Unified Modeling of Diafiltration Cascades: From Classical Designs to Novel Configurations

Rocus Dekkers

RMD-consult, Strausslaan 5, 2992 PC Barendrecht, The Netherlands
Email: rocus.dekkers@rmd-consult.nl

Abstract. This paper examines the wash efficiency of various multistage cascade diafiltration systems. In addition to the well-known batch, continuous co-current and counter-current systems, it introduces new concepts: batch counter-current and continuous counter-co-current configurations. Analytical formulas are available for all configurations to calculate wash efficiency with one washing factor. This approach allows for transparent comparison between different configurations and different numbers of stages in terms of solvent (e.g. wash water) usage and the required total membrane area. A thorough evaluation is conducted to assess the performance of each configuration. These models can be used for total cost minimization. Computation examples clarify the applications of the formulas.

Keywords: Modeling; Membranes; Diafiltration; Multistage; Batch ; Continuous; Co-current; Counter-current; Counter-co-current;

1 Introduction

Pressure driven membrane processes like micro-, ultra-, nano-filtration and reversed osmosis are widely employed in biotechnology, pharmaceutical and other industries for the concentration, purification and fractionation of their products [1,2,3,4,5]. As part of these processes diafiltration is used with the goal of obtaining higher purities and higher yields. With diafiltration a solvent is added to the retentate during membrane filtration where components which are more permeable to the membrane are washed out to a greater extent than the retained components. Examples of diafiltration applications are:

- High yield recovery of antibiotics from fermentation broth [6,7,8,9]
- Whey protein purification [10,11,12,13,14]
- Protein fractionation [15,16, 17, 18]

Modes of operation are batch and continuous diafiltration, each with distinct advantages depending on the scale and process requirements. In batch diafiltration, the retentate is held in a single vessel while fresh solvent is added either continuously or stepwise to maintain a constant volume as permeate is removed. This method is simple and commonly used at small scales. Continuous diafiltration especially in multi-stage configurations offers improvements in efficiency and scalability. Two common multistage arrangements are co-current and counter-current diafiltration. In co-current diafiltration, the feed solution and diafiltration solvent move in the same direction through multiple stages. On the other hand, in counter-current diafiltration, the solvent and feed move in opposite directions across successive stages.

In a case study Lipnizki et al. [19] compared batch, continuous co-current and counter-current diafiltration modes in terms of membrane usage, liquid consumption, and cost efficiency. Counter-current diafiltration, while demanding more membrane area, significantly reduces liquid consumption. Overall, counter-current diafiltration emerges as a promising approach for case-specific process optimization.

In this paper we give in a general systematic framework with analytical models for different multistage cascade diafiltration configurations. Novel configurations like batch counter-current and continuous counter-co-current are introduced. The models facilitate easy evaluation of different configurations in a spreadsheet.

The following general assumptions are used for the modeling of the diafiltration cascade configurations:

- All stages in a multistage configuration are equal.
- The rejection coefficient is constant.
- The permeate flux is constant.
- The concentration of the solute in the retentate is uniform in a stage.
- The concentration of the solute in the permeate is uniform in a stage.
- The diafiltration is performed at constant retentate volume i.e. ingoing solvent flow is equal to outgoing permeate flow.

2 Basic Batch

The basic batch operation as illustrated in figure 1, is a well-established concept in the literature. Nevertheless we present the mathematical derivation of the batch diafiltration equation here to provide a clearer understanding of the remaining of the paper. Additionally, the batch diafiltration serves as the reference point for all other diafiltration configurations discussed.

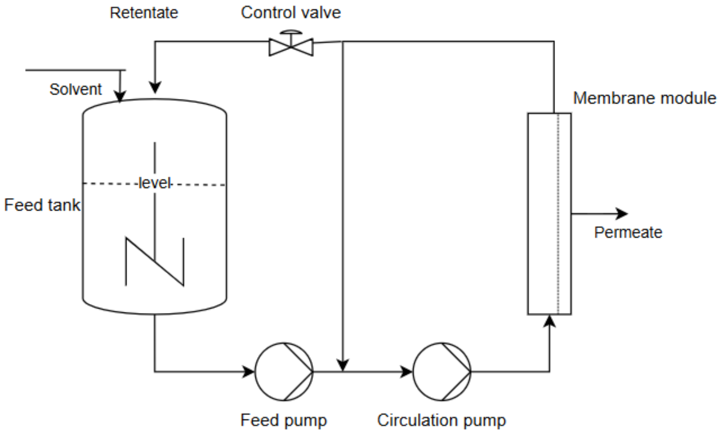

Figure 1. Batch membrane diafiltration.

The washing-out of the (micro-) solute is governed by the differential equation

$$V\frac{dx}{dt} = -S.y \quad x(t=0) = x_0 \tag{1}$$

Where V denotes the total volume of the retentate, x represents the solute concentration in the retentate, x_0 is the initial concentration of the batch (= “feed” concentration), S is the incoming solvent flow (equal to the permeate flow because of the constant volume operation) and y is the solute concentration in the permeate. The permeate flow S is given by

$$S = f.A \tag{2}$$

Where f is the permeate flux ($l/m^2/hr$) and A the total membrane area (m^2).

The solute concentration in the permeate is given by

$$y = (1-R)x \tag{3}$$

where R is the rejection coefficient for the solute.
Combining equation (1) and (3) gives as solution

$$x(t) = x_0 e^{-\frac{S(1-R)}{V}t} \tag{4}$$

So, for a batch with duration T the reduction factor in the solute is given by

$$\frac{x_b}{x_0} = e^{-a} \tag{5}$$

Where x_b is the solute concentration at the end of the batch and a is the washing factor given by

$$a = \frac{S(1-R)}{F} \tag{6}$$

Where F is the production capacity ("feed flow") of the batch unit given by

$$F = \frac{V}{T} \tag{7}$$

Note that for batch operation the washing factor a (6) is proportional with the membrane area in (2). Also the solvent usage is proportional with a.
The washing factor a is an essential parameter used throughout all diafiltration configurations in this paper. The solute reduction factor is usually specified because the solute is either an impurity in the retentate or a valuable component in the permeate with a required recovery yield. The necessary solute reduction factor is attainable by selecting an appropriate washing factor a, as described in equation (5).

3 Continuous operation

3.1 General

The continuous operation of diafiltration is a single or multistage operation as illustrated in figure 2 which shows a 3-stage co-current diafiltration.

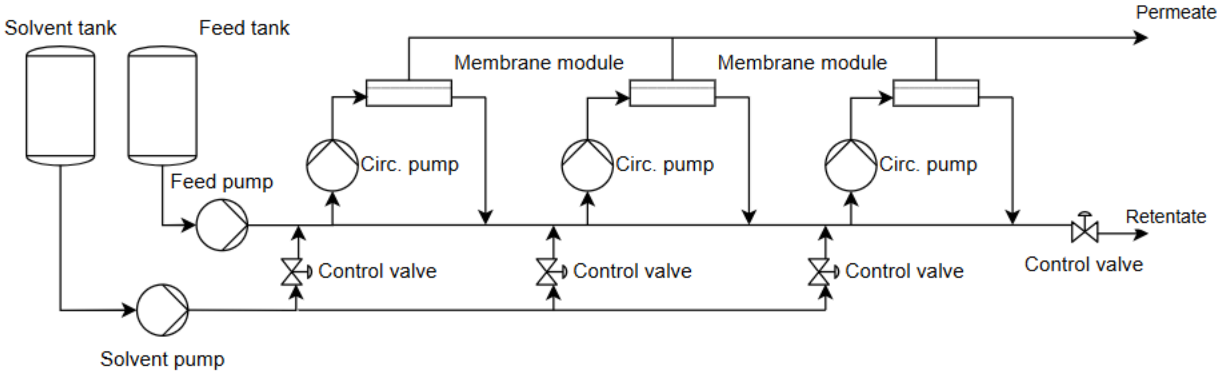

Figure 2. 3-stage continuous co-current diafiltration.

For analyzing the continuous operation we consider the solute balance over a stage as given in figure 3.

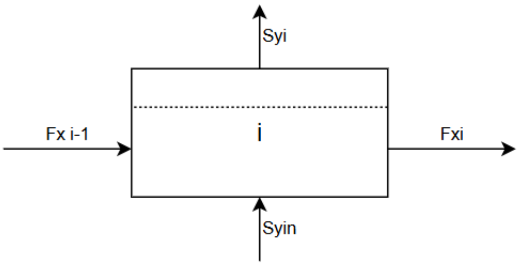

Figure 3. Solute balance of a stage in continuous diafiltration operation

Assuming steady state, the solute balance for stage i can with (3) be written as

$$Fx_i + S(1-R)x_i = Fx_{i-1} + Sy_{in} \tag{8}$$

When the solvent comes as permeate from another stage k, then

$$y_{in} = y_k = (1-R)x_k \tag{9}$$

With (6) and (9), the solute balance (8) can then be written as

$$(a+1)x_i - x_{i-1} - ax_k = 0 \tag{10}$$

When the solvent is fresh then $y_{in} = 0$ and (8) can be written as

$$(a+1)x_i - x_{i-1} = 0 \tag{11}$$

3.2 Co-current diafiltration

The continuous equivalent of a batch diafiltration is the co-current multistage diafiltration with solvent added in every stage. Figure 4a schematically gives the diagram for a cascade with 6 stages.

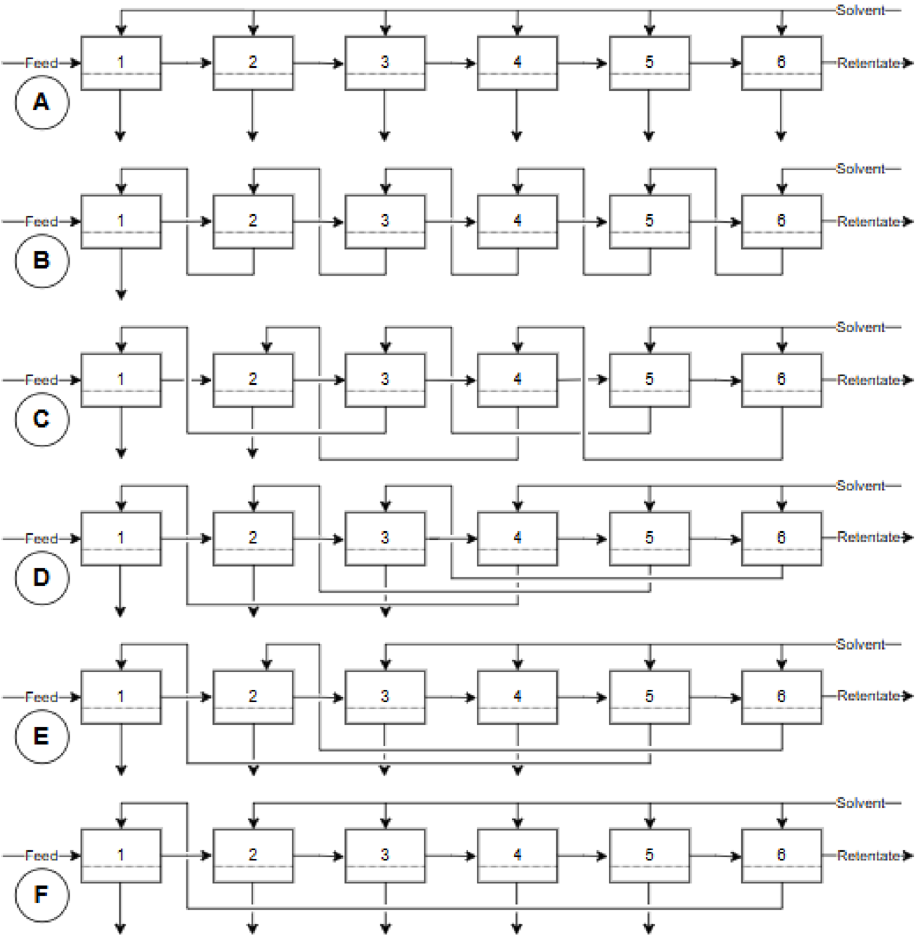

Figure 4. 6-stage continuous diafiltration configurations. (a) co-current, r=6; (b) counter-current, r=1; (c) counter-co-current r=2; (d) counter-co-current r=3; (e) counter-co-current r=4; (f) counter-co-current r=5.

With application of equation (11) for all stages, we get the following matrix equation for the solute balances of the stages 1-6:

$$\begin{pmatrix} a+1 & 0 & 0 & 0 & 0 & 0 \\ -1 & a+1 & 0 & 0 & 0 & 0 \\ 0 & -1 & a+1 & 0 & 0 & 0 \\ 0 & 0 & -1 & a+1 & 0 & 0 \\ 0 & 0 & 0 & -1 & a+1 & 0 \\ 0 & 0 & 0 & 0 & -1 & a+1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{pmatrix} = \begin{pmatrix} x_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{12}$$

Where x_0 is the feed concentration and x_6 the output concentration.
The equations for x_1 to x_6 can be solved directly, yielding the solute reduction factor

$$\frac{x_6}{x_0} = \frac{1}{(1+a)^6} \tag{13}$$

For a cascade with n stages we get

$$\frac{x_n}{x_0} = \frac{1}{(1+a)^n} \tag{14}$$

For a desired solute reduction factor, we can calculate the required washing factor with (14). Note that for a cascade co-current diafiltration the total membrane area and the total solvent usage is proportional to n times a. Comparing the total membrane area and total solvent usage with a batch diafiltration with the same capacity F we get:

$$\frac{A_{co}}{A_b} = \frac{n.a_{co}}{a_b} \quad \frac{S_{co}}{S_b} = \frac{n.a_{co}}{a_b} \tag{15}$$

Where A_{co}, S_{co} and a_{co} is the total membrane area, the total solvent usage and washing factor respectively of the n stage co-current diafiltration; A_b, S_b and a_b is the total membrane area, the total solvent usage and washing factor respectively of the batch diafiltration. The washing factor a_{co} is determined with (14) and a_b with (5) so that the (same) required solute reduction factor is obtained.

Note also that if we have an “infinity” number of stages with $a=a_b/n$ we get with (14) in the limit:

$$\lim_{n\to\infty} \frac{x_n}{x_0} = \lim_{n\to\infty} \frac{1}{\left(1+\frac{a_b}{n}\right)^n} = \frac{1}{e^{a_b}} = e^{-a_b} \tag{16}$$

Which is equal to the reduction factor (5) for a batch diafiltration.

3.3 Counter-current diafiltration

To minimize overall solvent use, the permeate from stage i+1 is reused to wash stage i. Figure 4b schematically gives the diagram for a counter-current cascade with 6 stages. With application of equation (11) for stage 6 and equation (10) for stages 1-5, we get the following matrix equation for the solute balances:

$$\begin{pmatrix} a+1 & -a & 0 & 0 & 0 & 0 \\ -1 & a+1 & -a & 0 & 0 & 0 \\ 0 & -1 & a+1 & -a & 0 & 0 \\ 0 & 0 & -1 & a+1 & -a & 0 \\ 0 & 0 & 0 & -1 & a+1 & -a \\ 0 & 0 & 0 & 0 & -1 & a+1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{pmatrix} = \begin{pmatrix} x_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{17}$$

These equations can be solved sequentially from the last row to the first row through a series of substitutions. Finally the solute reduction factor is given with the equation

$$\frac{x_6}{x_0} = \frac{1}{1 + a + a^2 + a^3 + a^4 + a^5 + a^6} = \frac{1 - a}{1 - a^7} \tag{18}$$

For a cascade with n stages we get

$$\frac{x_n}{x_0} = \frac{1 - a}{1 - a^{n+1}}, a \neq 1 \tag{19}$$

If a< 1 then the solute reduction (19) has an upper bound because

$$\lim_{n \to \infty} \frac{1 - a}{1 - a^{n+1}} = 1 - a \quad a < 1 \tag{20}$$

Similar reasoning as with co-current, gives the required total membrane area and the total solvent usage related to batch parameters as

$$\frac{A_{ct}}{A_b} = \frac{n.a_{ct}}{a_b} \quad \frac{S_{ct}}{S_b} = \frac{a_{ct}}{a_b} \tag{21}$$

Where index ct stands for counter-current.

3.4 Comparison of co-current and counter-current diafiltration

We define the wash efficiency of a continuous diafiltration with n stages as

$$\eta = \left(1 - \frac{x_n}{x_0}\right).100\ \% \tag{22}$$

Figure 5 compares the wash efficiency of co-current and counter-current diafiltration with a washing factor a=0.5 and a=1 for 1-10 stages. It is obvious that the wash efficiency of the co-current configuration is higher than counter-current for a given a (so membrane area per stage) and n, because of the fresh solvent use in every stage. With a=0.5 < 1 the wash efficiency is limited to 0.5 according to (19) and (20).

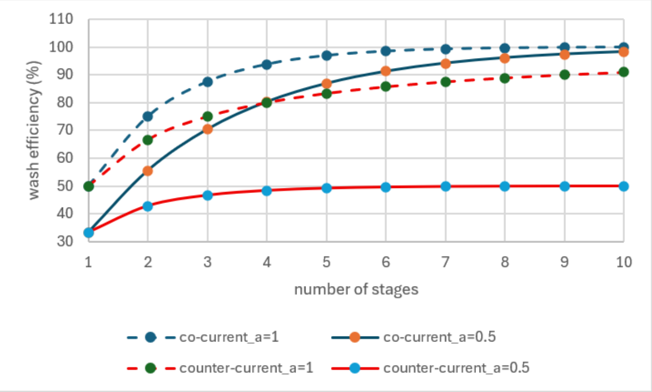

Figure 5. Co-current and counter-current wash efficiency as function of number of stages for washing factor=0.5 and washing factor =1.

To account for solvent usage, a comparison is made based on wash efficiencies of 95% and 99%. Tabel 1 gives the required washing factor a for a given wash efficiency, configuration and number of stages. The washing factor is calculated with (14) or (19) and Microsoft Excel solver add-in tool for obtaining the specified wash efficiency.

Table1. Washing factor a-parameter requirement for wash efficiency = 95% and wash efficiency = 99 % for co-current and counter-current multi-stage.

wash efficiency %	95	95	95	95	95	99	99	99	99	99
number of stages	2	4	6	8	10	2	4	6	8	10
co-current a_{co}	3.472	1.115	0.648	0.454	0.349	9.000	2.162	1.154	0.778	0.585
counter current a_{ct}	3.887	1.734	1.342	1.191	1.114	9.462	2.841	1.907	1.570	1.402

For a batch diafiltration (5) and (22) gives a_b=2.996, 95 % and a_b= 4.605, 99 % wash efficiency.
Taking the batch diafiltration as reference (100%) we use (15) and (21) for evaluation of the total membrane area and total solvent usage. Figure 6 gives the total solvent usage (%) and the total membranes area (%) for 95 % and 99 % wash efficiency.

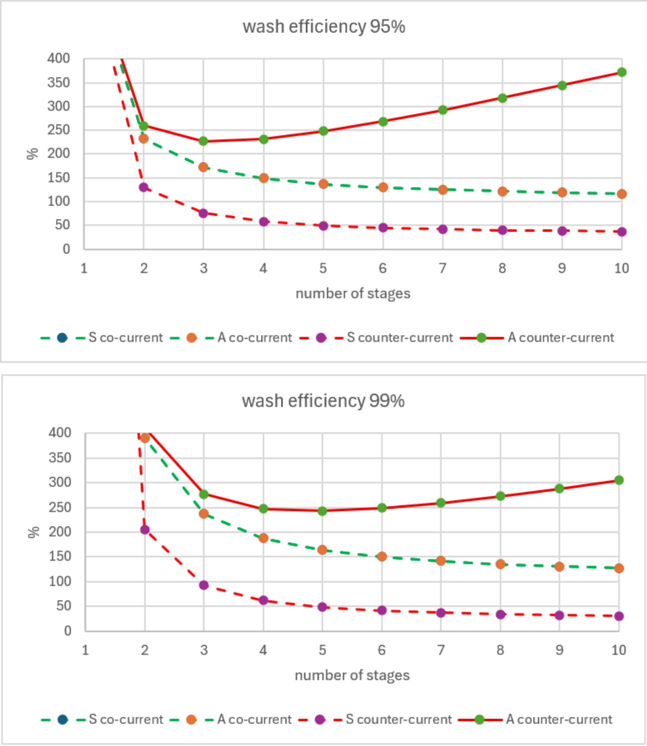

Figure 6. Solvent (S) and total membrane area (A) requirement for wash efficiency=95% and wash efficiency=99% for multi-stage co-current and counter-current. Note the A- and S-curve overlap with co-current.

For a given number of stages the total solvent usage of the counter-current cascade is less than that of the co-current cascade. For 3 stages or more the total solvent usage of the counter-current cascade is less than the batch configuration. Contrary the total membrane area for the batch is the lowest and the highest for counter-current configuration. Remarkably with the counter-current configuration: the number of stages should not be less than 3 with 95 % and 5 with 99 % wash efficiency. In a co-current cascade, achieving 100% batch limits for solvent use and membrane area requires so many stages that it is impractical. The use of a high number of stages with the counter-current configuration is limited, as it only marginally reduces total solvent usage and significantly increases the required membrane area.

3.5 Hybrid counter-current and co-current diafiltration

In the preceding section, it was demonstrated that continuous counter-current and co-current designs exhibit contrasting advantages and disadvantages regarding total solvent consumption and the total membrane area required. Therefor it could be interesting to look for hybrid counter-co-current configurations which compromise the solvent and membrane area usage. Figure 4c-f gives as hybrid example 2, 3, 4 and 5 co-current solvent additions for a 6-stage cascade configuration with counter-current. Solute balances for these setups can be modeled just as they are for co- and counter-current systems. The balances for e.g. a 6-stage counter-current cascade with 2 co-current solvent additions are defined with

$$\begin{pmatrix} a+1 & 0 & -a & 0 & 0 & 0 \\ -1 & a+1 & 0 & -a & 0 & 0 \\ 0 & -1 & a+1 & 0 & -a & 0 \\ 0 & 0 & -1 & a+1 & 0 & -a \\ 0 & 0 & 0 & -1 & a+1 & 0 \\ 0 & 0 & 0 & 0 & -1 & a+1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{pmatrix} = \begin{pmatrix} x_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{23}$$

The solution of (23) is given by

$$\frac{x_6}{x_0} = \frac{1}{(a+1)^6 - 4a(a+1)^3 + a^2} \tag{24}$$

For the general case with n stages and r solvent addition points the solute reduction factor is given with the with the recursive equations

$$D_0 = 1 \quad D_1 = a+1 \quad D_2 = (a+1)^2 \quad \dots \quad D_r = (a+1)^r$$

$$D_n = (a+1)D_{n-1} - aD_{n-r-1} \quad n \geq r+1 \tag{25}$$

$$\frac{x_n}{x_0} = \frac{1}{D_n}$$

Table 2 gives the required washing factor a for a given wash efficiency, number of solvent additions in the hybrid configuration and total number of stages. The washing factor is calculated with (25) and Microsoft Excel solver add-in tool for obtaining the specified wash efficiency.

Table 2. Required washing factor a-parameter for wash efficiency = 95 % and wash efficiency = 99% for different counter-co-current multi-stage configurations.

Wash efficiency %	95	95	95	95	95	99	99	99	99	99
Number of stages	2	4	6	8	10	2	4	6	8	10
a with r=1	3.887	1.734	1.342	1.191	1.114	9.462	2.841	1.907	1.570	1.402
a with r=2	3.472	1.250	0.860	0.713	0.639	9.000	2.274	1.349	1.027	0.870
a with r=3	3.472	1.144	0.727	0.571	0.492	9.000	2.179	1.214	0.876	0.712
a with r=4	3.472	1.115	0.677	0.510	0.427	9.000	2.162	1.172	0.819	0.647

Note that r=1, so 1 solvent addition point, is equivalent to standard counter-current.

Similar reasoning as with counter current flow, the required total membrane area and the total solvent usage related to batch parameters is given by

$$\frac{A_{ctr}}{A_b} = \frac{n.a_{ctr}}{a_b} \quad \frac{S_{ctr}}{S_b} = \frac{r.a_{ctr}}{a_b} \tag{26}$$

Where index ctr stands for counter-current with r solvent additions.
Taking the batch diafiltration as reference (100%) we use (26) for evaluation of the total membrane area and total solvent usage. Figure 7 gives the total solvent usage (%) and the total membranes area (%) for 95 % and 99 % wash efficiency for counter-co-current configurations. The configuration r=2 gives a significant reduction in total membrane area with respect to counter-current r=1, but on the other hand an increase of total solvent usage. Further increase to r=3 and especially r=4 gives much lower decrease in total membrane area.

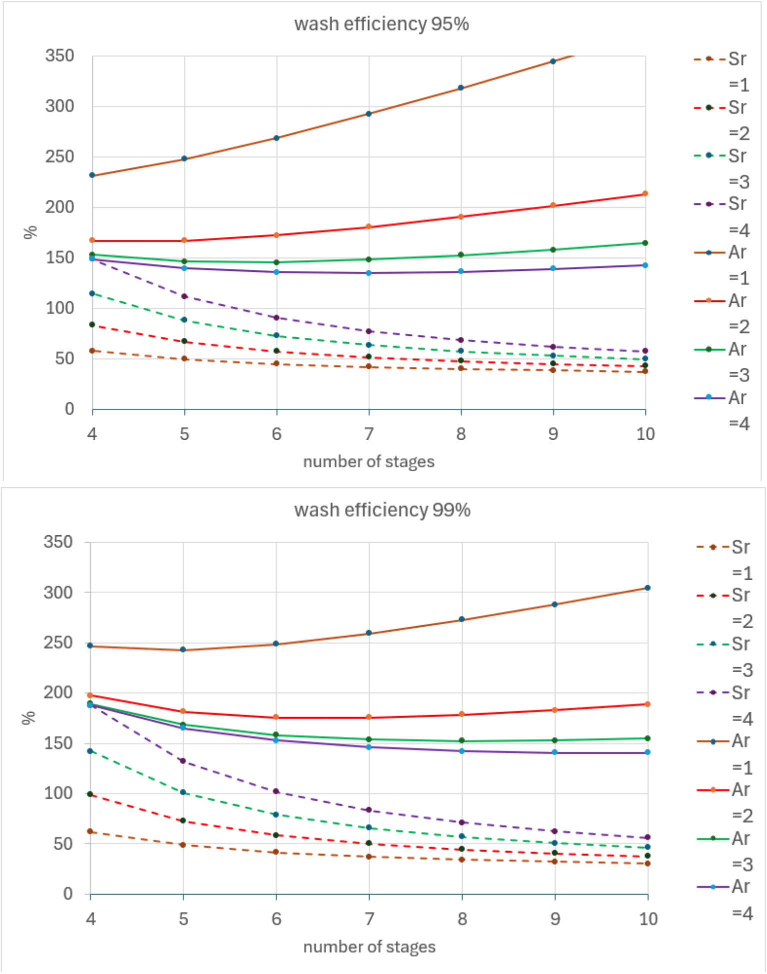

Figure 7. Solvent (S) and total membrane area (A) requirement for wash efficiency=95% and wash efficiency=99% for different multi-stage counter-co-current configurations: r=1,2,3,4.

3.6 Example of total cost minimization

The total membrane area A_{ctr}, total solvent usage S_{ctr} and number of stages n are all related to investment costs and operational costs. Investment costs may include membrane installation, housings, pumps, piping, instrumentation, and space requirements. But also about utilities and down-stream units. More total solvent usage requires larger equipment e.g., reversed osmosis unit if permeate contains valuable product. Operational costs may include membrane usage, solvent usage, electricity, and maintenance.

Suppose the total relative cost of a membrane installation is given by

$$Total\ relative\ Cost = \left(\frac{A_{ctr}}{A_b} + \frac{S_{ctr}}{S_b} + 0.1n\right).100\% \tag{27}$$

The objective is to minimize overall costs by selecting a configuration that achieves the required wash efficiency, specifically targeting either 95% or 99%, as applicable.
Table 3 gives the optimal solutions for 3 configurations: co-current, counter-current and counter-co-current.

Table 3. Optimal number of stages and a-parameter for minimal total cost with different contuous configurations.

	Wash efficiency 95%				Wash efficiency 99%			
	n stages	r solvent	wash a	tot. cost	n stages	r solvent	wash a	tot. cost
Co-current	6	6	0.6476	319	8	8	0.7783	350
Counter-current	4	1	1.7341	329	5	1	2.2344	341
Counter-co-current	6	3	0.7267	278	8	3	0.8761	289

The total costs of the co-current and counter-current configurations are nearly identical. But obviously the counter-co-current configuration with r=3 has the lowest total cost.
Note: The total costs at 95% and 99% wash efficiency are not directly comparable, since equation (27) calculates them relative to A_b and S_b, which depend on the targeted wash efficiency.

4 Multistage batch counter-current

The single batch diafiltration described in section 2 can be expanded to a multistage counter-current process, using the stage i+1 permeate as the wash liquid for stage i. In the final stage n, a fresh solvent is added. With a periodical operation, the batch systems are virtually moved after time T from stage i to i+1.
Finally the batch system ends at stage n and starts again with a new batch loading in stage 1. Actually the batch systems are not moving physically but a piping manifold arranges the switching of the wash liquids. In chromatography, this approach is known as "simulated moving bed". Figure 8 demonstrates the concept of a 4-stage batch counter-current system.

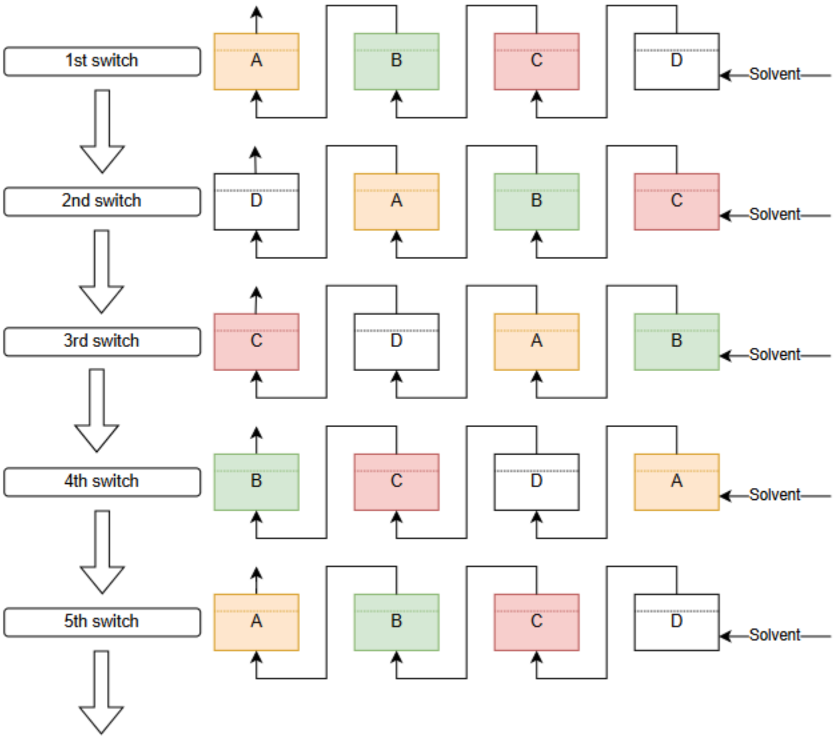

Figure 8. Schematic diagram of a 4-stage batch counter-current system.

Using equation (1) and (3) for the 4-stage batch counter-current system, the solute balances can be written as:

$$\frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} -\alpha & \alpha & 0 & 0 \\ 0 & -\alpha & \alpha & 0 \\ 0 & 0 & -\alpha & \alpha \\ 0 & 0 & 0 & -\alpha \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} \qquad \begin{pmatrix} x_1(0) \\ x_2(0) \\ x_3(0) \\ x_4(0) \end{pmatrix} = \begin{pmatrix} x_{10} \\ x_{20} \\ x_{30} \\ x_{40} \end{pmatrix} \tag{28}$$

Where

$$\alpha = \frac{S(1-R)}{V} \tag{29}$$

The solution of (28) is given by

$$x_4(t) = e^{-\alpha t} x_{40}$$

$$x_3(t) = e^{-\alpha t}(x_{30} + \alpha t x_{40})$$

$$x_2(t) = e^{-\alpha t}\left(x_{20} + \alpha t x_{30} + \frac{\alpha^2 t^2}{2} x_{40}\right) \tag{30}$$

$$x_1(t) = e^{-\alpha t}\left(x_{10} + \alpha t x_{20} + \frac{\alpha^2 t^2}{2} x_{30} + \frac{\alpha^3 t^3}{6} x_{40}\right)$$

For t=0 we have

$$x_{10} = x_0\ , x_{20} = x_1\,(T)\ , x_{30} = x_2\,(T), x_{40} = x_3\,(T) \tag{31}$$

With (6), (7) and (29) we have

$$\alpha T = a \tag{32}$$

Combining (30), (31) and (32) gives the following linear equations for $x_1(T)$, $x_2(T)$, $x_3(T)$ and $x_4(T)$, where for convenience we write x_1 for $x_1(T)$, x_2 for $x_2(T)$, x_3 for $x_3(T)$, x_4 for $x_4(T)$,

$$\begin{pmatrix} e^a - a & \frac{-a^2}{2} & \frac{-a^3}{6} & 0 \\ -1 & e^a - a & \frac{-a^2}{2} & 0 \\ 0 & -1 & e^a - a & 0 \\ 0 & 0 & -1 & e^a \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{33}$$

The solution of (33) is given with

$$\frac{x_4}{x_0} = \frac{e^{-a}}{(e^a - a)^3 - a^2(e^a - a) - \frac{a^3}{6}} \tag{34}$$

For the general case with n stages the solute reduction factor is given with the recursive equations

$$\begin{gathered} Q_1 = 1\,, Q_2 = e^a - a \\ Q_n = (e^a - a)Q_{n-1} - \sum_{j=2}^{n-1} \frac{a^j}{j!} Q_{n-j}\,, n \geq 3 \\ \frac{x_n}{x_0} = \frac{e^{-a}}{Q_n} \end{gathered} \tag{35}$$

Table 4 gives the required washing factor a for a given wash efficiency and number of stages for the batch counter-current configuration. The washing factor is calculated with (35), (22) and Microsoft Excel solver add-in tool for obtaining the specified wash efficiency.

Table 4. Required washing factor a-parameter for given wash efficiency and number of stages with batch counter-current diafiltration.

Wash efficiency %	95	95	95	95	95	99	99	99	99	99
Number of stages	2	4	6	8	10	2	4	6	8	10
Batch count-curr a	1,685	1.194	1.072	1,022	0.997	2.423	1.530	1.294	1.190	1.135

The required total membrane area and the total solvent usage related to single batch parameters is given by

$$\frac{A_{bct}}{A_b} = \frac{n.a_{bct}}{a_b} \qquad \frac{S_{bct}}{S_b} = \frac{a_{bct}}{a_b} \tag{36}$$

Where index bct stands for batch counter-current.

Taking the single batch diafiltration as reference (100%) we use (36) for evaluation of the total membrane area and total solvent usage. Figure 9 gives the total solvent usage (%) and the total membranes area (%) for 95 % and 99 % wash efficiency for batch and continuous counter-current configurations.

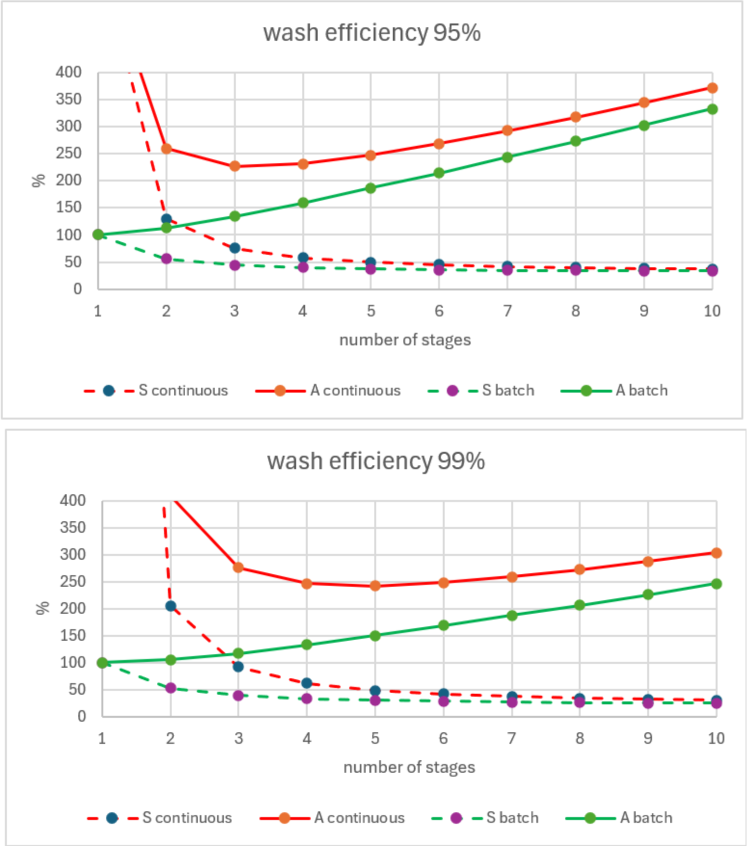

Figure 9. Total membrane area (A) and total solvent usage (S) for given wash efficiency and number of stages with continuous and batch counter-current diafiltration.

For an equal number of stages the batch counter-current configuration uses less total membrane area and less total solvent than the continuous counter-current configuration. With a larger number of stages, the difference becomes less.

5 Conclusions

A comprehensive model for diafiltration cascades has been developed, encompassing single batch, counter-current batch, continuous co-current, counter-current, and counter-co-current operations. The key parameter for all models is a defined washing factor.
Model equation (35) includes all batch configuration options.
Model equation (25) accounts for all continuous configurations.
The models are well-suited for quick evaluation of configurations in conceptual process design and scenario analysis.
Most industrial applications use continuous membrane systems [20], but batch counter-current diafiltration with 2 or 3 stages can be attractive.
Modern diafiltration approaches, such as continuous counter-co-current and batch counter-current methods, are now used in industrial micro- and ultrafiltration. Sophisticated process control is then a prerequisite for the effective operation of complex diafiltration configurations.

Conflicts of interest: The author declares no conflicts of interest.

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