membrane variability contributes to device-to-device performance consistency. Methods used to reduce variability in a device through selective layering is described herein.

In addition to reducing device variability, membrane device manufacturers desire to optimize and/or maximize device properties of a population of devices. As will be described, embodiments herein provide for methods to increase the average capacity (defined below) of a population of manufactured devices through selective layering as compared to a population manufactured by standard non-selective layering.

The ability to control device consistency is particularly important for multilayered filtration devices. For these devices, not only is the variability of the membrane important, but membrane variability can affect the interaction between the layers, as will be shown below.

It therefore would be desirable to provide a multi-layer membrane device with reduced performance variability, as well as a method of reducing the performance variability of such devices, notwithstanding the inherent variability of the membrane manufacturing process. From WO 02/05934 it is known to provide a membrane packet having a plurality of porous membranes, each porous membrane having a first region and a

second thinner region, whereby the membranes can be stacked as an integral unit.

US2002/175124 discloses a filtration capsule used for high-resolution virus removal, the capsule having a plurality of interfacially-contiguous asymmetric ultrafiltration membranes.

JP 2003 144128 concerns a laminated filter used for filtering beer made up of anisotropic precise filter membranes comprising a hydrophilic polymer containing polyethersulfone or polysulfone.

SUMMARY OF THE INVENTION

The method of the invention as defined in claim 1 provides multi-layer membrane filtration devices with reduced performance variability. The variability is reduced by combining two or more membranes with similar pore sizes, and carefully selecting the upstream membrane based upon its performance rating, in order to control the performance of the overall device.

The upstream or top membrane layer is the membrane layer that the feed stream fluid initially contacts and passes through. Conversely, the bottom layer is the last layer the fluid contacts and passes through.

The membranes do not necessarily need to be stacked. They can be separated within the device, or even contained

within separate devices. The membrane/device format is not limited to flat sheets, but can be in any format including pleated, spiral, or hollow fiber and can be applied to devices that are operated either in normal (or dead-ended) flow or tangential flow methods.

In an embodiment, selective layering in accordance with the invention reduces the capacity range of the devices when compared to random or non-selective layering. Range is defined as the difference between the high and low value of a property of a population of devices.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a bar graph showing throughput of 2-layer membrane devices containing high and low capacity membranes combined in different positions with respect to top (upstream) and bottom (downstream) position.

Figure 1a is a graph showing throughput of 3-layer devices containing high, medium, and low capacity membranes combined in different positions with respect to top (upstream), middle and bottom (downstream) position.

Figure 2 is a graph of a hypothetical distribution of membrane capacities;

Figure 3 is a graph of membrane capacity distribution showing a selection of top layer membrane and bottom layer membrane illustrating the invention;

Figure 4 is a graph of membrane capacity distribution showing another selection of top layer membrane and bottom layer membrane illustrating the invention;

Figure 5 is a graph showing the effect of layering on buffer permeability;

Figure 6 is a graph showing the effect of layering on LRV;

Figure 7 is a graph of membrane capacity distribution showing a selection of top layer membrane and bottom layer membrane not in accordance with the invention;

Figure 8 is a graph of hypothetical capacity, permeability and LRV distributions and correlations;

DETAILED DESCRIPTION OF THE INVENTION

Membrane manufacturing processes inherently result in some variability in membrane properties even though materials and process conditions are kept as constant as possible. Manufacturers typically carry out a battery of tests on membrane lots to ensure that the manufacturing process has produced membrane within established limits. Additionally, procedures can also be instituted to classify or “rate” each batch or roll of membranes after manufacture, based on performance. Membrane manufacturers use a variety of methods to rate membranes. For example,

for microporous membranes, versions of the well known bubble point test may be used to give a pore size rating. ASTM F-838-05 describes a method of LRV rating using *b. diminuta.* Ultrafiltration membranes are rated by testing with water soluble polysaccharides as described, for example, in G. Tkacik and S. Michaels, “A rejection profile test for ultrafiltration membranes and devices”, *Bio/Technology* ***9***, 941 (1991).

Membrane lots to be incorporated into multilayered devices for virus removal in biotherapeutics manufacturing may be tested by normal flow log reduction value (LRV)/capacity tests which challenge the membrane with the bacteriophage, such as ΦX-174, in a protein solution, such as bovine serum albumin (BSA), or human IgG. Virus retention (LRV) and capacity (volume filtered) at a predetermined end-point, such as 70-75% flow reduction, are measured, and relative performance values are obtained. Typically, water or another appropriate fluid, is used to measure permeability of the membrane.

The membranes from the given batch are then performance rated based upon the results obtained. All the membranes are qualified under a single standard of permeability, retention and capacity. That is, all qualified membrane is considered as a single product

meeting all specifications with regard to form, function and performance (including pore size rating). As with any product, there are tolerances in the specifications. Regardless of the tightness of the tolerances, there will inevitably be some finite performance variability within the specification tolerance range.

It is known that for stacked filters, the resistance to flow is additive, so that the flux of the stack will be approximately the average of the filters used to make the stack. Also, retention, as measured by LRV, is approximately additive, so that the LRV of a stack will be approximately the sum of the LRV's of the individual layers. However, the present inventors have surprisingly found that for multi-layer devices containing similarly rated membranes in each of the layers, the contribution of each layer to performance of the device does not necessarily follow such a predictable response, particularly where performance is defined in terms of capacity.

The present inventors have found that by providing multi-layer devices containing similarly rated membranes in each of the layers, each layer within the device contributes to performance. However, the contribution of each layer to performance of the device generally is not

equal, particularly where performance is defined in terms of capacity. As used herein, the term “capacity” is the volume of fluid that can be processed by the membrane before reaching a practical endpoint. In the case of constant pressure filtration, for example, that endpoint is defined as the condition at which the flux has decayed due to membrane fouling to a predetermined minimum.

The present inventors have found that in a multi-layer device containing similarly rated membranes, the upstream layer controls throughput capacity. Moreover, the inventors were surprised to discover that when selective layering was employed, the average capacity of a device, or of a population of devices, was higher that the average of the individual layers. Accordingly, once the capacity of each membrane of the lots to be used to make a population of devices is known, the upstream membrane of a multi-layer membrane device can be selected according to the methods herein to obtain the highest capacity for a single device, or the highest average for the population manufactured. As well, the range of capacity values for the device population will be smaller than that of the population of membranes from whence the devices were made. Additional performance criteria, such as retention and/or permeability, also can be used to measure performance, and

to base membrane selection on.

Added benefits are that the while the resultant flux of the selectively layered device is approximately the average of the layers, the range of values is smaller that that of the membranes used. The resulting LRV of selectively layered devices is similar to the average of the membranes used, with a smaller range.

By way of example, the effect of layer ordering on capacity can be demonstrated on normal flow virus filtration membranes, although the present invention is not so limited. Figure 1 shows that a double layer membrane capacity (defined as 75% flow decay from the initial non-fouled value) of an asymmetric polyethersulfone membrane commercially available from Millipore Corporation under the name VIRESOLVE PRO™, is controlled primarily by the capacity of the upstream layer membrane, regardless of the capacity of the bottom layer membrane. Thus, for the membrane roll designated as “low” capacity, two layers of this membrane had a throughput of about 500 L/m^2. For the membrane roll designated as “high” capacity, two layers of this membrane had a throughput of about 900 L/m^2. Throughput and capacity are equivalent terms. When “high” membranes were positioned upstream over “low” membranes that were placed in the downstream position, the capacity of these

devices were nearly equivalent to that of devices that contained two layers of “high” membrane. A similar result is apparent for membranes where the “low” capacity membranes were positioned upstream over “high” capacity membranes that were placed in the downstream position. The capacity of the multi-layer device was not negatively impacted by the relatively low throughput of the bottom layer membrane. The “low/high” combination shows that despite the relatively high capacity of the downstream layer, again the overall capacity of the multi-layer device is a function primarily of the upstream layer. Accordingly, if two or more membranes of known differing capacities are available for assembly into a multi-layer membrane device, the membrane available with the highest capacity can be selected as the upstream layer. To explain the selective layering approach, the capacity properties of membrane lots available to be made into devices is approximately formulated into a distribution as illustrated in Figure 2. A portion of the membrane capacity distribution is then selected as top layer membrane in order to reduce the range of device capacities compared to layering the membranes randomly, and to maximize capacity and/or minimize device-to-device capacity variability.

This phenomenon has also been demonstrated on three-

layer Optiscale-25 devices with Viresolve NFP membrane (Millipore Corporation, Billerica, Massachusetts). Viresolve NFP (Normal Flow Parvovirus) membranes clear parvovirus from recombinant or human plasma sources. U.S. Patent No. 5017292 discloses technology used to produce the Viresolve membrane. It provides a composite PVDF membrane comprising a porous membrane substrate and a tight side (the surface having smaller diameter pores) having ultrafiltration separation properties.

To demonstrate the effect on capacity, NFP membrane rolls with a range of average capacities were selected and labeled as high (H), mid (M) and low (L) capacity rolls.

Devices were built with various combinations, for example: HHH, HLL, MHH, MLL, LHH, LLL, etc. The first, second and third letter indicate upstream, middle and downstream layers, respectively, as shown below

H	M	L
H	H	H
H	H	H

These optiscales were tested for capacity using a BSA stream spiked with ϕx-174. Figure 1A shows relative capacity values for different layering combinations.

These results showed that when “Mid” capacity membrane (MMM) was used as a top layer over “High” capacity (HHH) or “Low” capacity (LLL) membranes, then devices with layered combination (MHH or MLL) showed capacity close to Mid capacity membrane. In other words, variability in relative capacity was reduced as a result of selectively placing “mid” capacity membrane as top layer. In this particular example, the range in relative capacity was reduced from about 1.0 to about 0.2.

Accordingly, if two or more membranes of known differing capacities are available for assembly into a multi-layer membrane device, the membrane with the capacity closest to the target capacity of the overall device is selected as the upstream layer. Using this approach, a portion of the membrane capacity distribution can be selected as top layer membrane, thereby reducing the range of device capacities compared to layering the membranes randomly.

In view of the relative influence of the upstream membrane layer, various layering strategies are possible. Selected embodiments of the invention are described based on the Figures 2 and 8. Figure 2 is a Gaussian distribution of capacity values calculated to represent membranes similar to those shown in Figures 5 and 6. Figure

8 represents correlated data of permeability to capacity and LRV to capacity. To make the simulations more realistic, the points of Figure 8 were generated from an actual linear correlation with a set degree of randomness to give the scatter plot shown. These points were then used to calculate the effects of various layering strategies.

To illustrate these strategies, a two-layer membrane device will be exemplified, although it should be understood that similar results can be obtained with devices having three or more layers. In this embodiment, a middle portion (e.g. ±10-20% of the midpoint of the distribution) of the capacity distribution is designated for the top or upstream membrane layer, with the remaining portion of the distribution to be used as the bottom layer membrane. This is illustrated graphically in Figure 3. By utilizing a top layer membrane from the middle of the capacity distribution curve, and a bottom layer membrane from the left or right side of the capacity distribution curve, the range of device capacities will be reduced compared to random layering, with no effect on mean capacity (Table 1).

Figure 4 illustrates another embodiment of a multi-layered membrane device. In the embodiment of Figure 4, the top layer membrane is randomly selected from the top

half of the capacity distribution curve, and the bottom layer membrane is randomly selected from the bottom half of the capacity distribution curve. In addition to decreasing the capacity range by half as in the embodiment of Figure 3, the embodiment of Figure 4 also increases the mean capacity as compared to random layering. Because this embodiment combines the upper portion capacity distribution (and therefore the upper portion permeability distribution and the lower portion retention distribution), with lower portion capacity distribution (and therefore lower portion permeability distribution and upper portion retention distributions, respectively), and because higher capacity membranes tend to also have higher permeability and lower virus retention (but all within the product specifications) variability in permeability and retention is reduced compared to random layering (Table 1).

Those skilled in the art will appreciate that to effectively employ the embodiments of Figure 3 and 4, the capacity distribution must be well defined and predictable. If the actual distribution does not match the distribution assumed to establish the top and bottom layer specifications, then there will be unequal numbers of top and bottom layer membranes. The top layer capacity range could be expanded to give a safety factor in allowable top

layer membrane, but this will diminish the variability reduction advantage of these strategies.

Variability in retention and permeability are also important performance factors to filter users. While capacity is controlled primarily by the top membrane layer, both layers in two-layer devices contribute to flux and retention. The resistivity (inverse of permeability) of each layer is additive.

The device retention is often expressed by the log reduction value (LRV):

$$LRV = -\log_{10}\left[\frac{C_p}{C_f}\right]$$

where C is the concentration of the target species to be retained by the membrane. LRV is generally additive for the two layers. As shown in Figures 5 and 6, the order of the membrane layers used in Figure 1 does not appreciably affect two-layer permeability or the two-layer LRV.

In a preferred another embodiment, retention and permeability variability can be minimized along with capacity variability. To that end, if the capacity distribution of Figure 2 is assumed along with the permeability and retention correlations to capacity as shown in Figure 8 (typically, membrane capacity correlates positively with permeability and negatively with

retention), the membrane layering of Figure 7 can be employed. Thus, the top and bottom layers are paired sequentially from opposite ends of the capacity distribution curve to minimize capacity variability, permeability variability and retention variability. Specifically, the membrane with a capacity of 750 l/m^2 (“Top Layer 1”) is combined with the membrane with a corresponding low capacity of 450 l/m^2 (“Bot. Layer 1”) to achieve a capacity of 750 l/m^2, etc.

The performance variability resulting from the various embodiments was calculated for a two-layer device and compared in Table 1. It can be seen that the method of Figure 7 allows for the lowest standard deviation in permeability and retention among all of the embodiments, with only slightly higher standard deviation in capacity compared to the embodiment of Figure 3 or random layering. The Figure 7 method also allows for higher mean capacity than the Figure 3 embodiment. Note that the Figure 3 embodiment can result in slightly increased permeability and retention variability compared to random layering. This occurs because the membranes with the extremes of permeability and retention are never combined with each other. The Figure 3 embodiment does have the advantage of the lowest capacity standard deviation.

TABLE 1

Layering Strategy	Capacity Mean	Capacity Std. Dev.	LRV Mean	LRV Std. Dev.	Permeability Mean	Permeability Std. Dev.
Random	600	70	7	0.85	20	1.4
Figure 3	600	29	7	0.86	20	1.5
Figure 4	656	41	7	0.65	20	1.0
Figure 7	656	41	7	0.40	20	0.8

In addition to the above advantages, the method of Figure 7 does not require a *priori* knowledge of the performance distributions as do the embodiments of Figure 3 and 4. Membranes can simply be paired according to this ranking system as they are available.

Since the method of the invention desires the maximum capacity, the highest capacity membrane is used for the top layer.

The lowest capacity, then by matching those with the highest capacity of the available membranes remaining with those with the lowest capacity of the available membranes remaining, etc. (i.e., the embodiment of Figure 7). The higher capacity layer is then designed as the upstream layer to create devices with reduced capacity variability compared to random layering.

For devices with more than two layers, alternative methods not in accordance with the invention are possible. The membranes could be placed into a groups of highest, lowest and a midrange capacity. The top layer is chosen from the highest capacity group, the bottom layer from the lowest capacity group, and the intermediate layers from the midrange group. The intermediate layers may be chosen randomly, or the may be arranged in descending order of capacity rating, and paired off as described to fill in the layers required for the device. Alternatively the midrange group may be sub-divided into sub-groups of descending average rating for each sub-group. The intermediate layers from second layer to second from bottom layer are then chosen from the descending capacity rating groups in order.

A calculation relating to selective layering combinations was conducted for a three-layer device using the same population of membranes used for Table 1. Because there are three layers, the capacity distribution was divided into three capacity sections (lower, center, and upper), with each section containing an equal portion of the total population.

In what is designated as method A, the top (upstream) layer is selected from the middle portion of the distribution, and the middle layer and bottom (downstream)

layers are selected randomly from the rest of the distribution. In what is designated as embodiment B, the top layer is selected from the middle portion of the distribution, the middle layer is selected from the upper section of the distribution, and the bottom layer is selected from the lower end of the distribution. In what is designated as method C, the top layer is selected from the upper portion of the distribution, the middle layer is selected from the upper section of the distribution, and the bottom layer is selected from the lower end of the distribution. In what is designated as method D, the top and bottom layers are selected as per Figure 7, and the middle layer is selected from the center portion of the distribution.

Table 2 shows the performance variability resulting from the various embodiments. All of the methods are advantageous compared to random layering (the existing state of the art) with respect to either mean capacity, performance consistency, or both. Embodiment B offers the lowest capacity variability, along with low LRV and permeability variability, but with the same mean capacity as random layering. Method D offers the lowest LRV and permeability variability, and has lower capacity variability and higher mean capacity than random layering.

TABLE 2

Layering Strategy	Capacity Mean	Capacity Std. Dev.	LRV Mean	LRV Std. Dev.	Permeability Mean	Permeability Std. Dev.
Random	600	70	10.5	1.04	13.3	0.80
A	600	19	10.5	0.63	13.3	0.53
B	600	19	10.5	1.04	13.3	0.80
C	678	34	10.5	0.63	13.3	0.53
D	678	34	10.5	0.52	13.3	0.45

What is claimed is:

1) A method of reducing performance variability in a multi-layered filtration device including an upstream membrane and a downstream membrane, comprising:

    a) selecting a target performance characteristic value for said device, wherein the target performance characteristic is capacity;
    b) selecting a population of membranes having the same performance characteristic value as said target performance characteristic value, the population comprising two or more batches having membranes manufactured from a particular manufacturing process as having the same performance characteristic value, each batch being characterized and sorted by its
    c) selecting as said upstream membrane, a membrane from one of said batches having a first performance characteristic value or range of values closest to the target performance characteristic value; and
    d) selecting as said downstream membrane a membrane from one of said batches having a second performance characteristic value or range of values; wherein said first performance characteristic value or range of values is lower than said second performance characteristic value or range of values.