High flux ultrafiltration
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Introduction

Ultrafiltration is often used as a pre-concentration step in purification of protein solutions. A problem is the build up of high concentrations of rejected protein at the membrane interface, a phenomenon known as concentration polarisation. This limits the fluxes that can be obtained during filtration; these can even reach a plateau, where they are independent of the applied pressure. The high concentration of rejected proteins at the membrane interface results either in a high osmotic pressure difference across the membrane interface, which reduces the effective pressure drop across the membrane considerably, or in the formation of a deposit or gel layer. The latter effect occurs if the concentration of protein at the membrane rises above its solubility limit.

Both effects can be modelled by relating the wall concentration of protein to the observed flux (Blatt 1970). When a gel layer forms, the wall concentration is equal to the solubility limit. When the flux is limited by the osmotic pressure difference, the concentration at the membrane surface is also virtually constant as small changes have a large effect on the osmotic pressure. Both descriptions predict the flux on the plateau to be proportional to the logarithm of the protein concentration in the feed. Therefore it is hard to distinguish between these mechanisms. For the frequently studied filtration of Bovine Serum Albumin (BSA), the osmotic pressure model is the more realistic one. BSA is highly soluble and gel formation is not likely to occur even at the high concentrations at the membrane interface. For charged molecules such as proteins away from their iso-electric point, transport of rejected material back from the membrane surface to the bulk solution not only depends on the concentration gradient in
the boundary layer, but is also driven by electrical repulsion between charged molecules. Bowen and co-workers (Bowen 1996a, Bowen 1995) have incorporated these electrical effects in their description of membrane filtration of BSA solutions. This approach is based upon the DLVO theory. Bellara and Cui (Bellara 1998) use the Maxwell-Stefan equations to model fluxes in ultrafiltration of BSA solutions. They assume the solution to be ideal, except for the calculation of the osmotic pressure jump at the entrance of the membrane.

So far, little attention had been paid to the transport behaviour of the smaller ions accompanying the protein. These ions influence the transport of proteins from the membrane interface back to the bulk solution. Their retention also has practical significance, as desalination is often desirable. Wesselingh and Vonk (Wesselingh 1995) have developed a simplified Maxwell-Stefan based model which takes electrical interactions between proteins and salt into account. One result is the prediction of negative rejections for co-ions, yielding an enhanced desalination of the solution. These negative rejections are similar to those observed in the nanofiltration of mixed salt solutions (Bardot et al. 1995, Bowen et al. 1996b). In this article we present experimental data on the concentration of protein solutions at different ionic strengths and pH values. Both fluxes and salt rejections are measured and the results compared with a Maxwell Stefan description.

Theory

The model used here is an extension of that of Wesselingh and Vonk (Wesselingh 1995). It takes mass transfer to be limited by a laminar boundary layer with a given thickness. We have used a multistep approach to calculate profiles of concentration and electrical potential instead of the one-step method of Wesselingh and Vonk. We take non-idealities into account and have the diffusivities depend on the volume fraction of protein. The resulting model is essentially the same as the one we have used to describe transport of salts through membranes (Noordman 1997, Vonk 1997). The difference is that one
component, the protein, is completely rejected. Transport of any component $j$ through the boundary layer is described by:

$$- \frac{x_j}{RT} \nabla T, p \mu_j - \frac{x_j z_j F}{RT} \nabla \Psi = \sum_k \frac{x_k N_j - x_j N_k}{C_{tot} D_{t,k}}$$  \hspace{1cm} (1)$$

The membrane passes salt ions freely. So transport through the membrane is governed by viscous flow:

$$N_j = -x_j C_{tot} \frac{K_h}{\eta} \Delta P$$  \hspace{1cm} (2)$$

Additional relations for the component fluxes are provided by the mass balances. As the protein is totally rejected, its flux is equal to zero. The concentrations in the permeate are governed by the fluxes of the salt ions and water:

$$N_i = N_w \frac{x_{i,p}}{x_{w,p}}$$  \hspace{1cm} (3)$$

**Boundary Layer Thickness**

The boundary layer thickness for a single dilute transferring component can be obtained from an empirical relation of the following kind:

$$Sh = A Re^b Sc^c$$  \hspace{1cm} (4)$$

These relations have been determined for several flow systems. Mass transfer in tubes is usually described by the equation of Dittus and Boelter, with the constant $A$ equal to 0.023, $b$ to 0.8 and $c$ to 0.33. In this work a stirred ultrafiltration cell is used. For stirred cells the constants are determined by the geometry of the cell. We have carried out experiments at a constant Reynolds number, so the exact value of exponent $b$ is not important and has been fixed at
0.8. The value of $c$ is given in most relations as 0.33 so we have also used this value. It remains to determine the constant $A$ from experiment. This is the only free parameter in our model.

For a multicomponent system, equation (4) results in different values for the boundary layer thickness for different components (due to different diffusivities). In our model a stagnant film layer is assumed with the same thickness for all components. This thickness is calculated using the diffusivity of the protein in equation (4). To take the effect of the Schmidt number on the mass transfer coefficients of the salt ions into account, we use corrected diffusivities:

$$D_{i,w}^{\text{corr}} = D_{i,w} \left( \frac{D_{pr,w}}{D_{i,w}} \right)^{0.33}$$

(5)

The mass transfer coefficients of the ions that are now the same as would be obtained in absence of protein under the same hydrodynamic conditions.

**Partitioning of Solvent and Solutes**

At the solvent-membrane interface we assume thermodynamic equilibrium. Solvent partitioning is described by the osmotic equilibrium equation:

$$RT \ln \gamma_i^l x_i = RT \ln \gamma_i^m y_i + V_w \Pi$$

(6)

Partitioning of the (ionic) solutes is described by the Donnan relation:

$$RT \ln \gamma_i x_i = RT \ln \gamma_i^m y_i + z_i F \Delta \Psi$$

(7)

Here we have neglected the pressure terms (which are small compared to the electrical terms).
Constraint Relations

There are several constraints on the values of the mole fractions in the membrane and the boundary layer. One condition is that electroneutrality must hold everywhere in the system:

\[ \sum z_j x_j = 0 \text{ and } \sum z_j y_j = 0 \]  

(8)

The other constraint is that all mole fractions should add up to one everywhere:

\[ \sum x_j = 1 \text{ and } \sum y_j = 1 \]  

(9)

The Charge of BSA

The charge of BSA is determined by the release of protons by the amino acids and specific adsorption of small ions. Tanford et al. (Tanford 1955a) have studied proton binding at different pH values and ionic strengths. Between pH values of 5 and 8 the amount of dissociated proton is almost independent of ionic strength. Scatchard et al. (Scatchard 1950) have studied the binding of chloride ions to albumin and described this by a two site binding model:

\[ \nu_{Cl^-} = \frac{n_1 k_1 [Cl^-] \gamma \exp(2w z_{pr})}{1 + k_1 [Cl^-] \gamma \exp(2w z_{pr})} + \frac{n_2 k_2 [Cl^-] \gamma \exp(2w z_{pr})}{1 + k_2 [Cl^-] \gamma \exp(2w z_{pr})} \]  

(10)

\( \nu_{Cl^-} \) is the number of Cl\(^-\) ions adsorbed on the albumin molecule and \( \gamma \) the activity coefficient according to the Debye-Hückel theory. The binding constants \( n_1, k_1, n_2 \) and \( k_2 \) are 10, 44 M\(^{-1}\), 30 and 1.1 M\(^{-1}\) respectively. The parameter \( w \) is given by:

\[ w = \frac{e}{8\pi\varepsilon k_b T} \left( \frac{1}{r_{pr}} - \frac{\kappa}{1 + \kappa(r_{pr} + l_{OHP})} \right) \]  

(11)
in which $l_{OHP}$ is the thickness of the outer Helmholtz layer (estimated to be 0.25 nm).

The total charge is the summation of the charges due to proton release and chloride binding:

$$ z_{pr} = z_{H^+} - v_{Cl^-} $$  \hspace{1cm} (12)

The charges we have calculated by combining equations (10) and (12) are given in Table 2.

**Thermodynamics**

The activities of salts in the presence of BSA have been extensively studied by Reboiras and co-workers (Reboiras 1978, Reboiras 1986, Ocon 1987). They have determined activities of alkali chlorides and potassium salts in solutions of iso-ionic Bovine Serum Albumin solutions by electromotive force measurements. They have modelled the mean activity coefficients of the salts using three contributions, one caused by binding of water to BSA, one caused by binding of anions to BSA, giving the latter a net negative charge and one caused by electrostatic effects.

BSA molecules in aqueous solutions bind a considerable amount of water. Reboiras et al. take this amount equal to 19.86 kg water per mole protein, irrespective of the BSA molality or ionic strength (Reboiras 1978). This water is not available for the salt ions, so these encounter a higher ionic concentration. The second contribution to the ionic activity coefficient is a correction for the anions bonded to BSA; this decreases the concentration of free anions. To describe the adsorption of anions to BSA, the adsorption model of Scatchard, equation (10), is used. The remaining contribution to the activity coefficients of the salt can be described completely by the Debye-Hückel equation for activities in salt solutions (BSA is not counted in the ionic strength used in this equation). The change in activity of the salt ions can be explained
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completely by binding on BSA of both ‘non-solvent’ water and anions, according to the model of Scatchard. From these results we conclude that interactions between BSA and salt, other than accounted for by equation (10) are negligible.

The activities of water can be calculated from data on the osmotic pressure. Vilker et al. (Vilker 1981) have measured osmotic pressures of BSA at high protein concentrations, at different pH values. Bowen et al. (Bowen 1996c) have presented a model based upon DLVO theory to describe these data. The osmotic pressure is made up of three contributions, an entropic pressure term accounting for the finite size of BSA molecules, an electrostatic repulsion and a Van der Waals attraction. The latter is only important at high concentrations, is complex and sensitive to the value of Hamaker constant used. Therefore we have decided to use a more simple description of the osmotic pressure of albumin solutions. We have combined the contribution of ions distributed by an ideal Donnan equilibrium and the contribution of entropic pressure. The latter part contains non-idealities, which are described by the equation of Carnahan and Starling (Carnahan 1969):

\[ \Pi_{RS} = \frac{RT \Phi \left(1 + \Phi + \Phi^2 - \Phi^3\right)}{V_{pr} \left(1 - \Phi\right)^3} \]  (13)

From this equation ‘rigid sphere’ activity coefficients for both water and BSA molecules can be derived. The ratio of mole fractions of water and BSA is related to the volume fraction of BSA by:

\[ \frac{x_w}{x_{pr}} = \frac{1 - \Phi}{\Phi} \frac{V_{pr}}{V_w} \]  (14)

As the mole fraction of water approaches unity this relation yields for the mole fraction of protein:

\[ x_{pr} = \frac{\Phi}{1 - \Phi} \frac{V_w}{V_{pr}} \]  (15)
The activity of water can now be derived from the osmotic pressure equation:

$$\ln \gamma_{RS,w} = -\frac{V_w}{RT} \Pi_{RS} + x_{pr}$$

which yields after combination with equations (13) and (15) and rearranging:

$$\ln \gamma_{RS,w} = \frac{V_w}{V_{pr}} \frac{\Phi^4 - 3\Phi^2}{(1 - \Phi)^3}$$

From the activity of water, the activity of BSA is calculated using the Gibbs-Duhem relation. This results in the following relation for the activity of BSA:

$$\ln \gamma_{RS,pr} = \ln(1 - \Phi) - \Phi \frac{\Phi^2 + 3\Phi - 7}{(\Phi - 1)^2}$$

The osmotic pressure of protein solutions can now be described by the following equation:

$$\Pi = -\frac{RT}{V_w} \left( \ln \gamma_{RS,w} + x_{pr} + x_{Na^+} + x_{Cl^-} \right)$$

This relation is tested against the data of Vilker et al. (Vilker 1981) in figure 1. The volume fraction is recalculated from the concentration $C_{pr}$ (in kg m$^{-3}$) by:

$$\Phi = \frac{C_{pr}}{M_{WBSA}} V_{pr}$$

The molar volume of the protein, $V_{pr}$, is set equal to 0.0687 m$^3$ mol$^{-1}$ (see below). The data at pH = 7.4 and 5.4 are described quite well by our approach. The osmotic pressures at pH 4.5 are overpredicted. Bowen et al. have obtained similar results using the DLVO theory (Bowen 1996c).
Fig. 1. Description of the osmotic pressure in BSA solutions based on the Carnahan-Starling equation combined with ideal Donnan distribution of salt ions, compared with experimental data as given by Vilker et al. (Vilker 1981).

**Diffusivities**

Due to the size of BSA molecules and the high concentrations of BSA in the boundary layer (especially near the membrane surface) the mobility of a BSA molecule is strongly reduced. Therefore the diffusivity of BSA will depend strongly on the local volume fraction. This dependency can be expressed by a hindrance factor $K(\Phi)$. The Maxwell-Stefan diffusivity is then given by:

$$D_{pr,w}^{MS} = D_{pr,w}^{0}K(\Phi)$$  \hspace{1cm} (21)

Usually diffusion data are given in terms of the Fickian diffusivity. This includes a thermodynamic correction factor to account for non-ideality (in the Maxwell-Stefan equations, the latter is incorporated in the driving force, while in the equation of Fick it is not). The Fickian and Maxwell-Stefan diffusivities are interrelated by the thermodynamic correction factor:
\[ D_{pr,w}^{Fick} = D_{pr,w}^{MS} \left( 1 + x_{pr} \frac{\partial \ln \gamma_{pr}}{\partial x_{pr}} \right) \tag{22} \]

The thermodynamic factor can be rewritten in volume fractions as:
\[ 1 + x_{pr} \frac{\partial \ln \gamma_{pr}}{\partial x_{pr}} = 1 + \Phi (1 - \Phi) \frac{\partial \ln \gamma_{pr}}{\partial \Phi} \tag{23} \]

The Maxwell-Stefan diffusivities can now be calculated from data on Fickian diffusivities by:
\[ D_{pr,w}^{MS} = \frac{D_{pr,w}^{Fick}}{1 + \Phi (1 - \Phi) \frac{\partial \ln \gamma_{pr}}{\partial \Phi}} \tag{24} \]

The Fickian diffusivity of BSA has been determined by both Gaigalas et al. (Gaigalas 1995) and Fair et al. (Fair 1978) near the iso-electrical point. This means that the diffusion measurement was not influenced by electrical potential gradients. Their results are plotted in fig. 2. They show a fair agreement and can be approximated by the following relation:
\[ D_{pr,w}^{Fick} = D_{pr,w}^0 (0.21 + 0.79 \exp(-4.7\Phi)) \tag{25} \]

The thermodynamic factor can be derived from the Carnahan-Starling equation. It is equal to:
\[ \frac{\partial \ln \gamma_{pr}}{\partial \Phi} = \frac{(6 + 3\Phi - 4\Phi^2 + \Phi^3)}{(\Phi - 1)^3} \tag{26} \]

So the Maxwell-Stefan diffusivity depends on the volume fraction of BSA as:
\[ D_{pr,w}^{MS} = \frac{D_{pr,w}^0 (0.21 + 0.79 \cdot \exp(-4.7\Phi))}{\Phi(6 + 3\Phi - 4\Phi^2 + \Phi^3)/(\Phi - 1)^2} \tag{27} \]
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Fig. 2. Fickian diffusivity of BSA, normalised to the diffusivity at infinite dilution, as a function of the volume fraction. Data by Fair et al. (Fair 1978) and Gaigalas et al (Gaigalas 1995). The drawn line presents the approximation for the diffusivity that is used in the present work.

The diffusivity of BSA at infinite dilution at 22 °C is equal to 5.7×10⁻¹¹ m² s⁻¹ (Fair 1978), which yields at 25 °C, after correction for change of water viscosity with temperature, 6.1×10⁻¹¹ m² s⁻¹.

The diffusivities of the ions are also hindered by large volume fractions of the protein. Therefore these diffusivities are corrected by:

\[ D_{i,w} = D_{i,w}^0 (1 - \Phi) \]  \hspace{1cm} (28)

Size of BSA

The dry volume of BSA is reported to be 0.734 cm³ g⁻¹ (Tanford 1961). With a molecular weight of 66.5 kg mol⁻¹ this is equal to 0.0488 m³ mol⁻¹. In addition, the amount of water bound to the protein has to be taken into account. This value is given by Reboiras et al (Reboiras 1986) to be to 19.9 kg water per mole of BSA. This results in a molar volume of 0.0687 m³ mol⁻¹.
Tanford et al. (Tanford 1955b) and Yang and Foster (Yang 1954) have found that under acidic conditions (pH < 4) a BSA molecule expands with decreasing pH. For the modelling of filtration at acidic conditions we have to take this into account. We have carried out one experiment under these conditions (at pH 3). At this pH, the molar volume can be obtained from the following relation:

\[
V_{pr} = \frac{1}{1.19 + 11.92\sqrt{I}}
\]  

(29)

Because the molecule is swollen at pH 3 the mobility of the molecule is also decreased. To account for this the diffusivity at infinite dilution is corrected by a factor:

\[
D_{pr, pH=3} = D_{pr, pH>3} \left( \frac{V_{pr, pH>3}}{V_{pr, pH=3}} \right)^{0.33}
\]

Other model parameters

The diffusivities of several ions at infinite dilution are given by Chapman (Chapman 1967). The coefficients for Na\(^+\) and Cl\(^-\) are equal to \(9 \times 10^{-3}\) and \(9 \times 10^{-3}\) m\(^2\) s\(^{-1}\) respectively. At low pH, the H\(^+\) ion becomes important and should be incorporated in the model. Its diffusion coefficient is \(9 \times 10^{-3}\) m\(^2\) s\(^{-1}\). The viscosity of the bulk solution is a function of the BSA concentration. A relation for this is given by Kozinski and Lightfoot (Kozinski 1972):

\[
\eta = \frac{10^{-3}}{1.11 - 0.00542C + 6.71 \times 10^{-6}C^2}
\]  

(30)

The hydraulic permeability, \(K_h\), is determined from pure water flux measurements. The only unknown parameter left in our model, the constant \(A\) in relation (4), is determined by comparing our model to experimental data, using the Marquardt-Levenberg procedure for parameter optimisation (Press
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1987). The fluxes are found to be more sensitive to variation in this parameter than the rejections, therefore and optimisation is performed by comparing calculated fluxes to experimental fluxes.

Solving the model equations

For the ultrafiltration of a solution with 4 components (H₂O, Na⁺, Cl⁻, BSA) the model consists of 3 viscous flow equations (2), 3 transport relations for the boundary layer (1), 2 mass balances (3) and the additional condition that the protein flux equals zero, 3 equilibrium equations at both the upstream and the downstream side of the membrane (6,7), and two constraint relations at each point in the system (8,9). At pH = 3 we have taken H⁺ as an extra component into account and extra transport equations for this ion (1,2) are needed. In addition an extra Donnan equation is required (7).

The boundary layer is divided into 10 layers (with 11 grid points). The gradients in the Maxwell-Stefan equations are approached by a central difference scheme according to Wesselingh and Krishna (Wesselingh 1990). The complete set of equations is solved for the molar fluxes, local mole fractions, pressures and electrical potentials, using the Newton-Raphson method (Press 1987).

Experimental

Materials

Albumin solutions are prepared by dissolving BSA Fraction V (Boehringer Mannheim) in a solution of NaCl (Merck). The pH is adjusted to 6.7 or 8.0 with NaOH (Merck), or to pH 4.8 or 3.0 with HCl (Merck).
Table 1. Dimensions of the ultrafiltration cell

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<table>
<thead>
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<td></td>
<td>volume</td>
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<td></td>
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<tr>
<td></td>
<td>height</td>
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</table>

Fig 3. Ultrafiltration set up

Equipment and measurements

Experiments are carried out in a fed-batch configuration as shown in figure 3. The ultrafiltration cell used was developed in our laboratory. Circular flat
membranes are placed on the bottom of the cell, which contains a porous plate to support the membrane. The cell contains a two blade stirrer in the top part of the cell which is driven by a magnetic coupling. Three baffles, separated by angles of 120° from each other, are inserted to improve mixing. To keep the temperature of the cell solution constant during filtration, a cooling jacket is placed around the cell wall. The cell can be connected to a pressurised storage vessel. Dimensions of the cell are given in Table 1.

The cell is pressurised by adding nitrogen gas to the storage vessel. The nitrogen flow is controlled by a pressure controller; that at the permeate side is atmospheric. Mixing of the feed solutions is accomplished by stirring the solution. Flat polyethersulfone membranes of type FILTRON OMEGA 30 kD are used. Before use the membranes are rinsed with deionized water (conductivity less than 1 µS cm⁻¹) for several hours. Then, prior to an experiment the membrane is exposed overnight to a 1% BSA solution of the same ionic strength and pH as applied in the experiment following. This will allow the membrane to be saturated with adsorbed BSA, thus preventing further adsorption. After this the membrane is shortly rinsed with pure water and the hydraulic permeability is determined. These values are summarised in Table 2.

<table>
<thead>
<tr>
<th>Cell $C_{pr}$ (kg/m³)</th>
<th>Supply Vessel $C_{pr}$ (kg/m³)</th>
<th>Cell $I$ (mM)</th>
<th>Supply Vessel $I$ (mM)</th>
<th>pH</th>
<th>$K_h$ (10⁻¹⁴ m)</th>
<th>$z_{pr}$ #</th>
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<td>5.06</td>
<td>6.7</td>
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<td>30.3</td>
<td>50.4</td>
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<td>-12.7</td>
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<td>3.0</td>
<td>12.9</td>
<td>+47.0</td>
</tr>
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</table>

# values as calculated at the start of the experiment
A solution of 10 g/L BSA is put in the ultrafiltration cell. From the storage vessel a solution of 50 g/L is supplied, balancing the loss of volume in the cell due to filtration. In this way concentrating of the protein solution in the cell is accelerated. Details on protein concentration, ionic strengths, pH values, hydraulic permeabilities of the membranes and charges according to the Tanford/Scatchard calculations are presented in Table 2. Experiments are carried out at 25 °C and at a stirring speed of 500 rpm.

Permeate fluxes are measured gravimetrically. Concentrations of BSA in both concentrate and permeate are determined by measuring UV absorption at 280 nm. Concentrations of sodium chloride are determined by automatic titration with an Ag-electrode using a Chlorocounter Type 80 apparatus manufactured by Marius Instrumenten, Utrecht, The Netherlands. The rejection of BSA turned out to be always larger than 98% in all experiments, so 100% rejection is assumed.

**Results**

The effect of ionic strength of the solution is shown in fig. 4. It is seen that the fluxes show the behaviour expected from electrostatic considerations. Fluxes increase with decreasing ionic strengths because screening of the charges of the protein is reduced at lower ionic strengths. Therefore protein molecules strongly repel each other, especially at the membrane surface where the concentration of protein is high. This electrostatic repulsion increases mass transfer of protein from the membrane surface back to the bulk. The concentration and thereby the osmotic pressure at the membrane surface are reduced and higher fluxes are observed.

The effects of solution pH on fluxes is shown for values above the iso-electric point in figure 5. The effect of a change in pH is similar to that of a change in ionic strength. The higher the pH the more negative the charge of the protein and the stronger electrostatic repulsion between protein molecules at the membrane surface. Again this enhances mass transfer of proteins back to the
bulk and causes a lower concentration at the membrane surface and thus a higher flux.

**Fig. 4.** Permeate flux as function of protein content of the feed during concentration of a BSA solution at pH 6.7 and various ionic strengths, $I$.

**Fig 5.** Permeate flux as function of protein content of the feed during concentration of BSA solutions with pH values at or higher than the iso-electric point.
Figure 6 shows the effect of a pH below the iso-electric point. Now the protein is positively charged. Again the fluxes are higher compared to the values obtained close to the iso-electric point (pH 4.8).

![Figure 6. Permeate flux as function of protein content of the feed during concentration of a BSA solution with acidic pH and a pH near the iso-electric point.](image)

The trends observed in the experimental results are well described by the Maxwell-Stefan based model. The model predicts higher fluxes at lower ionic strengths. It also predicts higher fluxes when the pH is far from the iso-electric point. At very high pH values, the model starts to overpredict the experimental results, however, as is shown at pH 8. This is probably due to thermodynamics starting to deviate from our description. The constant $A$ in equation (4) was determined by the optimisation procedure to be 0.0533. The resulting mass transfer coefficients for BSA, Na$^+$ and Cl$^-$ are 3.15, 25.4 and 33.0 $\mu$m/s respectively.

The rejections of the salt observed during protein concentration are shown in figures 7 and 8. Plotted is the rejection of the chloride ion. It can be seen that this rejection is negative at pH values above the iso-electric point. At these pH values the charge on the protein has the same sign as the chloride ions. Due to concentration polarisation of the protein there will be an accumulation of negative charges at the membrane which results in repulsion of chloride ions, attraction of the positive sodium ions and a net negative electrical potential near
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**Fig 7.** Rejection of the chloride ion as function of protein content of the feed during concentration of BSA solutions with different pH values. (□), pH = 3.0; (▲), pH = 4.8; (○), pH = 6.7; (■), pH = 8.0.

**Fig 8.** Rejection of the chloride ion as function of protein content of the feed during concentration of a BSA solution at pH 6.7 and different ionic strengths. (■), 5 mM; (□), 10 mM; (○), 15 mM; (×), 50 mM; (▲), 150 mM.
the membrane surface. The concentration of sodium and chloride ions in the membrane are equal due to the electroneutrality condition. The Donnan equilibrium at the entrance of the membrane forces the sodium concentration to be reduced and the chloride concentration to be raised such that the concentration of the latter becomes higher than in the feed solutions and negative rejections are obtained. This is shown in Figure 9. Concentration and potential profiles are plotted as calculated with our model using feed concentrations of BSA and salt of 50 g/L and 5 mM respectively and a pH of 6.7.

![Fig 9. Concentration and electrical potential profiles in the boundary layer and membrane as calculated for a 50 g/L BSA solution, pH 6.7 and an ionic strength of 5 mM. Concentrations of Na⁺ and Cl⁻ are normalised to the feed concentration of Cl⁻, the concentration of BSA is normalised to the bulk concentration of BSA. The potential Ψ is normalised by multiplication with F/RT.](image)

The rejection is influenced by the ionic strength of the solution. Above the iso-electric point the rejection is strongly negative at low ionic strength (down to -0.7 at 5 mM and a pH of 6.7); it becomes less negative at higher salt
concentrations. Higher salt concentrations reduce the repulsion of the protein, so that chloride concentrations at the membrane interface are higher (though still lower than in the feed solution). We see that the rejection is close to zero at the iso-electric point.

At low pH the rejection plot turns upside down. Now chloride is the counterion that is attracted by the protein and sodium the co-ion that is repelled. In this situation the chloride rejection becomes positive (and the rejection of sodium ions negative).

The trends in the rejections are all predicted by the model. The description is quite good for the experiments at different pH values and ionic strengths. Both negative rejections (at higher pH) and positive rejection of chloride (at pH 3) are predicted quantitatively. It is also predicted that the rejection of chloride becomes more negative with decreasing ionic strength.

**Conclusions**

It has been shown that both ionic strength and pH play an important role in the ultrafiltration of protein solutions. The fluxes are higher at lower salt concentrations and go through a minimum at the iso-electrical point. At pH values above the iso-electrical point the rejection of the chloride ion is negative due to electrostatic repulsion by the negatively charged protein molecules. This rejection becomes more negative at increasing pH and decreasing ionic strength. Because the protein is positively charged at acidic conditions, the rejection of the anion now becomes positive. The trends in both rejection and flux are well described by the Maxwell-Stefan theory.

**Symbols**

\[ C \quad : \text{concentration mol m}^{-3} \]
\[ D \quad : \text{diffusion coefficient, m}^2 \text{ s}^{-1} \]
\[ d \quad : \text{diameter, m} \]
\[ e \quad : \text{unit charge, C} \]
Chapter 4

\[ F \]: Faraday constant, C mol\(^{-1}\)

\[ I \]: ionic strength, mol m\(^{-3}\)

\[ K_h \]: hydraulic permeability, m

\[ k \]: mass transfer coefficient, m s\(^{-1}\)

\[ k_B \]: Boltzmann constant, J K\(^{-1}\)

\[ l \]: thickness, m

\[ M_w \]: molar mass, kg mol\(^{-1}\)

\[ N \]: molar flux, mol m\(^{-2}\) s\(^{-1}\)

\[ n \]: rotation speed, s\(^{-1}\)

\[ P \]: pressure, Pa

\[ R \]: gas constant J mol\(^{-1}\) K\(^{-1}\)

\[ r \]: radius, m

\[ T \]: temperature, K

\[ V \]: partial molar volume, m\(^3\) mol\(^{-1}\)

\[ x \]: mole fraction in boundary layer

\[ y \]: mole fraction in membrane

\[ z \]: charge number of ion

\[ \gamma \]: activity coefficient

\[ \varepsilon \]: di-electric permittivity, F m\(^{-1}\)

\[ \eta \]: viscosity, Pa s

\[ \kappa \]: Debye-Hückel parameter (inverse Debye-Hückel radius), m\(^{-1}\)

\[ \mu \]: chemical potential, J mol\(^{-1}\)

\[ \Phi \]: volume fraction of protein

\[ \Pi \]: osmotic pressure jump at entrance or exit of membrane, Pa

\[ \Psi \]: electrical potential, V

\[ Re \]: Reynolds number, for stirred cell: \( Re = \rho n d_{st}^z / \eta \)

\[ Sc \]: Schmidt number, \( \eta/\rho D \)

\[ Sh \]: Sherwood number, \( kd_h / D \)

**Subscripts**

\[ h \]: hydraulic

\[ i \]: ion

\[ j,k \]: component index
Concentration and desalination of protein solutions

OHP : outer Helmholtz plane

\( p \) : permeate

\( pr \) : protein

\( tot \) : total

\( s \) : sphere

\( st \) : stirrer

\( w \) : water

\textit{Superscripts}

\( corr \) : corrected

\( Fick \) : Fickian

\( MS \) : Maxwell-Stefan

\( 0 \) : At zero concentration

\textbf{References}


Concentration and desalination of protein solutions


