Reduction of Membrane Fouling in the Ultrafiltration of Binary Protein Mixtures

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It is well known that separation efficiency and solute rejection change when two or more proteins are ultrafiltered. This phenomenon is primarily due to membrane fouling and is not significantly influenced by concentration polarization. If membrane fouling is the dominant resistance, then negative transmembrane pressure pulsing might significantly reduce this barrier.

A study was performed to determine the effect of negative transmembrane pressure pulsing on solute rejection for an albumin and gamma-globulin mixture in ultrafiltration. Pulsing improved solute flux for all cross-flow rates investigated including turbulent conditions by as much as two orders of magnitude. Under certain pulsing conditions, substantially higher solute flux was obtained for operations involving increased concentration polarization. This study reveals that negative transmembrane pressure pulsing can be effective in lowering the solute flux resistance that is observed in binary protein mixture ultrafiltration.

Introduction

Despite considerable progress, ultrafiltration continues to possess many limitations that prevent it from becoming a viable separation alternative in many industrial and medical applications. This is particularly true in the area of protein fractionation. The separation of proteins in dilute solution by ultrafiltration is generally effective only for macromolecules of significant size difference. In fact, it has been widely accepted that at least one order of magnitude in molecular weight difference is necessary for successful separation in standard ultrafiltration (Nelsen, 1977). Although poor separation efficiency may be due to wide pore-size distributions in the membrane, it may also involve concentration polarization, solute-solute interaction, resistances associated with protein deposition, adsorption, and pore plugging, or a combination of these factors. While concentration polarization can be controlled through modification of operating conditions, the latter resistances are not reversible with such changes and are often lumped under the general term of membrane fouling. Figure 1 illustrates how each of these resistances may occur. The resistances caused by these phenomena may be so severe that design of narrower pore-size distribution membranes may have only a minimal effect in improving protein fractionation.

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Considerable research has been focused on the elimination of concentration polarization in ultrafiltration, which has been considered the dominant resistance to permeate flux (Michaels, 1968; Blatt et al., 1970; Jönsson and Trägårdh, 1990). This accumulation of retained solutes at the membranes surface acts like an additional resistance in series with the membrane

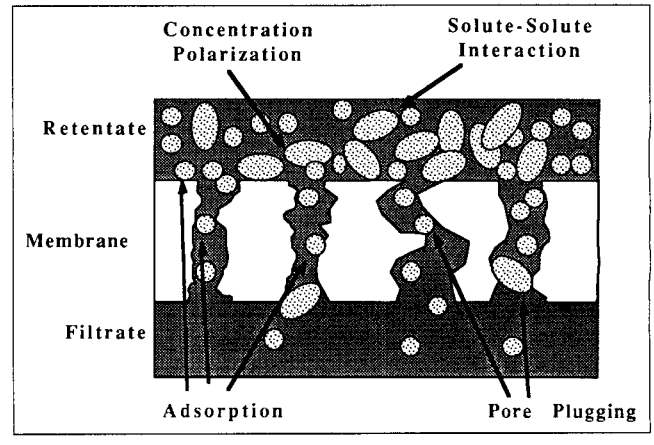

Figure 1. Location of various resistances to mass transport in membrane separation.

that further reduces the permeate flux by as much as an order of magnitude. While it is still debated whether the resistance associated with concentration polarization can be attributed to a thermodynamic (osmotic pressure) or hydraulic barrier, it has been shown that the increase in cross-flow shear rate can reduce its effect (Michaels, 1968). This effect has been modeled quantitatively by several researchers (Michaels, 1968; Blatt et al., 1970; Shen and Probstein, 1977; Trettin and Doshi, 1980; Isaacson et al., 1980; Gekas and Hallstrom, 1987).

The concept of backflushing (reversal of flow through the membrane), both with liquids and air, has also been employed to clean the membrane surface at intermittent points throughout an operation cycle for both hollow fiber and flat sheet membrane systems (Michaels, 1980; Von Baeyer et al., 1983, 1985; Belfort et al., 1980; Fane and Fell, 1987). Backflushing of the membrane usually occurs for a period on the order of minutes or seconds in a cycle measured on the order of hours. It is thought that backflushing facilitates removal of the "gel layer," which causes the flux to decay at a rate proportional to $t^{-1/2}$ (Trettin and Doshi, 1980).

Other mechanisms for reduction of the resistance due to concentration polarization include boundary-layer removal devices (Doshi, 1980), pulsatile retentate flow (Ozdural et al., 1979; Galletti et al., 1983; Jaffrin et al., 1984), vibrating modules (Charm and Lai, 1971), and positive transmembrane pressure pulsing (Bauser et al., 1986). These methods have been found to increase the permeate flux by as much as 100%.

While the above methods have been successful in improving overall permeate flux by reducing primarily concentration polarization, little research has been done to address the classical problem of reduced solute rejection when mixtures of macromolecules are ultrafiltered (Blatt et al., 1970; Ingham et al., 1980). Analysis of this problem requires consideration of membrane fouling associated with solute-membrane interaction (adsorption and pore plugging) and solute-solute interaction.

Studies by Ingham et al. (1980) demonstrated that protein adsorption, not concentration polarization, was the most significant factor in solute rejection. Protein adsorption appeared to have had a more pronounced effect on solute rejection than concentration polarization. More recently, Robertson and Zydney (1990) demonstrated that protein adsorption reduced the diffusional transport of albumin (69,000 Dalton) through 100,000 and 300,000 MWCO membranes by a factor of two.

Solute-solute interaction also affects the transport of solute through membranes. Ingham et al. (1980) showed that modification of the interaction of lysozyme and albumin by adjusting ionic strength altered the rejection of lysozyme by polysulfone membranes.

Although solute-solute interaction has some effect on solute flux reduction, this phenomenon occurs even in systems containing a single species. Michaels (1980) reported that membranes normally considered to be albumin-retentive actually show little rejection of albumin in the first few minutes of operation. In addition, Swaminathan et al. (1980) observed that the time to reach steady-state flux in the filtration of albumin solutions through 100,000 MWCO membranes was approximately 270 seconds, while steady-state retention occurred in about 10 minutes.

Models for describing a membrane's capacity to separate a solute from the solvent is usually described by either Eq. 1 or Eq. 2.

By retention coefficient:

$$R = 1 - S_o \tag{1}$$

where $S_o = C_p/C_b$, the observed sieving coefficient, describes the ratio of the difference in the concentrations of species A in the permeate and bulk solution.

By true membrane retention:

$$r = 1 - S_i \tag{2}$$

where $S_i = C_p/C_w$ is the intrinsic sieving coefficient and C_w is the apparent concentration of the solute at the wall (the membrane surface). The latter expression has the advantage of separating the membrane characteristics from effects of concentration polarization. The wall concentration, however, is not easily determined.

The classical relationship of the observed sieving coefficient to steric hindrance was proposed by Ferry (1936),

$$R = 1 - S_o = [\lambda(\lambda - 2)]^2, \tag{3}$$

where

$$\lambda = \frac{r_{\text{solute}}}{r_{\text{pore}}}. \tag{4}$$

Although this model corrects for the effect of concentration polarization on the retention of the solute, it does not account for pore plugging, deposition, or adsorption that can occur within the membrane structure during protein separation processes. Zeman (1983) proposed a modification of the Ferry model that accounted for the reduction of the membrane pore radius due to solute adsorption in the pore. Thus,

$$R = 1 - S_o = [\lambda'(\lambda' - 2)]^2, \tag{5}$$

where

$$\lambda' = \frac{r_{\text{solute}}}{r_{\text{pore}} - \Delta r_{\text{pore}}}. \tag{6}$$

The change in the pore radius, Δr_{pore}, reflects the thickness of the adsorbed solute layer.

Prediction of the adsorbed thickness layer is quite complicated; depending on solute, solution properties, and membranes, this value has been observed as being both a monolayer dispersion of solute and multilayer adsorption in separate studies (Nilsson, 1990).

Deen (1987) in his extensive review on the theory of hindered transport of macromolecules through pores, pointed out that solute-pore interaction is not well understood currently. As a first approximation, Zeman (1983) relates Δr_{pore} to the intrinsic viscosity of the solute.

The resistances to solute flux, particularly for protein mixtures, significantly reduce the applicability of ultrafiltration in solute fractionation. If the dominant resistance to solute flux is not concentration polarization, but membrane fouling, then methods must be found that effectively decrease solute rejection and improve selectivity. The objective of this study was to examine negative transmembrane pressure pulsing as an

effective means of enhancing solute flux and separation efficiency in the ultrafiltration of binary protein mixtures.

Negative Transmembrane Pressure Pulsing

The novel process of negative transmembrane pressure pulsing was developed to effectively minimize the forces associated with membrane fouling phenomenon before it reaches a near irreversible state (Rodgers, 1989). As solute begins to permeate through the membrane, the likelihood for a protein molecule or molecules to become lodged or trapped is high since the path through the membrane is tortuous and the pore diameter for selective membranes is on the order of the size of the solute. In addition, there is evidence that adsorption of proteins onto surfaces is a dynamic process. The time scale for adsorption depends highly on the nature of the protein, the properties of the available surface sites, and the type of adsorption force, that is, electrostatic, hydrogen bonding, hydrophobic interaction or charge transfer (Dillman and Miller, 1973; Lok et al., 1983; Bessinger and Leonard, 1981; Cheng et al., 1985; Andrade, 1985; Silberberg, 1985). Once adsorption interaction begins, the required force necessary to remove the molecule increases with time until the process is complete.

The objective of negative transmembrane pressure pulsing is to provide high-frequency forces that reduce time-dependent adsorption and/or pore plugging while maximizing solute throughput and separation efficiency. This is accomplished by frequent reversal of pressure forces at high amplitudes. This process differs fundamentally from backflushing and backwashing in that the pulsing frequencies are on the order of fractions of seconds, instead of minutes. In addition, transmembrane pressure pulsing is a dynamic process and thus introduces transient effects not found in conventional ultrafiltration backflushing. When the transmembrane pressure is reversed, it is hypothesized that additional forces due to accelerating fluids and inertia are introduced on the initially adsorbing or lodged proteins. This dislodges the protein effectively, and as a result, the protein is again entrained in the fluid and may either begin readsorption at a new location or be carried out in the filtrate by convection. Since this force is a function of the time-derivative change of velocity of the fluid near the protein, rapid directional change maximizes these forces.

The pulsing process might also facilitate solute transport away from the membrane surface into the bulk flowing stream and thus alter the solute concentration profile near the wall. This would momentarily reduce the concentration polarization resistance and might facilitate both solvent and solute flux.

Figure 2 illustrates the operating pressure and the transmembrane pressure for a process pulsed at 0.5 Hz. In this study, the pulse duration is defined as the time during a period in which the transmembrane pressure is negative. The pulse amplitude is defined as the absolute value of the transmembrane pressure at its most negative point.

Experimental data of ultrafiltration of binary protein mixtures with variations in pulse frequency and amplitude were used to determine the effectiveness of transmembrane pressure pulsing.

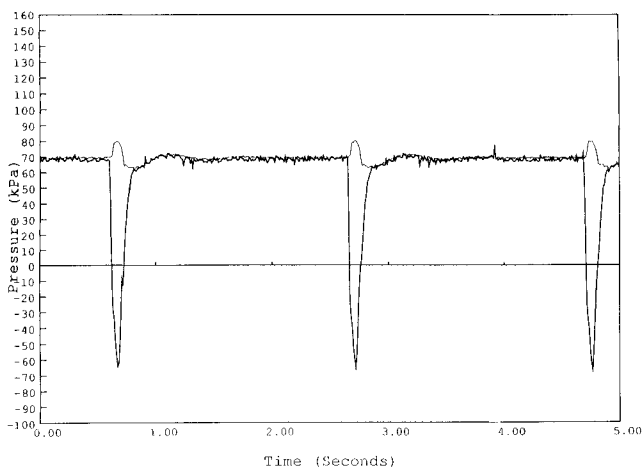

Figure 2. Example of operating pressure and transmembrane pressure curve operated at 0.5 Hz.

Dark curve is transmembrane pressure. Light curve is pressure on retentate side.

Experimental Apparatus Design

The experimental apparatus for the flat-sheet ultrafiltration system is shown in Figure 3. Fluid in the 2-L feed reservoir was pressurized by nitrogen gas and forced through the membrane test module. A peristaltic pump acted as a back-pressure control and flow control, and also recycled retentate through a flowmeter back to the feed reservoir. Permeate was collected in graduated test tubes whose collection time was controlled by a sample collector controller. Pulsing was initiated by a timer that simultaneously signaled two solenoids. The solenoid in the filtrate path closed the filtrate line, while the solenoid distal to the filtrate path opened to allow nitrogen gas to pressurize the filtrate side of the membrane support press. The solenoids were de-energized by termination of the signal from the controller. An oscilloscope provided monitoring of the pressure signals from sensors located upstream and downstream of the membrane on the retentate side and on the filtrate side of the press. At selected times, these signals were captured by data acquisition apparatus controlled by an Apple II computer. Pressure data were stored and later downloaded to a VAX 11/750 for analysis.

The ultrafiltration module was a modified Babb-Grimsrudd Dialyzer cell (Grimsrud and Babb, 1966). The cell consisted

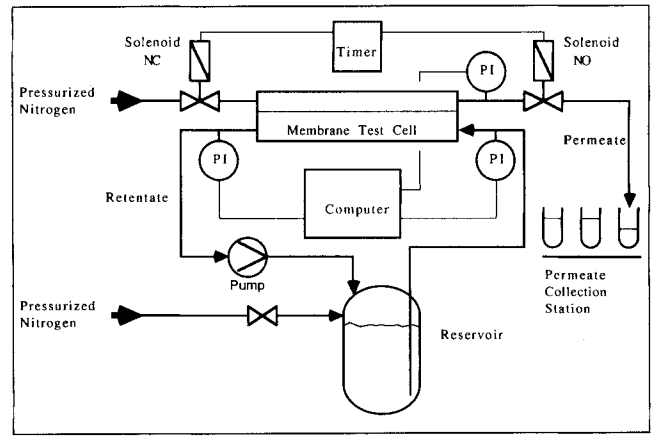

Figure 3. Transmembrane pressure pulsed ultrafiltration apparatus.

of two Lexan plates with the interior hollowed and replaced with membrane channel supports. Both sides of the membrane support pad consisted of a layer of fine neoprene pins, 0.3 mm in diameter and 0.4 mm in height, which were equally spaced in rows with a diagonal distance of 1 mm between them. These pins provided adequate support for both sides of the membrane during transmembrane pressure pulsing. It was estimated that laminar flow assumptions were valid for this geometry with Reynolds numbers (based on hydraulic diameter of the channel) less than 40 (Panton, 1984, Schlichting, 1979). The cross-sectional chamber area was 1.56×10^{-5} m^2. The total width of the flow channel is 3.9×10^{-2} m, and the channel length is 10×10^{-2} m. The nominal membrane surface area was 5.5×10^{-3} m^2. Pressure tests indicated that the module was capable of handling constant pressures in excess of 276 kPa with negligible leakage.

The feed entered the membrane module from the bottom so that channeling and improper wetting of the membrane were eliminated. This had no effect on concentration polarization. This eliminated pulse gas interaction with the membrane that could cause a reduction in the available transport area and introduce surface forces within the pores.

The pulsing system consisted of two solenoids (Allenair, Mineola, NY, Model 2CD8S-120) and an electronic timer (Eagle Signal, Austin, TX). The timer was capable of cycling at 0.01-second intervals and set both the frequency and duration of pulse. Minimum duration of the system was limited by the input and release rate of pressure inside the ultrafiltration module filtrate section.

Materials and Methods

For these studies, solutions combining 1% (kg/100 L) albumin (69,000 Dalton, fraction *V* powder, Sigma Chemical Co., St. Louis, no. A-8022, lot no. 85F-0007) and 0.3% γ-globulin (159,000 Dalton, powder, Sigma Chemical Co., no. G-7516, lot no. 56F-9374) in 0.15-M NaCl at 7.4 pH were prepared and refrigerated. As a preservative 0.02% sodium azide was used.

Albumin concentrations were determined using a modified bromcresol green colorimetry reagent (Sigmas, BCG Albumin Reagent Kit). Calibration curves were determined using known albumin concentrations. A Gilford spectrophotometer (Oberlin, OH, Model 240) was used to measure absorbance at 628 nm. Disposable microcuvettes (Fisher Scientific, St. Louis), with adequate operating absorption range, were used during sampling. Addition of IgG into solution did not interfere with this analysis. This method was found to determine albumin concentration as low as 0.007%.

Gamma-globulin concentrations were also determined by colorimetry (Sigma, no. 560). Since this method is based on the Hopkins-Cole reaction (Fearson, 1920) where the reagent reacts with tryptophan, it was necessary to correct for the presence of albumin in the solution. IgG concentrations were corrected using the results of the albumin analysis. This method has a concentration detection of IgG of as low as 0.007%.

Preliminary preparations were performed by flushing the operating system with 0.02% sodium azide solution. During this time, the refrigerated protein solution was warmed gradually to 25°C.

For each run, fresh 100,000 MWCO membranes were cut to size carefully from either cellulosic sheet stock (YM-100, courtesy of Amicon Corp., Lexington, MA, lot nos. 2912, 2977, 3444), polysulfone on polypropylene web sheet stock (Millipore PTHK), defect free polysulfone sheet stock (Millipore PVHK), or composite polyvinylidene difluoride sheet stock (Millipore PZHK) (all, courtesy of Millipore Corporation, Bedford, MA, lot nos. 092686, AB282430, and 122288PZ2A, respectively). The cellulosic and polysulfone membranes were pretreated by soaking in distilled water for one hour to remove the glycerin. The polyvinylidene difluoride membranes were wet with 1% Triton X-100 in 80% ethanol prior to use.

After pretreatment, the membranes were placed into the test module and a hydraulic permeability test was performed. The water was then removed from the system and replaced with the protein solution. The run at which to operate was then randomly selected. The operating parameters were then selected and ultrafiltration was carried out for one hour. Dynamic pressure data were monitored continuously. Measured volumes of samples were collected every one minute. The average flux and concentration associated with each collected sample were then determined immediately. Albumin and gamma-globulin retention, selectivity, albumin, IgG, and permeate flux and estimated feed concentration were subsequently calculated.

Studies were also performed to determine whether transmembrane pressure pulsing may have damaged the membrane. After some runs were complete, the system was allowed to operate without pulsing for several minutes while data acquisition continued. In some cases, the protein solution was then replaced with water and another hydraulic permeability test was performed.

Propagation of error analysis was used throughout the study, and error was determined for solute concentrations, flux, and selectivity.

Results and Discussion

Ten cases, using cellulosic membranes, were operated at a positive transmembrane pressure held constant at 65 ± 5.4 kPa and a pulse amplitude of 51 ± 12.7 kPa. The cross-flow shear rate was varied between 160 s^{-1}, 700 s^{-1}, and at turbulent cross-flow conditions. The turbulent condition was obtained by increasing the cross-flow flow rate to 4.2 $cm^3 \cdot s^{-1}$. Because of the special design of the flow channel, the actual shear rate was not determined. However, the average pressure drop across the retentate flow channel was 12.9 ± 1.50 kPa for the turbulent case as compared to 2.6 ± 1.18 kPa for the 700 s^{-1} case. The pulse frequencies were 0 Hz, 0.5 Hz, 2 Hz, and 5 Hz. Seven additional studies using polysulfone membranes and two cases using composite polyvinylidene difluoride membranes were also performed using the same operating conditions at a cross-flow shear rate of 700 s^{-1}.

The hydraulic permeability were $(1.85 \pm 0.116) \times 10^{-6}$ $m \cdot s^{-1} \cdot kPa$, $(1.6 \pm 0.29) \times 10^{-6}$ $m \cdot s^{-1} \cdot kPa^{-1}$, $(2.66 \pm 0.036) \times 10^{-6}$ $m \cdot s^{-1} \cdot kPa^{-1}$, and $(4.4 \pm 1.17) \times 10^{-6}$ $m \cdot s^{-1} \cdot kPa^{-1}$, for the cellulosic, polysulfone (PTHK), defect-free polysulfone (PVHK), and polyvinylidene difluoride (PZHK) membranes, respectively.

Effect of pulsing on permeate flux

The results of the overall permeate flux after one hour for

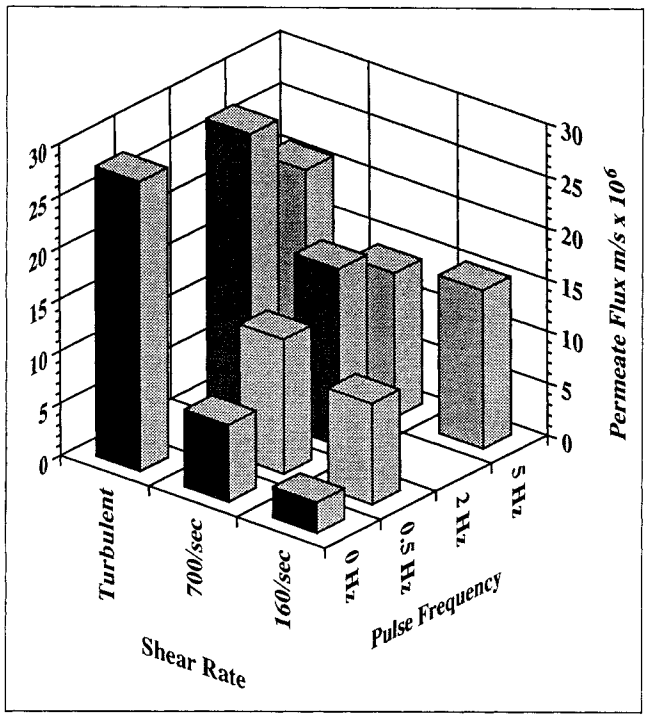

Figure 4. Permeate flux vs. pulse frequency and shear rate.

50-kPa operating pressure, 50-kPa pulse amplitude, cellulosic membrane. Average error (1.24 ± 0.63) × 10^{-6} m·s^{-1}.

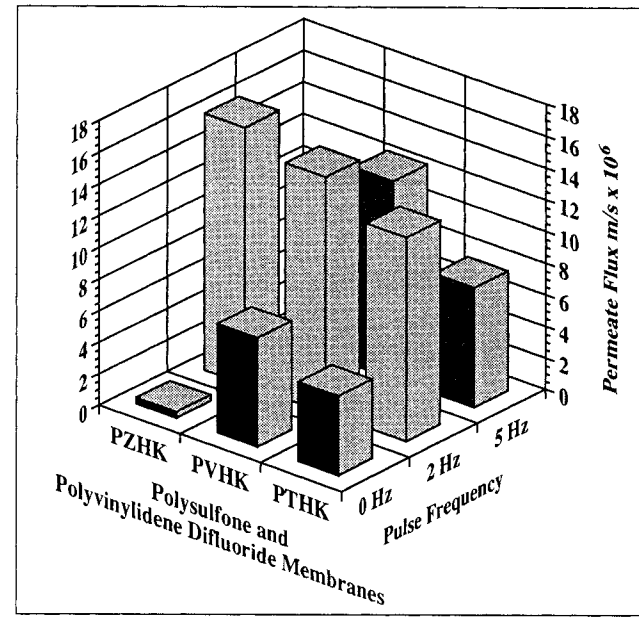

Figure 5. Permeate flux vs. pulse frequency for polysulfone and composite polyvinylidene difluoride membranes.

50-kPa operating pressure, 50-kPa pulse amplitude, 700-s^{-1} cross-flow shear rate. Average error (2.07 ± 2.97) × 10^{-6} m·s^{-1}.

all of these cases are shown in Figures 4 and 5. For the cellulosic membrane studies, the systems operated at cross-flow shear rates of 160 s^{-1} and 700 s^{-1} with transmembrane pressure pulsing enhanced the total permeate flux as much as fivefold. For the hydrophobic membranes, a factor of three and 100 increase in permeate flux was observed for the polysulfone cases and the polyvinylidene difluoride membranes, respectively. Total permeate flux did not increase when the system was operated under turbulent flow conditions. In general, cross-flow shear rate increased permeate flux.

In conventional laminar flow ultrafiltration, the permeate flux increases to the 1/3 power of the cross-flow velocity (Isaacson et al., 1980). Thus, the same increase in permeate flux under the laminar flow conditions during pulsing is equivalent to results achieved by increasing cross-flow shear rate by 120 times for nonpulsed ultrafiltration.

The effect of pulsing on the resistance to permeate flux was actually greater than what is presented by permeate flux data. This is because pulsing reduces both the average pressure and the ultrafiltration time during a cycle. The average positive transmembrane pressure for the pulsed cases was 47 ± 6.6 kPa compared to an average of 64 ± 5.1 kPa for the nonpulsed cases. This is due to the reduction of positive transmembrane pressure for a short time as the pressure decreases to approach negative transmembrane pressure and return. Also, the percentage of time that the system was in the ultrafiltration phase was 94 ± 1% for the 0.5-Hz cases, 80 ± 2% for the 2-Hz cases, and 60 ± 1% for the 5-Hz cases.

These facts suggest that the analysis of an apparent permeability may give additional insight to the effect of pulsing on the permeate flux resistance. The apparent permeability is the permeate flux divided by the fraction of actual ultrafiltration period during the cycle and the average positive transmembrane pressure. Albeit a linear correction for a nonlinear phenomenon, the apparent permeability better demonstrates the actual permeability of the membrane during the ultrafiltration period of the cycle. The apparent permeability was then normalized with respect to the hydraulic permeability of each membrane. The normalized permeability is summarized in Figures 6 and 7. The normalized permeability increased with the frequency of pulsing in all, but one, cases. The actual increase in normalized permeabilty was observed to be a maximum of 64 times for the polyvinylidene difluoride membranes, 6 times for the polysulfone membranes, and 14.5 times for the cellulosic membranes. Apparent permeability increased by a factor of two for the turbulent studies using cellulosic membranes. This observation, coupled with a reduction in permeate flux from pulsing during the turbulent cross-flow studies indicate that, although pulsing may reduce resistances to permeate flux, the loss of ultrafiltration time and average transmembrane pressure during the cycle can offset this benefit. It is unclear why the apparent permeability decreased with an increase in frequency for the standard polysulfone membranes. However, others factors such as tolerances in membrane characteristics and pulse amplitude have not been considered.

It is postulated that the resistances to permeate flux due to concentration polarization and membrane fouling were reduced during transmembrane pressure pulsing. To understand the direct effect of transmembrane pressure pulsing on concentration polarization, a study was performed using a system containing a totally retained protein (Rodgers, 1989; Rodgers and Sparks, 1991). In this study, albumin (69,000 Dalton) was used with 30,000 MWCO regenerated cellulose membranes (YM-30, Amicon Div., Grace, MA).

Transmembrane pressure pulsing was found to reduce con-

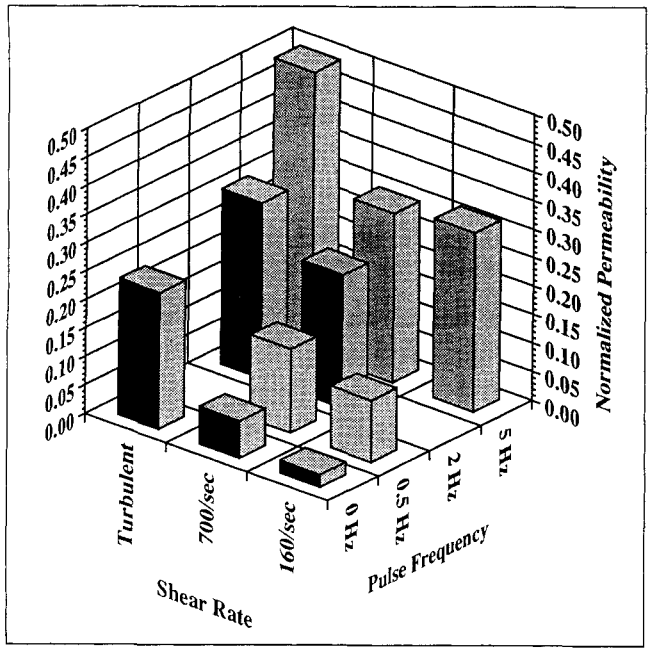

Figure 6. Normalized permeability vs. pulse frequency and shear rate.

50-kPa operating pressure, 50-kPa pulse amplitude, cellulosic membrane. Average error 0.01 ± 0.005.

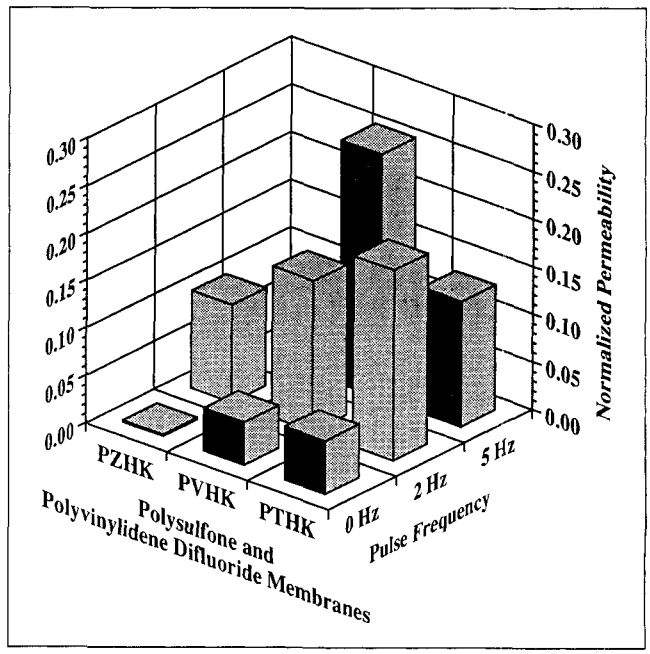

Figure 7. Normalized permeability vs. pulse frequency for polysulfone and composite polyvinylidene difluoride membranes.

50-kPa operating pressure, 50-kPa pulse amplitude, 700-s^{-1} cross-flow shear rate. Average error 0.01 ± 0.015.

centration polarization resistance for the laminar flow cases, but not significantly for the turbulent flow studies. In addition, the increase in solute concentration reduced the effect of transmembrane pressure pulsing. Pulse frequency was found to be the dominant factor and higher frequencies were required to obtain flux improvement as the shear rate or bulk concentration was increased. Only a nominal negative transmembrane pressure value of 9 ± 2.7 kPa was necessary to maximize permeate flux. It was determined that the mechanism for enhanced solvent transport under low wall shear rate conditions might be caused by minute wall motion that disrupted the concentration polarization layer. This reduced the average wall concentration reducing the resistance to permeate flux.

It is difficult to determine from permeate flux alone the quantitative reduction of either membrane fouling resistance or polarization resistance for our current study. This is because the transport of solute through the membrane may result in pore obstruction that can reduce permeate flux. Thus, the resistance with respect to membrane fouling and concentration polarization are coupled and it is unclear how pulsing independently affects either. However, the above observations for the totally retained proteins can be extended to these studies to provide an estimate of the reduction in membrane fouling resistance.

If pulsing reduces the effect of concentration polarization, then it is obvious that the pulsing frequency must be such that the ultrafiltration periods during pulsing are not significantly greater than the polarization development time. As a first approximation, the time scale for concentration polarization development was determined using an order-of-magnitude analysis of the two-dimensional, transient, convective-diffusion equation with constant diffusivity for a totally retained solute. As shown in the Appendix, the characteristic time, based on a thermodynamic resistance to permeate flux, can be written as

$$\theta = \frac{D_s}{[L_p(\Delta P - \alpha\Delta\pi)]^2} \tag{7}$$

were L_p is the hydraulic permeability of the membane, ΔP is the transmembrane pressure, α is the reflection coefficient, and $\Delta\pi$ is the osmotic pressure difference between the solute at the membrane surface and in the pore.

The characteristic time for polarization development was less than 1/100 second for our current studies, which is about 15 times faster than the characteristic time for the totally retained studies. Since the characteristic time is based on the hydraulic permeability and is a linear approximation, it is an underestimation of the actual development time of polarization. Nevertheless, this implies that the effect of pulsing on the concentration polarization resistance during turbulent cross-flow shear rates for this study would be even less than that observed for the totally retained protein study. As mentioned above, pulsing did little to reduce the polarization resistance in the totally retained protein study when operated with turbulent cross-flow conditions. Therefore, it can be assumed that in this study, during turbulent cross-flow conditions, pulsing did not significantly affect concentration polarization resistance. Thus, we may use the turbulent flow data to determine qualitatively how pulsing may effect membrane fouling resistance.

Assume a general form of permeate flux as:

$$J = \beta \frac{\Delta P - \alpha\Delta\pi}{(R_m + R_p + R_f)}, \tag{8}$$

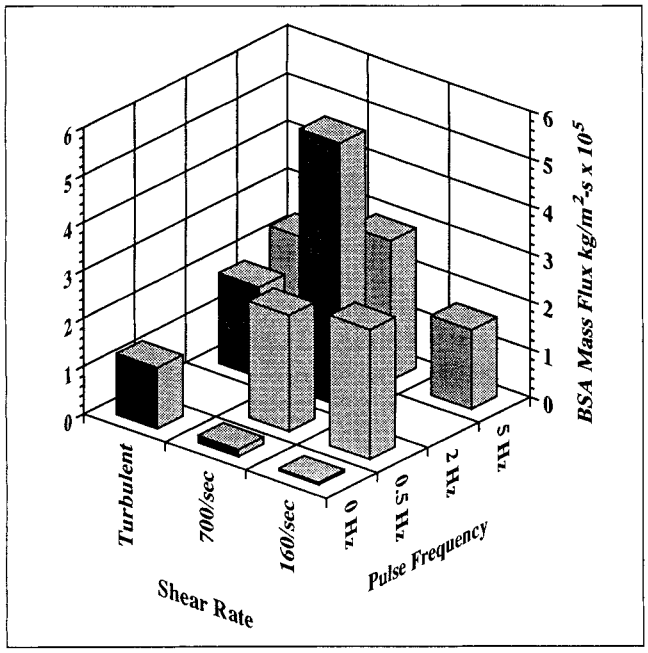

Figure 8. Albumin mass flux vs. pulse frequency and shear rate.

50-kPa operating pressure, 50-kPa pulse amplitude, cellulosic membrane. Average error $(0.32 \pm 0.16) \times 10^{-5}$ kg·m^{-2}·s^{-1}.

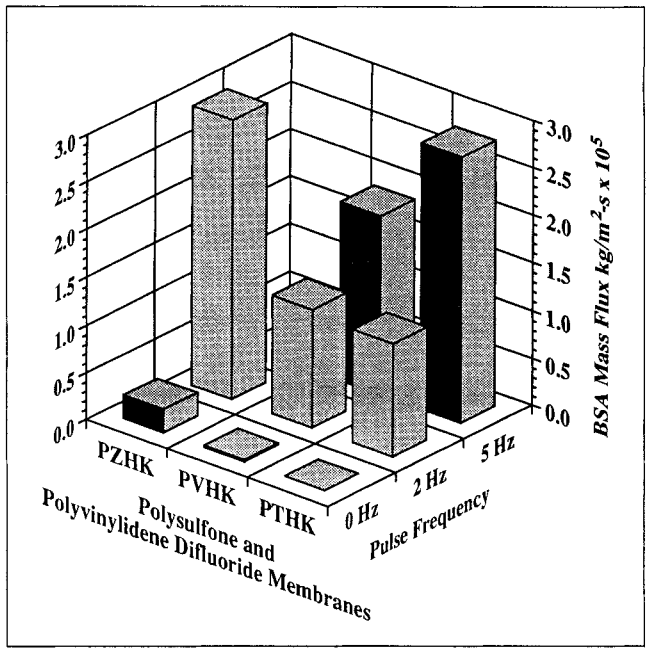

Figure 9. Albumin flux vs. pulse frequency for polysulfone and composite polyvinylidene difluoride membranes.

50-kPa operating pressure, 50-kPa pulse amplitude, 700-s^{-1} cross-flow shear rate. Average error $(0.41 \pm 0.77) \times 10^{-5}$ kg·m^{-2}·s^{-1}.

where ΔP is the hydraulic transmembrane pressure, α is the reflection coefficient, $\Delta\pi$ is the osmotic pressure difference across the membrane, β is a proportionality constant, and R_m, R_p and R_f are the membrane resistance, the polarization resistance and resistance due to membrane fouling, respectively. The results from the normalized permeability data indicate that pulsing either reduced the concentration at the membrane wall and thus reduced $\Delta\pi$, or reduced R_p and/or the resistance due to membrane fouling. From the normalized permeability data it is possible to determine the maximum reduction in membrane fouling resistance to permeate flux by examining the limiting case where the resistance due to polarization and $\Delta\pi$ become negligible. We begin by taking the ratio of the normalized permeability for the nonpulsed case and the pulsed case such that

$$\frac{N_{po}}{N_{pp}} = \frac{R_m + \varphi R_{fo}}{R_m + R_{fo}}, \tag{9}$$

where N_{po} is the normalized permeability of the nonpulsed case, N_{pp} is the normalized permeability of the pulsed case, R_{fo} is the membrane fouling resistance for the nonpulsed case, and φ is the fraction of R_{fo} remaining during the pulsed case. Recognizing that R_m is the inverse of the hydraulic permeability for the membrane and solving Eq. 9 results in the value of 0.32 for φ or a maximum reduction in membrane fouling resistance of 68%. This value would decrease as the polarization resistance is increased. Further quantitative analysis of this is the subject of a future study.

Effect of pulsing on solute flux

Solute flux is a combination of the permeate concentration of a particular species and the permeate flux. Thus, an increase in either solute concentration in the filtrate or the permeate flux will increase the solute flux. Transmembrane pressure pulsing was effective in improving solute flux for all cross-flow shear rates evaluated in these studies. Figure 8 through 11 show the mass flux of albumin and IgG, respectively. The average errors for the albumin and gamma-globulin flux for the cellulosic membranes were $(0.32 \pm 0.16) \times 10^{-5}$ kg·m^{-2}·s^{-1} and $(0.14 \pm 0.07) \times 10^{-5}$ kg·m^{-2}·s^{-1}, respectively. For the polysulfone and composite polyvinylidene difluoride membranes, the average errors in the albumin flux and the gamma-globulin flux were $(0.41 \pm 0.77) \times 10^{-5}$ kg·m^{-2}·s^{-1} and $(0.16 \pm 0.24) \times 10^{-5}$ kg·m^{-2}·s^{-1}, respectively.

Figures 8 through 11 show that the albumin and γ-globulin mass flux were increased markedly during moderate pressure pulsing. For the cellulosic membrane, the albumin flux was increased by a factor of 10, 38 and 1.8 times over the nonpulsed cases for the shear rates of 160 s^{-1}, 700 s^{-1}, and the turbulent condition, respectively (Figure 8). Solute flux was most enhanced when the shear rate was 700 s^{-1}. Likewise, the albumin flux increased by a factor of nearly 100 for the polysulfone membranes and by a factor of 10 for the polyvinylidene difluoride membranes when pulsed at 5 Hz and 2 Hz, respectively (Figure 9).

Because the change in solute flux was not proportional to the solvent flux change, it is clear that membrane fouling, not concentration polarization, was the most significant resistance overcome by pulsing to improve solute flux. The reduction in the concentration polarization resistance is generally the result of a reduction in the apparent wall concentration. This can be accomplished by an increase in shear rate or by transmembrane

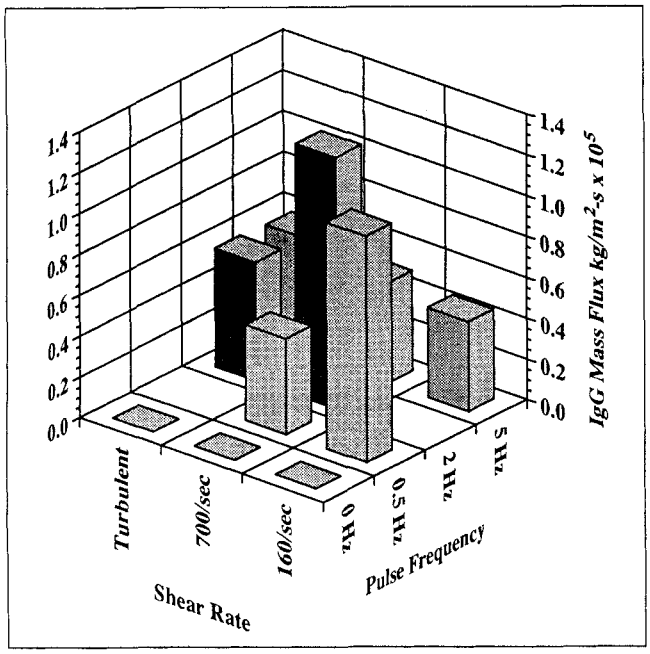

Figure 10. γ-globulin mass flux vs. pulse frequency and shear rate.

50-kPa operating pressure, 50-kPa pulse amplitude, cellulosic membrane. Average error 0.14 ± 0.07 × 10^{-5} kg·m^{-2}·s^{-1}.

pressure pulsing. If it is assumed that the sieving coefficient for the membranes was nearly constant as the polarization resistance is reduced, the expected result would be a reduction in the permeate concentration and an increase in retention.

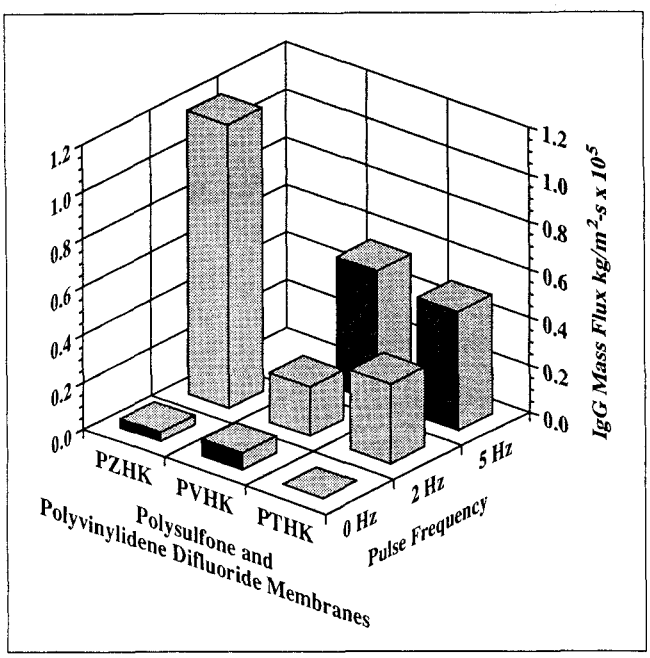

Figure 11. γ-globulin mass flux vs. pulse frequency for polysulfone and composite polyvinylidene difluoride membranes.

50-kPa operating pressure, 50-kPa pulse amplitude, 700-s^{-1} cross-flow shear rate. Average error (0.16 ± 0.24) × 10^{-5} kg·m^{-2}·s^{-1}.

However, as can be seen from Table 1, the increase in solute flux was in many cases the result of both an increase in the permeate flux and the solute concentration in the filtrate. As an example, the solute flux for BSA using the cellulosic membranes increased by 37 times over the conventional case when operated at 700 s^{-1} while pulsing at 2 Hz. This was a result of increasing the solute concentration by a factor of 16 and the permeate flux by 2.3. Thus, it is postulated that pulsing reduced the potential for pore blockage or adsorption resulting in an increase in the true sieving coefficient. These results suggest that membrane fouling is the most dominant resistance to solute flux and is overcome by pulsing.

Figures 8 and 10 also reveal that an optimum may exist for increasing solute flux by transmembrane pressure pulsing. Increasing the pulse frequency for some cases operated at 160 s^{-1} and 700 s^{-1} resulted in a decrease in permeate flux. This may be related to the fact that pulsing not only reduces membrane fouling but concentration polarization. As such, higher frequency pulsing may reduce membrane fouling but also reduces the apparent wall concentration. Therefore, the solute concentration in the permeate is reduced because the wall concentration is reduced, although the sieving coefficient has improved. If this is the case, then an optimum may exist that maximizes solute flux. This is the subject of future research.

If membrane fouling is reduced due to transmembrane pressure pulsing, then the pulse amplitude should be important in improving permeate concentration. To evaluate whether solute flux was affected by pulse amplitude, studies were compared in which all parameters were held constant except for pulse amplitude. In two cases, cellulosic membranes were used and the system was operated with a pulse frequency of 2 Hz and a cross-flow shear rate of 700 s^{-1}. The transmembrane pressure for the two runs averaged 48 ± 3.3 kPa and the average pulse amplitude was a maximum of 9 kPa for one case and 64 kPa for the other. The ultrafiltration time was, respectively, 86% and 79% of the overall time of operation for the two cases.

The result demonstrated that the lower pulse amplitude run did not improve solute flux over the nonpulsed case. However, the higher pulse amplitude resulted in a significant increase in solute flux. The case with a pulse amplitude of 9 kPa produced a mass flux of albumin of only (0.06 ± 0.26) × 10^{-5} kg·m^{-2}·s^{-1}, while the case with the pulse amplitude of 64 kPa resulted in an albumin flux of (5.5 ± 0.38) × 10^{-5} kg·m^{-2}·s^{-1}. As a comparison, the case with no pulsing produced an albumin flux of (0.15 ± 0.18) × 10^{-5} kg·m^{-2}·s^{-1}, which is comparable to the case when pulsed at 9 kPa. The increase in pulse amplitude resulted in a factor of 90 increase in solute flux with an increase in permeate flux of only 37%. These results are shown in Table 1.

The fact that substantial pulse amplitude is necessary to increase solute flux implies that membrane fouling is the resistance most affected by pulsing. However, the type of membrane fouling affected is not obvious. Studies were performed at lower operating pressures and pulse amplitudes to determine if the resistance to solute flux was predominantly pore plugging or adsorption. If the dominant resistance was pore plugging, then the required force to establish a significant difference in the solute flux would be approximately the same magnitude as the operating pressure that lodged the particle in the pore. The results indicated that operating the system at lower operating and pulse pressures resulted in substantial loss in solute

Table 1. Results from 1% Albumin/0.3% γ-Globulin Studies (After 1 hour)

Membrane Type	Shear Rate s^{-1}	Oper. Pres. kPa	Max. Pulse Amp. kPa	Pulse Freq. Hz	BSA % kg/100 l	IgG % kg/100 l	Solvent Flux $m/s \times 10^6$	BSA Mass Flux $kg/m^2 \cdot s \times 10^5$	IgG Mass Flux $kg/m^2 \cdot s \times 10^5$	Selectivity L_A/L_B
Cellulosic	160	70	0	0	0.019	0.001	2.9	0.05	0.00	1.7±1.8
Cellulosic	160	49	44	0.5	0.281	0.062	9.7	2.73	0.60	1.5±0.2
Cellulosic	160	44	43	5	0.031	0.000	15.2	0.47	0.00	0.5±0.3
Cellulosic	700	60	0	0	0.020	0.000	7.4	0.15	0.00	6.4±6.6
Cellulosic	700	51	73	0.5	0.187	0.027	12.9	2.54	0.37	1.0±0.5
Cellulosic	700	50	64	2	0.324	0.073	17.0	5.50	1.23	1.5±0.2
Cellulosic	700	46	9	2	0.005	0.000	12.4	0.06	0.00	1.5±1.5
Cellulosic	700	17	25	2	0.016	0.012	12.1	0.19	0.14	1.6±0.6
Cellulosic	700	51	50	5	0.209	0.035	13.9	2.91	0.49	7.2±5.8
Cellulosic	Turbulent	63	0	0	0.046	0.000	27.9	1.28	0.00	3.0±2.7
Cellulosic	Turbulent	58	49	2	0.070	0.022	27.0	1.88	0.58	3.2±1.6
Cellulosic	Turbulent	38	36	5	0.112	0.027	20.9	2.33	0.57	5.8±3.6
Polysulfone	700	56	0	0	0.004	0.001	5.0	0.02	0.01	1.0±2.6
Polysulfone	700	50	67	2	0.154	0.064	12.6	1.93	0.81	1.4±0.4
Polysulfone	700	40	66	5	0.375	0.066	7.6	2.80	0.50	1.7±0.2
Polysulfone (Defect Free)	700	59	0	0	0.003	0.010	6.9	0.02	0.07	0.2±0.2
Polysulfone (Defect Free)	700	44	65	2	0.084	0.014	14.9	1.25	0.21	0.8±0.3
Polysulfone (Defect Free)	700	33	61	5	0.150	0.044	12.5	1.87	0.55	0.8±0.1
Polysulfone Difluoride	700	57	0	0	0.571	0.097	0.4	0.25	0.04	2.1±0.2
Polysulfone Difluoride	700	46	62	2	0.182	0.074	16.2	2.94	1.19	0.6±0.1

flux. Reducing the operating pressure from 50 kPa to 17 kPa and the pulse amplitude from 64 kPa to 25 kPa resulted in a reduction in albumin flux from 5.5×10^{-5} kg·m^{-2}·s^{-1} to 0.2×10^{-5} kg·m^{-2}·s^{-1}. These results are shown in Table 1. Although further research is necessary to confirm this hypothesis, this observation implies that pore plugging may not be as significant as adsorption in membrane fouling.

Effect of pulsing on retention

As mentioned above, the increase in solute flux may be interpreted as being due to an increase in the true sieving coefficient. This implies the true retention coefficient was reduced for both albumin and gamma-globulin during some aspects of pulsing. However, the true retention coefficient requires the apparent wall concentration which is difficult to determine. Nevertheless, the observed retention coefficient, which is based on the bulk concentration of proteins, can provide some insight into how significant a change in membrane properties was observed due to pulsing.

The observed retention coefficient for albumin using the cellulosic membranes was 0.95 ± 0.007 to 0.98±0.007 for the nonpulsed cases. This was reduced to a minimum of 0.68 ± 0.007 after pulsing at 2 Hz. For the IgG observed retention was reduced from 1.00 ± 0.023 to 0.76 ± 0.023 during the same run. For the polysulfone membranes, the albumin and IgG retention were reduced from 1.00 ± 0.007 and 1.00 ± 0.023 to 0.625 ± 0.007 and 0.78 ± 0.023, respectively. For the polyvinylidene difluoride membrane, the albumin and gamma-globulin retention was actually increased for 0.43 ± 0.007 and 0.68 ± 0.023 to 0.818 ± 0.007 and 0.75 ± 0.023, respectively. The latter observation may be due to a significant variation in the apparent wall concentration between the pulsed and nonpulsed case. This may be reflected by the vary large increase in solute flux upon pulsing. The value of the retention coefficient being less than one for the polyvinylidene difluoride membrane may be associated with albumin being preferentially adsorbed by the membrane.

Effect of pulsing on selectivity

The selectivity of a membrane system is a ratio of the permeabilities of the solutes. The permeability for solutes is equal to the solute flux divided by the apparent concentration driving force. For species A, the permeability can be written as:

$$L_A = \frac{J_A}{(C_b - C_p)} \tag{10}$$

where J_A is the solute flux.

Thus, for species A and B, the selectivity may be defined as:

$$\alpha = \frac{L_A}{L_B} \quad \text{or} \quad \alpha = \frac{L_B}{L_A} \tag{11}$$

depending on the reference solute.

The selectivity was evaluated for each run using the ratio of albumin permeability with respect to IgG permeability. Despite the fact that solute flux was improved from pulsing, there was no improvement in selectivity. The selectivity was not changed significantly for any of the cases. These values are shown in Table 1. When IgG flux was not detectable at the one-hour point in the run, selectivity was based on data taken earlier in the run.

It is not surprising that selectivity was not improved after pulsing since pulsing may make larger pores accessible which are normally blocked in conventional ultrafiltration. In addition, although the molecular weight ratio of the two species is 2.4, the ratio of the Einstein-Stokes radius is only 1.5. This value was determined by using the relationship:

$$\log r_{\text{solute}} = 0.470 \log M_w - 0.513 \tag{12}$$

presented by Granath and Kvist (1967). Thus, although selectivity may be improved for these species, it is not likely to be high using these membranes.

The results from this study provide a hypothesis as to why the introduction of IgG in an albumin solution reduces albumin flux significantly. Since pulsing increased both IgG flux and albumin flux, albumin transport through the 100,000 MWCO membranes may be primarily through the largest pores. It has been shown (Fane et al., 1981) that 10% of the pores in the membrane are large and transport over 50% of the solvent through amorphous membranes. Of these 10%, a fraction of these pores are large enough to transport the solute through the membrane. It is plausible, therefore, that only a small amount of IgG is necessary to block these pores and thus significantly reducing the albumin flux.

By reducing the effect of membrane fouling on solute transport, transmembrane pressure pulsing effectively allowed the separation process to perform closer to the native properties of the membrane. It is likely that transmembrane pressure pulsing in some cases may even reduce selectivity since this process clears the larger pores that are originally blocked by the larger globulin proteins.

It is speculated that if a sharp cutoff membrane was used to separate selected species, improvement in selectivity would be noted from transmembrane pressure pulsing when membrane fouling is the predominant resistance. Normally, these membranes plug easily, but with transmembrane pressure pulsing, there might be a significant improvement over conventional ultrafiltration practice. The development of such narrow pore-size distribution membranes would then be warranted.

Conclusion

The results of these studies indicate that transmembrane pressure pulsing may be an effective method to overcome membrane fouling for binary protein solutions. Solute flux was enhanced by nearly two orders of magnitude, while overall permeate flux was increased by approximately a factor of two.

Although the averaged permeate flux during pulsing with turbulent cross-flow was actually reduced, normalized permeate flux, corrected for the actual ultrafiltration time, increased from 28% to 49% of the hydraulic permeability with pulsing in the turbulent flow cases. Thus, the effect of pulsing on permeate flux would have been more enhanced; however, the ultrafiltration time lost during pulsing and the reduction in average transmembrane pressure offset additional gains. This loss in ultrafiltration time and average pressure is a significant limitation in the applicability of transmembrane pressure pulsing.

Preliminary estimates showed that transmembrane pressure pulsing could have reduced membrane fouling resistance to permeate flux up to as much as 60% when operated with turbulent cross-flow conditions.

This research also revealed that the reduction in concentration polarization via an increase in shear rate is not as effective in increasing solute flux as transmembrane pressure pulsing. This is because shear rate increases cannot significantly reduce membrane fouling as well as reduce the apparent wall concentration which effectively reduces the concentration of the solute in the permeate. Pulsing, on the other hand, increases the sieving coefficient of the membrane by reducing membrane fouling. As a result, the highest solute fluxes were observed during operations with laminar cross-flow and significant pulsing.

The observed retention coefficient of albumin was reduced from as high as 0.99 to as low as 0.63 during pulsing. This represents a significant advance in addressing the problem of the loss of some protein throughput when another protein is introduced into the feed. No increase in selectivity, however, was observed since the gamma-globulin retention decreased proportionally. This is not surprising considering the pore-size distribution of the membranes studied and the relative size difference of the two proteins. It is apparent that transmembrane pressure pulsing allows the membrane to operate more toward its native characteristics.

Transmembrane pressure pulsing required a significant pulse amplitude of about 50 kPa to be effective in reducing solute flux resistance. However, only a nominal pulse amplitude of 9 kPa was necessary to see improvements in permeate flux due to pulsing. This provides evidence that pulsing may provide apparent forces that overcome a percentage of the adsorption force. Further research is under way to verify this.

Throughout the study, no damage to the membrane was observed during pulsing. However, these studies were operated only for one hour. Additional studies are necessary to determine the capacity of conventional membranes during pulsing for long-term use. However, it is feasible that specific membranes may be designed for pulsed operations.

Observation that pulsing worked more effectively to increase solute transport with laminar cross-flow implies that this method may be useful in the removal of certain solutes in solution while minimizing the loss of solvent. As an example, this may be quite useful in separations of single solutes in nutrient-rich medium.

This study provided a foundation for future studies to seek both the optimum transmembrane pressure pulsing conditions and better understanding of the mechanisms of membrane fouling.

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Notation

c = concentration
C_b = solute concentration in the bulk
c_o = initial concentration
C_p = solute concentration in the permeate
c_w = solute concentration at the membrane wall
C_w = solute concentration at the membrane wall
D_s = local diffusivity of solute
J = solvent flux
J_A = solute flux of species A
J_B = solute flux of species B
L = characteristic length in x direction
L_A = solute permeability of species A, $J_A/(C_b - C_j)$
L_B = solute permeability of species B, $J_B/(C_b - C_j)$
L_p = hydraulic permeability
M_w = molecular weight of solute
N_{po} = normalized permeability for nonpulsed case
N_{pp} = normalized permeability for pulsed case
r = true retention coefficient, $1\text{-}S_i$
R = observed retention coefficient, $1\text{-}S_o$
R_f = membrane fouling resistance

R_{fo} = membrane fouling resistance for nonpulsed case
R_m = membrane resistance
R_p = polarization resistance
r_{pore} = pore radius
r_{solute} = solute radius
S_i = intrinsic sieving coefficient, C_f/C_w
S_o = observed sieving coefficient, C_f/C_b
t = time
U = dimensionless velocity, u/u_{max}
u = velocity in x direction
u_{max} = maximum velocity in x direction
v = velocity in y direction
V = dimensionless velocity, v/v_w
v_f = velocity of solvent on filtrate side of membrane
v_w = velocity in y direction at the membrane wall, $L_p(\Delta P - \alpha\Delta\pi)$
x = direction parallel to membrane surface
y = direction normal to membrane surface

Greek letters

α = reflection coefficient
α = selectivity, L_A/L_B or L_B/L_A
β = proportionality constant for permeate flux model
δ = characteristic length in y direction
ΔP = transmembrane pressure
$\Delta\pi$ = osmotic pressure difference between solute at membrane surface and in the pore
Δr_{pore} = change in pore radius
η = dimensionless length, x/L
φ = fraction of R_{fo} remaining during the pulsed case
λ = ratio of solute radius to pore radius, r_{solute}/r_{pore}
λ' = ratio of solute radius to modified pore radius, $r_{solute}/r_{pore} - \Delta r_{pore}$
θ = characteristic time
τ = dimensionless time, t/θ
ξ = dimensionless length, y/δ
ψ = dimensionless concentration, $(c\text{-}c_o)/c_o$
ψ_w = dimensionless concentration at wall $(c_w\text{-}c_o)/c_o$

Subscripts

A = species A
b = bulk
B = species B
p = permeate
s = solute
w = wall

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Appendix

In determining the characteristic time for the development of the concentration polarization boundary layer, we begin with the transient convective-diffusion equation for a single solute. Assuming constant density and diffusivity and invoking the boundary layer approximations result in:

$$\frac{\partial c}{\partial t}+u\frac{\partial c}{\partial x}+v\frac{\partial c}{\partial y}=D_s\frac{\partial^2 c}{\partial_y{}^2} \tag{A1}$$

subject to the boundary conditions

$$c(0,x,y)=c_o$$

$$c(t,0,y)=c_o$$

$$c(t,x,\delta)=c_o$$

$$\text{at } y=0 \qquad -D_s\frac{\partial c}{\partial_p}+v_w(c_w)c=(1-R)v_f c \tag{A2}$$

where x is the longitudinal distance perpendicular to the membrane surface, y is the distance normal to the membrane surface, and $v_w(c_w)$ is a function of wall concentration expressed in terms of the boundary condition

$$v(c_w)\approx L_p(\Delta P-\alpha\Delta\pi). \tag{A3}$$

We now define the dimensionless variables to be:

$$\eta=\frac{x}{L}\ \xi=\frac{y}{\delta},\ \tau=\frac{t}{\theta},\ \psi=\frac{(c-c_o)}{c_o},\ V=\frac{v}{v_w}\text{ and }U=\frac{u}{u_{\max}}$$

where L, δ, and θ are the characteristic lengths and time.

Substituting these relationships into Eqs. A1 through A3 results in:

$$\frac{\partial\psi}{\theta\partial\tau}+\frac{Uu_{\max}}{L}\frac{\partial\psi}{\partial\eta}+\frac{Vv_w}{\delta}\frac{\partial\psi}{\partial\xi}=\frac{D_s}{\delta^2}\frac{\partial^2\psi}{\partial\xi^2} \tag{A4}$$

with boundary conditions

$$\psi(0,\eta,\xi)=0$$

$$\psi(\tau,0,\xi)=0$$

$$\psi(\tau,\eta,\delta)=0$$

$$\text{at } \xi=0 \qquad -\frac{D_s}{\delta}\frac{\partial\psi}{\partial\xi}+v(\psi_s)\psi=(1-R)V_f v_f\psi \tag{A5}$$

$$v_w(\psi_w)\approx L_p(\Delta P-\alpha\Delta\pi). \tag{A6}$$

Since selection of the characteristic time θ is somewhat arbitrary, it is advantageous to express it in terms associated with the development of the concentration polarization boundary layer. In this regard, it is appropriate to define it with respect to the direction normal to the membrane surface y and its characteristic distance δ.

The characteristic distance δ can be determined from the boundary condition at $\xi=0$. For a totally retained solute $R=1$ and the boundary condition can be expressed as:

$$\text{at } \xi=0 \qquad \frac{D_s}{\delta}\frac{\partial\psi}{\partial\xi}=v(\psi_w)\psi. \tag{A7}$$

Applying Eq. A6 and recognizing that the coefficient on the righthand side of the equation is unity allows us to define:

$$\delta\equiv\frac{D_s}{L_p(\Delta P-\alpha\Delta\pi)} \tag{A8}$$

Multiplying Eq. A4 by δ/v_w and substituting Eq. A8 results in:

$$\frac{D_s}{L_p{}^2(\Delta P-\alpha\Delta\pi)^2}\frac{\partial\psi}{\theta\partial T}+\frac{Uu_{\max}D_s}{L_p{}^2(\Delta P-\alpha\Delta\pi)^2L}\frac{\partial\psi}{\partial\eta}+V\frac{\partial\psi}{\partial\xi}=\frac{\partial^2\psi}{\partial\xi^2} \tag{A9}$$

Thus, the characteristic time for unsteady-state development of the concentration polarization boundary layer may be defined as:

$$\theta\equiv\frac{D_s}{L_p{}^2(\Delta P-\alpha\Delta\pi)^2} \tag{A10}$$

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