ANALYSIS OF MEMBRANE PROCESSES

In the Introduction-to-ChE Course

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The introductory course in most chemical engineering departments is designed to meet a broad range of educational goals. They typically include: 1) providing information that will enable students to determine if chemical engineering is the "correct" major for them; 2) providing a foundation for subsequent courses in the curriculum; and 3) teaching significant chemical engineering principles, particularly in the area of mass balances.[1] Traditional introductory courses, *e.g.*, those based on the classical book by Felder and Rousseau,[2] focus primarily on the use of steady-state mass (and energy) balances to describe the behavior of a wide range of chemical processes. These courses often include a small section on transient processes at the end of the semester, such as Chapter 11 in the Felder and Rousseau[2] text or Chapter 7 of Himmelblau.[3] Russell and Denn[4] take a very different approach, emphasizing transient balance equations right from the beginning. This approach has the advantage of allowing the instructor to focus on the key concepts of "rate" and characteristic times, an aspect that is often lost in courses that emphasize steady-state processes.

One of the challenges of introducing students to transient mass balances is a lack of interesting and effective problems that analyze the behavior of non-reacting systems (batch reactor problems provide a very effective introduction to time-dependent reacting systems). Russell and Denn[4] devote more than an entire chapter to the analysis of draining and filling tanks—a problem that illustrates the important concepts but one that generates very little excitement and enthusiasm among the students. Himmelblau[3] also uses the tank draining problem as a primary example, along with problems on diluting a salt solution with water. Felder and Rousseau[2] try to make the tank draining problem a little more interesting by examining the water level in a reservoir during a period of drought and the water volume in a storage tank that has a leak. But students often see these problems as artificial, in part because of the seemingly arbitrary functions given for the rate of inflow and outflow, and they provide little opportunity for the students to think about process design considerations.

The University of Delaware uses the text by Russell and Denn[4] as the basis for its introductory chemical engineering course, which is taught in the spring semester of the freshman year. The course is divided into three main sections:

- *Transient mass balances in nonreacting systems*
- *Transient mass balances in reacting systems, including the analysis of batch reactors and CSTRs*
- *Interfacial mass transfer*

The traditional material in this course has been supplemented with a series of membrane problems specifically designed to illustrate the key concepts involved in the analysis of transient mass balances. These membrane problems are "real," they are easy for students to relate to, they tend to be much more interesting than the traditional tank draining and filling problem, they provide a much better introduction to the range of problems and application areas of interest to chemical engineers, and they give students an opportunity to think about real design issues, even when they are freshmen.

APPLE JUICE CONCENTRATION USING REVERSE OSMOSIS

Apple juice can be concentrated by a reverse osmosis sytem

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using the fed-batch process shown in Figure 1. Fresh juice is fed to a recycle tank, with the juice from the recycle tank then passing through the reverse osmosis unit where water is removed through the membrane. The concentrated juice is returned to the recycle tank—the system is designed to operate so that the volume in the recycle tank remains constant throughout the process. At the end of the process, a concentrated juice product is obtained in the recycle tank. It can be frozen and sold as "apple juice concentrate" or the concentrated juice can be shipped and then reconstituted at a remote site by simply adding water. This latter process can lead to significant cost-savings since a much smaller volume of juice needs to be shipped across the country. One of the concerns with this process is that the membrane is never "perfect," meaning that there will be a small loss of flavor components through the membrane during the concentration process. This is why many juice companies will specifically advertise on the label that their juice is "not from concentrate." Cheryan and Alvarez[5] provide a more detailed discussion of membrane processes for juice concentration.

The goal of the problem is to evaluate the fraction of flavor components that are lost during a process designed to take 10,000 L of fresh juice and produce 500 L of apple juice concentrate. To simplify the analysis, we assume that the concentration of flavor components in the filtrate stream collected through the membrane is equal to a certain fraction (S) of the flavor concentration in the stream that enters the membrane unit. This latter assumption is simply the definition of the membrane sieving coefficient. This type of constitutive relation must be determined experimentally, playing a role analogous to the rate expression in batch reactor problems.[4]

The problem is solved by writing both total and component mass balances around the recycle tank and the reverse osmosis unit (shown by the dashed line in Figure 1):

$$\frac{d(\rho V)}{dt} = \rho_{feed} Q_{feed} - \rho_{filtrate} Q_{filtrate} \quad (1)$$

$$\frac{d(VC)}{dt} = Q_{feed} C_{feed} - S Q_{filtrate} C \quad (2)$$

where C is the concentration of the flavor components in the feed tank. If we make the assumption of a constant (uniform) density, then the total mass balance simply reduces to $Q_{filtrate}=Q_{feed}$ since V is constant. This conclusion is also valid for a juice in which the density is a linear function of the flavor concentration.[4] The component mass balance is then readily integrated to give

$$\ell n\left[\frac{C_{feed} - SC}{(1-S)C_{feed}}\right] = -\left(\frac{SQ_{feed}t}{V}\right) \quad (3)$$

where the concentration of flavor components in the recycle tank at the start of the process is equal to C_{feed}. This equation can be easily solved for the final concentration of flavor components, with t evaluated as the time required to process 10,000 L of juice (or in this case, to add 9,500 L of juice to the 500 L initially present in the recycle tank). The overall flavor recovery is then evaluated as the ratio of the final mass of flavor components in the juice (VC_{final}) to the initial mass of flavor components

$$\text{Recovery} = \frac{VC_{final}}{V_{total}C_{feed}} = \frac{V - V(1-S)\exp\left[-S\left(\frac{V_{total}-V}{V}\right)\right]}{SV_{total}} \quad (4)$$

where V_{total} is the total amount of juice (in this case, 10,000 L).

In addition to solving the mass balance equations, there are a number of interesting design issues that the students can begin to think about, such as what would happen to the final concentration of flavor components in the recycle tank if it were poorly mixed. For example, if the recycle stream is returned to the top of the recycle tank, then the concentration of flavor components will be lower in the bottom of the tank (near the tank exit), which will reduce the amount of flavor that is lost through the membrane. Although this situation cannot be modeled quantitatively this early in the curriculum, the qualitative behavior of the system is quite easy to explain. The discussion of mixing provides a great opportunity for the instructor to talk about the residence time in the recycle tank and the different design approaches that can be used to achieve good mixing in a large tank.

The students can also be asked to consider what (if any) difference would occur if the juice concentration were accomplished using a batch process instead of the fed-batch system shown in Figure 1. In this case, all of the juice is placed in a single large tank, the feed stream entering the

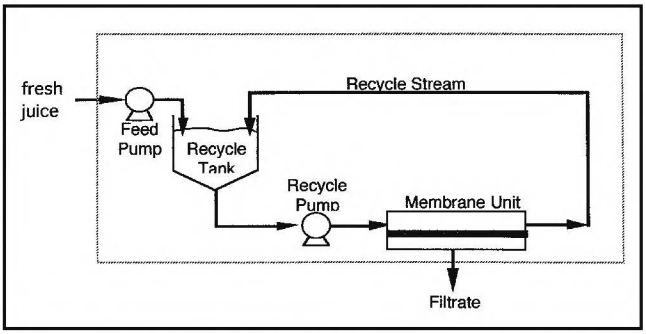

Figure 1. *Fed-batch system for producing apple juice concentrate.*

tank is eliminated, and the volume in the tank decreases with time as fluid is removed through the membrane. This problem can either be analyzed qualitatively based on physical insights about the batch process, or the students can develop and solve the mass balance equations for the batch system (easily assigned as a homework problem after presenting the fed-batch analysis in class). The final expression for the flavor recovery in the batch system is simply

$$\text{Recovery} = \left(\frac{V_{final}}{V_{initial}}\right)^{S} \tag{5}$$

It is relatively easy to show that there is always less flavor lost using the batch process. This is because the concentration of flavor components in the recycle tank in the fed-batch process increases much more rapidly than that in the batch system due to the smaller volume in the recycle tank, leading to a greater passage of flavor components through the membrane. Given that result, the students can think about why one might still decide to use a fed-batch process for the juice concentration. One practical reason is that it can be difficult to maintain a well-mixed solution as one goes from an initial volume of 10,000 L to a final volume of 500 L in the batch process. The lack of mixing not only affects the flavor loss, it also affects the filtrate flow rate that can be achieved in the membrane unit. The batch process also requires the use of a very large (and expensive) feed tank. In addition, the fed-batch process provides greater design flexibility for use in multiple processes in a single commercial facility.

IMPURITY REMOVAL FROM RECOMBINANT THERAPEUTIC PROTEINS

The biotechnology industry now produces a wide range of therapeutic proteins using recombinant gene technology. The DNA of interest is cloned into an appropriate microorganism or mammalian cell line, enabling those cells to produce the desired protein using their natural metabolic processes. Current commercial recombinant products include: insulin for the treatment of diabetes, tissue plasminogen activator used as an anti-clotting agent for the treatment of stroke and heart attack, human growth hormone for the treatment of dwarfism, and erythropoietin as a red blood cell stimulating agent for the treatment of anemia. A nice review of recombinant gene technology is provided by Glick and Pasternak.[6]

One of the critical issues in the production of therapeutic proteins is the high degree of purification that must be achieved, particularly since these molecules are typically given directly into the bloodstream by intravenous injection. The bulk of the purification is typically done using some combination of affinity, ion exchange, and/or hydrophobic interaction chromatography. Small impurities (*e.g.*, buffer components and excess salt), however, are generally removed by membrane diafiltration. Van Reis and Zydney[7] provide a nice review of the principles of diafiltration for bioprocessing applications.

The traditional material in this course has been supplemented with a series of membrane problems specifically designed to illustrate the key concepts involved in the analysis of transient mass balances.

The diafiltration process looks very similar to the apple juice concentration shown in Figure 1. The membrane is nearly fully retentive to the protein of interest, but allows relatively unhindered passage of the small impurity through the membrane. The solution containing the therapeutic protein is contained in the recycle tank, and a protein- and impurity-free buffer solution is continually added to the tank to maintain a constant solution volume while the impurity is washed through the membrane.

The transient mass balance for the constant volume diafiltration process is

$$V\frac{dC}{dt} = -SQ_{filtrate}C \tag{6}$$

where S, the membrane sieving coefficient, is equal to the ratio of the impurity concentration in the filtrate solution to that in the feed. Equation (6) can be integrated to give a simple decaying exponential relating the impurity concentration at time t to the initial concentration of the impurity in the protein solution. The results are more conveniently expressed in terms of the total volume of protein-free buffer that must be used to reduce the impurity concentration to a desired target level

$$\frac{C_{final}}{C_{initial}} = \exp\left(-\frac{SV_{buffer}}{V}\right) \tag{7}$$

The membrane diafiltration can be used in combination with an ultrafiltration process to achieve protein concentration and impurity removal in a single processing step.[7]

This same diafiltration process is also used as part of a viral inactivation step. For example, an appropriate solvent or detergent is first added to the protein solution to achieve a concentration that is sufficient to inactivate nearly all viruses. The solvent/detergent is then removed by diafiltration, typically to a target of less than 10 ppm (parts per million). This is an ideal opportunity to talk about product safety issues,

including the need to achieve essentially complete virus removal/inactivation while at the same time avoiding denaturation of the recombinant protein product and minimizing potential complications from the presence of trace amounts of any viral inactivation agents. It is important for students to recognize that even though the membrane diafiltration is very effective at removing residual solvents and detergents, it is impossible to achieve 100% removal of these components using a finite volume of diafiltration buffer—the exponential decay provides an asymptotic approach to zero concentration.

UREA REMOVAL DURING HEMODIALYSIS

Another interesting membrane problem that is readily incorporated into the introductory mass balance course is analysis of urea removal during hemodialysis.[8] Hemodialysis is currently used to treat chronic kidney failure in more than 500,000 patients around the world—patients who would die within about two weeks without the availability of this type of artificial kidney. Urea removal in hemodialysis can first be examined by analyzing a transient batch process for removing urea from blood across a semi-permeable membrane (top panel in Figure 2). The dialysate contains all the key salts and sugars normally found in plasma to insure that these components aren't removed during the dialysis. The membrane is impermeable to all blood cells and proteins, but it allows urea to be removed at a rate that is proportional to the concentration difference between the blood and the dialysate solution

$$\dot{m}_{transfer} = k_m A\left[C_{blood} - C_{dialysate}\right] \qquad (8)$$

where k_m is the membrane mass transfer coefficient (or permeability) and A is the membrane area. Component mass balances are written for the urea concentration in the blood and in the total system (blood plus dialysate)

$$V_{blood}\frac{dC_{blood}}{dt} = -k_m A\left[C_{blood} - C_{dialysate}\right] \qquad (9)$$

$$V_{blood}\frac{dC_{blood}}{dt} + V_{dialysate}\frac{dC_{dialysate}}{dt} = 0 \qquad (10)$$

where we have assumed that the volumes of the blood and dialysate compartments remain constant during the dialysis. The system mass balance (Eq. 10) is directly integrated to develop an expression for $C_{dialysate}$ in terms of C_{blood}. If presented in class, it is helpful to ask the student what will happen at long times before actually solving the equations. Many students don't appreciate that the system will approach steady state with $C_{blood} = C_{dialysate}$. The steady-state solution can easily be developed by setting the derivatives equal to zero and solving the resulting algebraic equations. The full solution is readily developed by integration of Eq. (9) to give

$$\ell n\left[\frac{C_{blood}}{C_{blood,0}}\left(1+\frac{V_{blood}}{V_{dialysate}}\right)-\frac{V_{blood}}{V_{dialysate}}\right] = -k_m At\left(\frac{1}{V_{blood}}+\frac{1}{V_{dialysate}}\right) \qquad (11)$$

where $C_{blood,0}$ is the urea concentration in the blood at the start of the dialysis. It is easy to show that Eq. (11) approaches the steady-state solution in the limit of $t \to \infty$ as required.

After analyzing the transient hemodialysis system, the students can think about why this isn't the way hemodialysis is actually performed clinically. Most students recognize the problem of having a large portion of the patient's blood outside of the body, and some will even appreciate the logistical challenge of insuring that the right blood is returned to the right patient. It thus becomes relatively easy to motivate the need for using a continuous-flow system for hemodialysis (bottom panel of Figure 2). A simple solution for this problem can be developed by assuming that the urea concentrations are at steady state and that the blood and dialysate solutions are both well-mixed. The steady-state assumption can often be confusing since the urea concentration in the patient's blood clearly decreases with time during the hemodialysis. But the time constant for concentration changes in the dialyzer is so much shorter than the time constant for the body due to the small extracorporeal volume, that it is appropriate to use this type of pseudo-

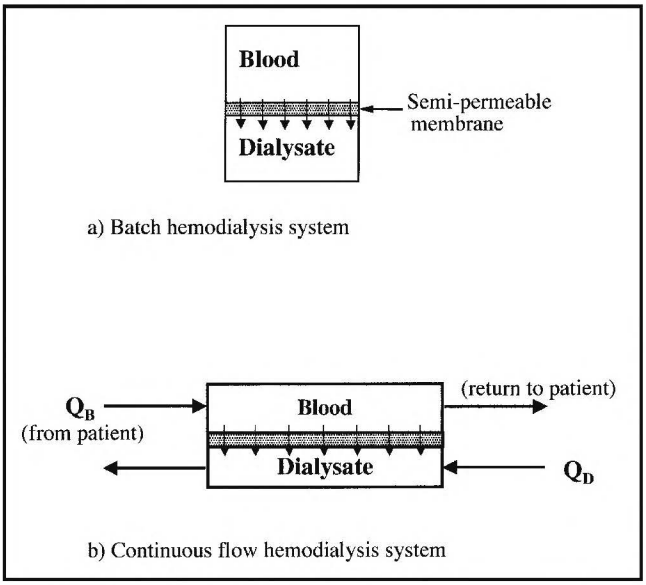

Figure 2. *Hemodialysis systems for urea removal. Top panel shows a batch system; bottom panel shows continuous-flow process.*

steady-state approximation. The final result is

$$\frac{C_{Bout}}{C_{Bin}} = \frac{Q_B\left(1+\frac{k_m A}{Q_D}\right)}{Q_B\left(1+\frac{k_m A}{Q_D}\right)+k_m A} \qquad (12)$$

where C_{Bout} and C_{Bin} are the urea concentrations in the blood leaving and entering the dialyzer, and Q_B and Q_D are the blood and dialysate flow rates. More sophisticated solutions can be developed for countercurrent flow if the students are able to handle the concepts and mathematics required for analysis of the position-dependent differential mass balances in this system.[8]

Although the well-mixed analysis provides a simple analytical expression, most students don't immediately appreciate the implications of the final result. For example, the analysis clearly shows that the outlet urea concentration in the blood doesn't go to zero as the membrane area becomes infinite. In addition, this equation seems to imply that increasing the blood flow rate is detrimental since it increases the urea concentration in the blood stream that is returned to the patient (although it also increases the rate of urea removal from the body). This leads nicely into a discussion of the key design criteria for the dialyzer.

It is also relatively easy to couple analysis of the hemodialyzer with the transient mass balances describing the urea concentration within the body (treated as a well-mixed "tank"). The resulting equations can be used to examine the performance of a clinical dialysis session at reducing the urea concentration to a safe level. Current clinical practice is for patients with complete kidney failure to undergo four-hour dialysis sessions three times a week, 52 weeks a year. The total cost of providing hemodialysis in the United States is approximately $15 billion per year, essentially all of which is paid by the Federal government. This is a great opportunity for a discussion about some of the ethical and economic issues involved in the development and delivery of expensive new medical technologies, an issue that is likely to become even more important in the coming years.

Another hemodialysis design issue that can be worth discussing is the importance of minimizing the extracorporeal blood volume while maintaining a large surface area for mass transfer. Current clinical dialyzers use a parallel array of more than 10,000 narrow hollow fiber membranes (inner diameter of about 200 μm) to achieve a surface area of close to two square meters. Smaller diameter fibers, approaching the 6-8 μm diameter of the blood capillaries within the kidney, would further increase the ratio of surface area to blood volume. Blood clotting becomes a major problem in these very narrow fibers, however, even in the presence of a strong anticoagulant like heparin. This leads nicely into a discussion of biomaterials and some of the issues involved in the development of truly biocompatible polymeric materials that still maintain the desired mechanical and mass transport characteristics needed for this type of biomedical device.

SUMMARY

The membrane problems described in this paper provide an attractive set of examples for introducing students to key concepts in the analysis of transient material balances in nonreacting systems. Related problems can also be developed for the analysis of gas separation membrane processes *(e.g.,* the production of oxygen from air) and on the behavior of membrane reactors (*e.g.,* the use of palladium membranes to remove hydrogen and thereby improve product yield in equilibrium-limited dehydrogenation reactions).

All of these membrane problems are of real commercial interest, they provide students some exposure to new application areas of chemical engineering, and they give the instructor an opportunity to introduce basic concepts of process design at a very early stage in the curriculum.

Student response to these problems in the Introduction to Chemical Engineering course at the University of Delaware has been outstanding. They definitely appreciate being able to analyze real-world problems even as freshmen, and they clearly enjoy the opportunity to begin thinking about process design issues. In addition, these membrane examples give students a perspective into the kinds of problems and processes that they will encounter throughout their undergraduate chemical engineering education.

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