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# Outside-in hemofiltration for prolonged operation without clogging

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ABSTRACT

Hemofiltration (HF) is used extensively for continuous renal replacement therapy, but long-term treatment is limited by thrombosis leading to fiber clogging. Maximum filter life is typically less than 20 h. We have achieved for the first time continuous and consistent hemofiltration for more than 100 h using outside-in hemofiltration with the blood flow into the inter-fiber space (IFS). Although thrombi do deposit in the IFS, they have minimal affect on the blood flow and filtrate flux due to the three-dimensional system of interconnected hydrodynamic flow channels in the IFS. Microscopic examination of sections of the fiber bundle showed that deposited thrombi have dimensions about the size of the gaps between the hollow fibers and remain isolated from each other. A simple mathematical model is developed to describe the effect of thrombus deposition on the fluid flow that accounts for the enhanced performance arising from the interconnected flow. The hydrodynamic advantage of outside-in HF decreases at low anticoagulant concentration due to the instability in the blood and the very high volume fraction of thrombi that deposit in the entrance zone of the filter. These results clearly demonstrate the significant potential advantages of using outside-in hemofiltration for long-term renal replacement therapy.



## 1. Introduction

Hollow fiber membranes are employed in numerous applications due to their high membrane packing density (membrane area per unit device volume) and low manufacturing costs. However, fiber clogging can be a major limitation in some systems. The impact of fiber clogging becomes particularly significant when the feed contains a high volume fraction of dispersed particles that can aggregate and adhere to the lumen of the hollow fibers.

Fiber clogging is a particular issue in blood hemofiltration used for removal of fluid and uremic toxins in renal replacement therapy [1]. The pores of hemofiltration membranes have to be sufficiently small to prevent protein loss from blood plasma, while the surface properties of the fiber lumens need to provide high membrane hemocompatibility and minimal thrombosis. However, despite significant advances in membrane materials development, fiber clogging due to thrombus deposition in the fiber lumens currently limits the maximum filter life to 15–40 h in applications of both Continuous renal replacement therapy (CRRT) [2] and hemodialysis [3]. The development of wearable ultrafiltration devices that can effectively prevent hypervolemia in congestive heart failure patients is currently limited by the lack of reliable long-term hemofiltration without filter clogging.

One approach that has been used to minimize fiber clogging in many industrial applications is to use "outside-in filtration". In this case, the feed flows into the inter-fiber space (IFS) of the fiber bundle while permeate is removed through the fiber lumens. Outside-in filtration has been an enabling technology in immersed (or submerged) membrane bioreactors and removal of particulates in water purification, allowing activated sludge with high particulate loadings to be processed for extended periods of time [4,5]. However, these systems use suspended hollow fibers that are free to move, with the fiber surface kept clean (at least in part) by aeration of the fluid in the bioreactor.

The objective of this study was to examine the potential of using outside-in filtration for long-term hemofiltration. The outside-in configuration has been used previously in membrane oxygenators, although in this case the primary motivation was the improved mass transfer characteristics with blood flow outside of the fibers [6]. Limited previous work has shown that this configuration may be attractive in blood microfiltration using hydrophobic membranes (plasmapheresis) [7], but we are unaware of any previous work on outside-in hemofiltration. Initial work was focused on developing a simple mathematical model to describe

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the effects of thrombus deposition on fluid flow in conventional versus outside-in hemofiltration. Experimental studies were performed to demonstrate for the first time successful blood processing in hemofiltration for $>100$ h using the outside-in mode of operation. These results have important implications for the development of improved hemofiltration processes capable of providing long-term renal replacement therapy and in the treatment of hypervolemia in congestive heart failure patients.

## 2. Model development

### 2.1. Simplified model for outside-in hemofiltration

The key advantage of the outside-in configuration is the 3-dimensional and highly interconnected flow path in the inter-fiber space (IFS). Thrombus deposition in intraluminal conventional hemofiltration typically occurs at or near the entrance of an individual hollow fiber, completely blocking the entire length of that fiber leading to a significant increase in the axial pressure drop for flow through the module. Thus, in principle, the deposition of $N$ thrombi (where $N$ is the number of hollow fiber membranes in the module) would lead to complete blockage of the module. In contrast, thrombus deposition in the inter-fiber space will have little effect on the axial pressure drop since the blood flow is able to pass around the blockage as shown schematically in Fig. 1. Deposition of the same $N$ thrombi would occupy only a very small volume fraction of the inter-fiber space, providing minimal disturbance to the blood flow.

The effect of "interconnectivity" on flow has been examined previously in both depth filters [8–10] and membranes [11,12]. Ho and Zydney [11] evaluated the flow distribution around a blockage on the upper surface of a symmetric membrane as a function of the pore interconnectivity, defined as the ratio of the Darcy permeability in the normal and transverse flow directions. Surface blockage on membranes with highly interconnected pores had minimal effect on the total hydraulic resistance to flow (until the upper surface is nearly totally blocked) since the fluid is able to flow around and under the surface blockage as it percolates through the porous structure of the membrane. The same phenomenon occurs in depth filters, with particle blockage occurring throughout the filter but causing relatively little change in the total resistance until the pore space within the filter is very highly plugged [8–10].

In order to obtain additional insights into the effects of thrombus deposition on the fluid flow behavior in conventional and outside-in hemofiltration, a simple mathematical model was developed to describe the axial pressure drop due to flow in the inter-fiber space. We assume that thrombi are mono-disperse with diameter ($d$) approximately equal to the inter-fiber spacing [Fig. 2]. Two limiting cases are examined: (a) uniform distribution of thrombi within the inter-fiber space, i.e., the number of thrombi in any cross-section of the fiber bundle is constant, and (b) preferential clotting near the entrance region of the module.

As discussed by Herzig et al. [8], the pressure drop in a partially clogged bed can be approximated as

$$\frac{\Delta P}{\Delta P_o} = \left(\frac{\varepsilon_o}{\varepsilon}\right)^3 \tag{1}$$

where $\Delta P_o$ and $\varepsilon_o$ are the axial pressure drop and porosity of the initial (unclogged) IFS, and $\varepsilon$ is the porosity of the partially clogged IFS. For a uniform hexagonal array of hollow fibers (Fig. 2), the initial porosity is given as

$$\varepsilon_o = 1-\left(\frac{a}{b}\right)^2 \tag{2}$$

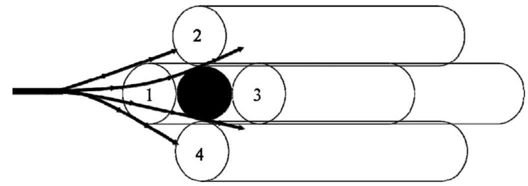


**Fig. 1.** Illustration showing flow distribution around a single thrombus (clot) in the inter-fiber space.

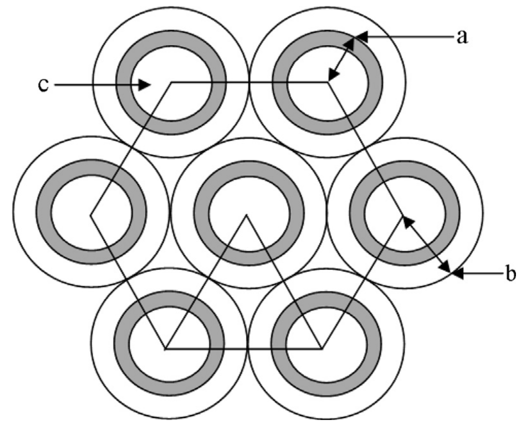


**Fig. 2.** Schematic illustration of a hexagonal array of hollow fibers. (a) external radius of fiber, (b) cell radius around each fiber, and (c) fiber lumen.

**Table 1**
Dialyzers/filters used with key geometric characteristics.

| | | Surface area ($m^2$) | Fiber ID (μm) | Fiber length (cm) |
|---|---|---|---|---|
| Gambro H6 | High flux | 0.6 | 200 | 10 |
| Sorin DHF0.2 | High flux | 0.25 | 200 | 14.5 |
| Fresenius F3 | Low flux | 0.4 | 200 | 20 |
| Minntech HF 400 | High flux | 0.3 | 200 | 12 |
| Spectrum P-D1-030E-100-01N | High flux | 0.0115 | 500 | 20 |
| Asahi Rexeed 15R | High flux | 1.5 | 185 | 33.4 |
| Asahi Rexeed 15LX | Low flux | 1.5 | 185 | 33.4 |
| Minntech Renaflo Mini | High flux | 0.05 | 620 | 15 |

where $a$ is the outer radius of the hollow fiber membrane and $b$ is the radius of the cylinder defined by the mid-point between adjacent fibers. Eq. (2) neglects the "triangular" gap between the fibers. The porosity of the partially clogged IFS is evaluated by simple geometric considerations as

$$\varepsilon = \varepsilon_o\left[1-\frac{2n}{3N}\left(\frac{d}{L}\right)\right] \tag{3}$$

where $n$ is the number of deposited thrombi, $N$ is the number of hollow fibers, $L$ is the fiber length, and $d$ is the diameter of a thrombus, assumed to be equal to the interfiber spacing, i.e., $d=2(b-a)$. A typical hollow fiber hemofilter (see Table 1) has $d=200$ μm and $L=20$ cm, which corresponds to $\varepsilon=0.9993\varepsilon_o$ and $\Delta P=1.002\Delta P_o$ when $n=N$. It would take $n=1500N$ for the porosity of the inter-fiber space to drop to zero (at which point the axial pressure drop would become infinite).

If all of the thrombi deposit in the entrance region of the hollow fiber module ($L_{ent}$), the porosity in this region will be given by Eq. (3) but with $L=L_{ent}$. In this case, the total axial pressure drop is given by the sum of the pressure drop across the entrance length