2214	0.9951	0.2025	−0.2616	0.9971
7	15 Nov	0.4331	−0.3655	0.9692	0.1952	−0.2456	0.9938
8	16 Nov	0.5409	−0.1346	0.9914	0.1549	−0.1984	0.9869
9	22 Nov 1	0.5116	−0.1296	0.9658	0.1603	−0.1755	0.9887
10	22 Nov 1	0.5251	−0.1234	0.9850	0.0966	−0.1297	0.9629

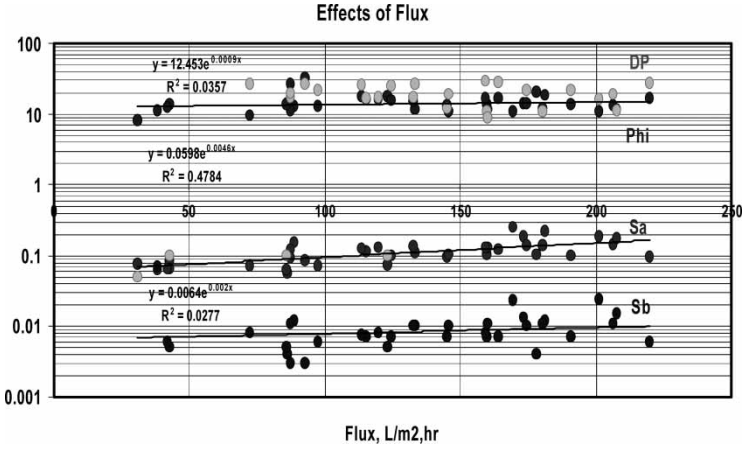

Figure 8. Effects of permeate flux.

data. Note from Fig. 9 that we removed as much as 90% of the product through the filter membrane.

There is probably some confounding of the two effects described in Figs. 8 and 9, but the data scatter makes this point moot for the present. In any event the combined effect is small.

The practical significance of these findings is that the experimental apparatus sketched in Fig. 4 should act very much like the model shown in Fig. 5, with q equal to Q. In other words data obtained from the apparatus of Fig. 5 can be used directly in design of large-scale systems. The reason for this is the very small dependence of the S_i and F on P/F.

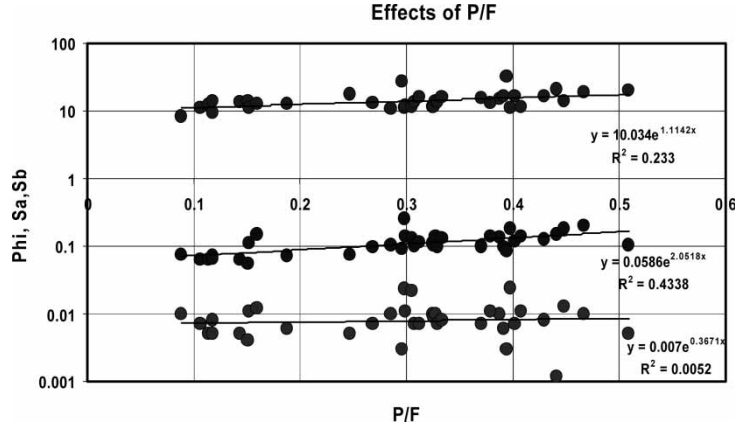

Figure 9. Effects of fractional cut.

Solvent Replacement Experiments

A very substantial number of runs were now made in the apparatus of Fig. 4, with Q controlled to maintain the original volume V, to investigate the effects of solvent replacement. One major goal was to determine the utility of a redesigned filter, a true diafilter, described later in this discussion and shown schematically in the lower configuration of Fig 3. The primary measured values were solute concentrations in the reservoir, the permeate, and the retentate streams, and the flow rates of these streams, as a function of time, the operating temperature, and the trans-membrane pressure drop. Temperatures were maintained via ice baths and ranged from about 2 to 9 centigrade.

A sample of the data from which these decay rates were determined is shown in Fig. 10, and a summary of all calculated sieving coefficients is given in Fig. 11. Data shown as circles and diamonds in this latter figure are made from decay rates of the reservoir and permeate solute concentrations of α-lactalbumin, respectively; squares represent ratios of permeate to retentate compositions for β-lactoglobulin. Figure 11 shows all results obtained for this series except for three preliminary runs where the techniques were still being developed. Concentration ratios suffer from sampling errors in the measurement of lactalbumin concentrations, and reservoir concentrations appear to be most susceptible. The cause is believed to be incomplete mixing. However, both permeate and reservoir concentrations do decay exponentially as expected.

Filtration rates of the more permeable solute, α-lactalbumin, were of greatest interest, and the plot of Fig. 10 is characteristic. Shown here are an instantaneous reservoir and permeate concentration of α-lactalbumin as a function of the accumulated permeate volume. This volume, at the end of

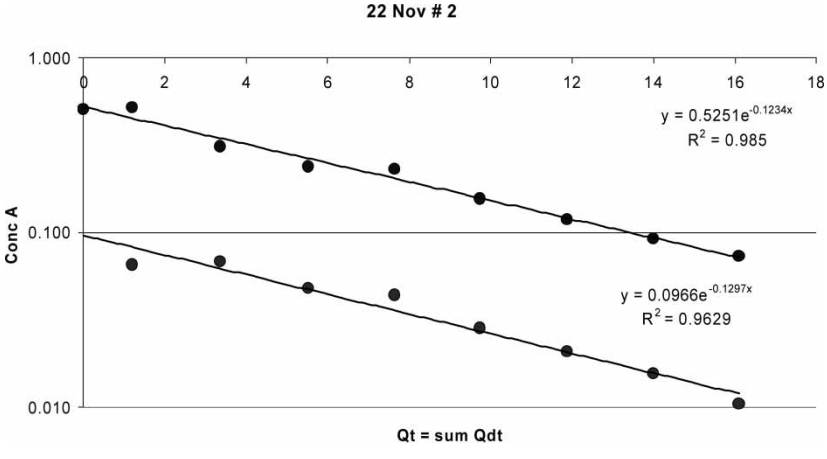

Figure 10. Lactalbumin decay rates.

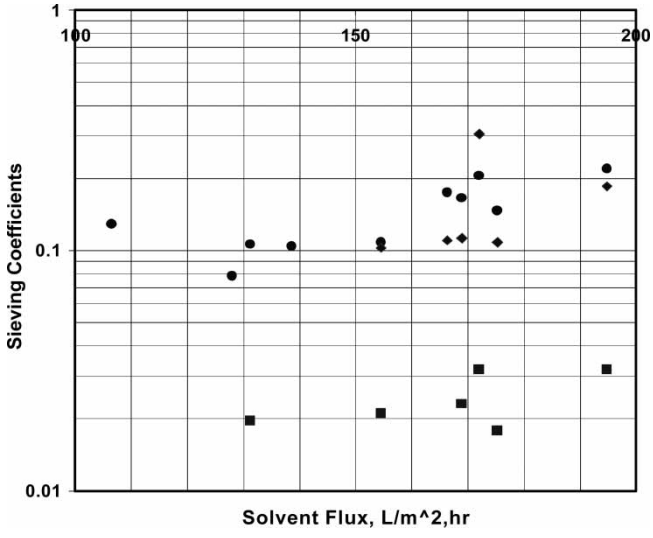

Figure 11. Summary of observed sieving factors.

the time in question determined as the sum of incremental volumes, is estimated as the product of the recorded flow rate and incremental time. Table 1 shows the correlations made by regression analysis of the data. Here the coefficient and arguments are for correlations of

$$\begin{aligned} c_i &= Coeff \cdot [-Arg \cdot t] \\ Arg &= (QS_i/V) \end{aligned} \qquad (25, 26)$$

Where "Q" is trans-membrane flow rate and "V" is the total volume of permeate collected over filtration time "t".

It is important to note that in the great majority of analyses the concentrations dropped exponentially with accumulated permeate volume, as predicted by the above analysis.

A similar analysis was not possible for the β-lactoglobulin as the measurements of concentration were subject to considerable random error: concentrations used were too low compared with the sources of random error. Averages over the various time periods were used instead. The average value over all runs was 0.023.

DISCUSSION

It is now time to discuss the significance of the data, and the most important result is the pronounced effect of the solvent replacement within the filter to increase global separation factors relative to the local values. We first illustrate this point by showing the progressive increase of global separation factors

during filtration with the extent of solvent replacement. We next describe the behavior of a three-stage cascade for fractionating mixtures of the whey proteins α-lactalbumin and β-lactoglobulin. We show in this representative situation that solvent replacement more than doubles the stage separation factor relative to local values and that insensitivity to local values makes it quite easy to predict the degree of improvement obtained. We then consider the means to obtain a satisfactory design to provide reasonably uniform solvent replacement with presently available technology. We begin with three examples

(1) The Effect of Solute Depletion on Global Separation Factors
Here we examine the effects of solute depletion for a diafilter (the lower filter configuration of Fig. 3) that just replaces solvent lost across the membrane at all points, and we start with the equation developed above:

$$\Phi_{A,glob} = e^{(S_A - S_B)\tau} \tag{27}$$

We consider three specific cases, corresponding to local separation factors, $\Phi_{A,loc}$, of 10, 20, and 40 respectively. The results of calculation are shown graphically in Fig. 12 as $\Phi_{A,glob}/\Phi_{A,loc}$ vs. the fraction of entering species, "A," that has permeated the membrane. They show that the effect of solute depletion, the well-known cross-flow effect, is substantial as expected. They also show that the magnitude of $\Phi_{A,glob}/\Phi_{A,loc}$ is only very slightly dependent upon the magnitude of $\Phi_{A,loc}$. In

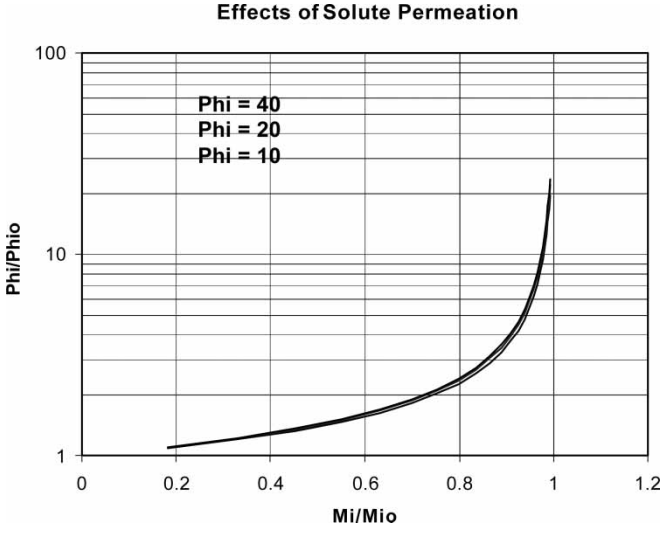

Figure 12. Insensitivity of global separation factors to local values.

fact considering the scatter of sieving coefficient data seen in the literature to date the effect is negligible over the wide range shown in the figure. This greatly simplifies the separator design.

(2) Whey Cascades

We now build upon the above example by revisiting the fractionation of α-lactalbumin/β-lactoglobulin separation already described elsewhere (2, 8) and described in Fig. 13. We begin by calculating mole ratios and mole fractions of the device shown, assuming a global separation factor $\Phi_{A,glob}$ of 21 and a feed mole fraction of α-lactalbumin of 0.1954 with the reminder β-lactoglobulin. We thus build directly on data and analyses reported previously (2, 8) and proceed stepwise as follows:

$$
\begin{aligned}
&X_1 = Y_3 = Z = 0.1954/0.8046 = 0.242854 \; \textit{GIVEN}\\
&x_1 = y_3 = z = 0.1954\\
&Y_1 = \Phi X_1 = 21 \cdot 0.242854 = 5.09994\\
&y_1 = Y_1/(1+Y_1) = 0.836064\\
&X_3 = Y_3/\Phi = 0.242854/21 = 0.011564\\
&x_3 = X_3/(1+X_3) = 0.011432\\
&X_2 = X_3 \cdot \sqrt{\Phi} = 0.011564 \cdot 4.582576 = 0.052993\\
&x_2 = X_2/(1+X_2) = 0.050328\\
&Y_2 = Y_3 \cdot \sqrt{\Phi} = 0.242854 \cdot 4.582576 = 1.112897\\
&\quad = \Phi X_2 = 1.112853\\
&\quad = Y_1/\sqrt{\Phi} = 1.112898\\
&y_2 = Y_2/(1+Y_2) = 0.526716
\end{aligned}
\qquad (28-39)
$$

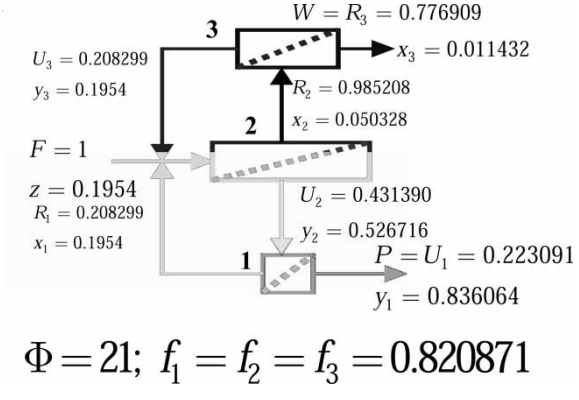

Figure 13. Overview of a whey cascade.

We keep this large number of digits to facilitate comparisons by the reader and to show that the cascade is truly ideal.

Next we recalculate the mole balances, and we begin with the overall balances:

$$F = P + W;\ zF = y_1 P + x_3 W$$

$$W = P\left[\frac{y_1 - z}{z - x_3}\right] = P\left[\frac{0.836064 - 0.1954}{0.1954 - 0.011432}\right] = \left[\frac{0.640664}{0.183968}\right]$$

$$= 3.482475P$$

$$P = 0.223091;\ W = 0.776909 \qquad (40-42)$$

We next make balances about stage 1:

$$U_2 = P + R_1;\ 0.526716U_2 = 0.836064P + 0.1954R_1$$

$$R_1 = \left[\frac{0.836064 - 0.526716}{0.526716 - 0.1954}\right]P = \frac{0.309348}{0.331316} \cdot 0.223091 = 0.208299$$

$$U_2 = P + R_1 = 0.208299 + 0.223091 = 0.431390 \qquad (43-45)$$

and stage 3:

$$R_2 = U_3 + W;\ x_2 R_2 = y_3 U_3 + x_3 W = x_2(U_3 + W)$$

$$U_3 = W\left[\frac{x_2 - x_3}{y_3 - x_2}\right] = 0.776909\left[\frac{0.050326 - 0.011432}{0.1954 - 0.050326}\right] = 0.208299$$

$$R_2 = 0.208287 + 0.776909 = 0.985208 \qquad (46-48)$$

This completes the mole balances for the system, and it only remains to determine the fraction of α-lactalbumin f_i permeating each stage "i":

$$f_1 = f_2 = f_3 = 0.820871 \qquad (49)$$

The identity of these fractions for the three stages is one of the simplifying features of ideal cascades, and here the large number of digits carried emphasizes this point.

It is now a simple matter to determine the local separation factors producing this separation from the Ex. 1 and specifically the behavior shown in Fig. 12 summarizes the key results. It may be seen here that

$$\Phi_{local} \approx \Phi_{global}/2.6 = 21/2.6 = 8.1 \qquad (50)$$

A brief look at the above data shows that the assumption of 21 for the global separation factor is actually conservative. Figure 12 also shows that the extent of amplification of separation factors produced

by solvent replacement is very insensitive to their magnitude. It may be shown that both product purity and fractional permeation increase with the global separation factor. The behavior shown here is for the whey protein separation with feed mole fraction, z_A, of 0.1954.

It remains however to implement the solvent replacement in a suitable device, and we now turn to this problem.

(3) Module Design

We have now extended the preliminary discussion of solvent management to a clear demonstration of the importance of solvent replacement during diafiltration, and it is time to consider ways to implement this principle in a practical setting.

We begin by noting that the Pellicon© filter we have been using appears to provide a close approximation of the rectilinear flow, and therefore that the addition of one additional channel as suggested in Fig. 3 can produce a direct mathematical analog of the transient operation shown in Fig. 7. One need only replace time by position in the flow direction divided by the mean flow velocity. Such a device would then follow the above theory for solvent replacement reasonably well. One would however, have to consider convective dispersion in the flow direction (1). In any event, this device, simple conceptually, does not appear to be currently available.

For the immediate future then we must seek alternatives, and there are at least two. For large installations, where multiple filters are used, one can arrange an individual diafilters in series, with a solvent addition ahead of each unit. As the number of such units increases, the system behavior will approximate continuous solvent addition ever more closely.

However, there is one very attractive possibility for the batch operations shown in Fig. 14. One can use the same batch system used in this study,

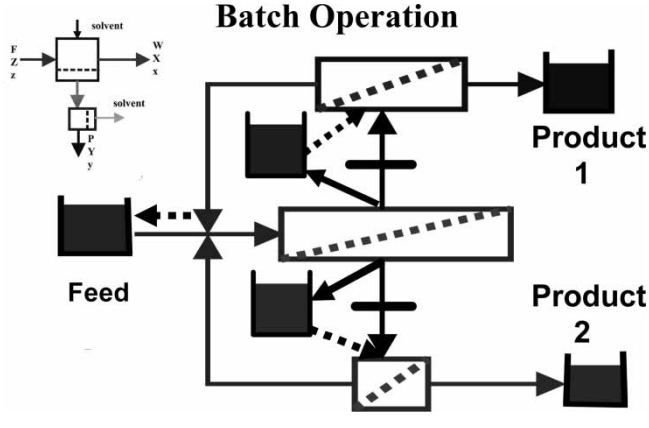

Figure 14. A three-stage batch cascade.

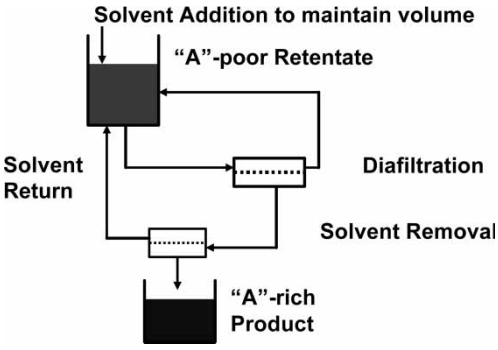

Figure 15. A proposed batch diafiltration for major amplification of global separation factors.

modified only to recycle the solvent. The result, sketched in Fig. 15, is even more flexible than that used in this study as one can add an additional solvent as suggested in the figure. One can then maintain an optimum solute concentration throughout, and, potentially more important, obtain an additional cross-flow effect in the filter shown. This latter possibility could significantly increase effective selectivity even further as suggested in Table 2. It is suggested here that just replacing the tank volume while using a conventional diafilter can more than double the observable separation factor Φ_{global}. Using a solvent replacing diafilter can give observable separation factors about six times the local value.

For the purposes of discussion it is assumed here that the ratio of the permeate to feed is such that global separation factors are 2.5 times the local value. This is almost certainly a conservative estimate, but it remains to make a rigorous and detailed calculation. That is a non-trivial task and must be deferred to a later manuscript.

These simple estimates do show that solvent replacement can provide major improvements in system performance and strongly suggests a redesign of the filters used. Moreover, it can be seen from Fig. 7 that the benefits of solvent replacement increases sharply with the fraction of species "A" removed, i.e. with the magnitude of local separation factor.

Table 2. Approximate effects of solvent replacement

Tank	Diafilter	Global separation factor
No replacement	No replacement	10
Complete replacement	None	25
Complete replacement	Complete replacement	62.5

CONCLUSION

The above described experimental data and transport modeling show both the benefits of continuous solvent addition during diafiltration and simple means for achieving this type of operation. These benefits are expressed by showing that global stage separation factors are significantly higher than local values and that the degree of improvement increases with the magnitudes of the local values. Using batch operation of the type suggested in Fig. 15 can increase the separations factors much further.

The simplicity of achieving this benefit in batch processing is particularly important for the short term as at present continuous processing is rare if achieved at all (7). Adapting existing designs for continuous solvent addition will require a non-trivial redesign of existing diafilters, but no great difficulties are anticipated. The additional membrane need not have any selectivity, but it will be important that the pressures in the solvent compartment are always higher than in the retentate space, and it will be highly desirable that the pressure drops across this new membrane not vary widely.

The only limitations to the equipment productivity are provided by the concentration polarization and the mechanical strength of the membrane supports and housing. The data presented here show no major effects of trans-membrane flux over four orders of magnitude, and there is no indication that we have been approaching any practical limit. This and the essential simplicity of the basic designs suggest that membrane cascades should be formidable competitors to both chromatographic processes and simulated moving beds. Fouling however, can be increased via concentration polarization, and this problem has not yet been investigated by us.

Membrane cascades are particularly attractive where stage separation factors are large, and there are many such applications already of commercial interest. The whey protein separation used here is a good example for low-cost biologicals, and there are at least two promising examples among the therapeutic proteins: multimers and degradation products.

Membrane filters have already been shown to be effective for the resolution of enantiomers (13) and proteins (12) through reversible complexing of one component with a non-permeating additive, and this principle can certainly be extended – perhaps even to such large-scale applications as the fructose-glucose fractionation. Here colloidal adsorbents might replace soluble additives.

Ultimately success or failure may depend upon such well-recognized problems as membrane life and fouling. Fortunately there are vigorous and able groups working on just these problems. In our case it will also be important to reduce the data scatter shown in the above figures. Much of this problem may well result from the primitive nature of our apparatus. We have been working with very limited funds.

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