Evolution of synthetic membranes for blood purification: the case of the Polyflux family

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Introduction

Transport in biological systems is controlled by membranes functioning as barriers between compartments with various degrees of specificity. In 1972, Singer and Nicolson [1] introduced a breakthrough view on structures of cell membranes with their fluid mosaic model. Their findings emerged along colloid chemistry-based organization of hydrophilic–hydrophobic polymer molecules and structures to form the cell membrane. Obviously, these principles also influenced the design of artificial membranes for therapeutic purposes. The general functional features involved in membrane separation processes, whether a natural cell membrane or an artificial membrane, concern either the process or the structure of the barrier, i.e. diffusion and convection of solutes along a pressure or concentration gradient, adsorption to generate a barrier for certain molecules, patch-like or mosaic-like structures to prevent or limit unspecific interaction, short transport channels for fast transport, nano- and micro-dimensions to suppress unspecific interaction and enable selectivity, narrow pore distribution to sharpen cut-off profiles, and optimized cross-filtration flux. In biological organisms, a number of additional functional elements of membranes are applied: active epithelial layers supported by basement membrane structures such as glomerular membranes, confluent tightly connected layers of endothelial cells, and strictly ordered hydrophilic–hydrophobic molecular arrangements in cellular bi-layer membranes. The function of the artificial kidney has relied from the beginning on principles laid down in renal physiology or, later, in biophysical principles in synthetic membranes whose functions were approaching those of the human glomerular membrane. Diffusion and convection predominantly have been combined to achieve the desired blood purification.

Today, haemodialysis is basically divided into two categories: blood purification by low-flux and high-flux dialysis membranes [2–13]. Low-flux dialysis includes the standard haemodialysis technique in which dialysers with low hydraulic permeability are utilized. Blood and dialysate flows are at 250 and 500 ml/min, respectively, and the average duration is 4 h. When dialysate surface area is increased, blood and dialysate flows are increased up to 400 and 800 ml/min, respectively, and the treatment is defined in these circumstances as high efficiency haemodialysis. In this treatment, the clearance for small molecules is remarkably increased and the treatment time can generally be shortened, but the clearance for medium to large molecules is still very low due to the sieving characteristics of the membrane [14–30].

Classic cellulosic membranes such as Cuprophan were typically hydrogel-type low-flux membranes (i.e. permeability to water in the range of 5–6 ml/h × mmHg × m²), strongly hydrophilic and remarkably thin (6–12 μm) to permit an optimal utilization in diffusive transport of water-soluble solutes for treatments such as haemodialysis. On the other hand, classic high-flux synthetic membranes were originally fully hydrophobic, strongly asymmetric and with a wall thickness of 40–60 μm. They were originally employed in convective therapies such as haemofiltration [31] due to their high hydraulic permeability (i.e. 30–40 ml/h × mmHg × m²) and their elevated sieving coefficients.

In a subsequent step, membrane structures have been adapted to fulfil the demand for increased diffusive permeability matched with tailored convective properties. This was achieved by (i) using polymer blends of hydrophilic and hydrophobic polymers; (ii) reduction of the wall thickness; and (iii) structural modifications.
of the membrane morphology and surface. These modifications have permitted their application in new techniques such as high-flux haemodialysis and haemodiafiltration [32–35] in which diffusion and convection are conveniently and efficiently combined.

When high flux membranes are utilized, three different approaches can be chosen.

(i) Haemofiltration is a fully convective treatment in which large amounts of ultrafiltrate are produced and replaced by an ultrapure substitution fluid [36], and no dialysis fluid is present. This technique offers the advantage of excellent clearances for large molecules. The treatment, however, has only been clinically applied in Europe because of the need for large quantities of substitution fluid in commercially prepared bags or in continuous therapies for acute renal failure (e.g. CVVH).

(ii) Haemodiafiltration is a form of therapy in which diffusive and convective transport occurs simultaneously. Dialysate is circulated countercurrent to blood, but the amount of ultrafiltration exceeds the programmed patient weight loss, and therefore the final fluid balance is achieved by the infusion of appropriate amounts of substitution fluid in the arterial or venous line [37–39]. This allows different modes, i.e. pre- or post-dilution. Due to high costs related to replacement solutions, new approaches have been proposed in Europe for performing haemofiltration and haemodiafiltration [40–42]. Part of the fresh dialysate is diverted from its line to the dialyser, is filtered and finally used as an ultrapure replacement solution. These on-line treatments have the advantage of reduced costs, unlimited production of substitution fluid and no need for commercially prepared fluids in bags. On the other hand, the microbiological and chemical purity of the on-line produced fluid may represent a concern since no on-line controls can be made; however, advanced bioanalytical assessment and increasing clinical experience indicates high fluid quality of on-line processed substitution/infusion fluids.

(iii) High-flux dialysis is a technique in which highly permeable dialysers are utilized in conjunction with an accurate ultrafiltration control by the dialysis machine. Because of the nature of the hollow fibre dialyser, the correct fluid balance is achieved thanks to an internal filtration in the ‘proximal’ part and a backfiltration in the ‘distal’ part of the filter [43]. As a consequence, some of the advantages of removing larger molecules are maintained because of the internal convection, while the need for replacement solution is avoided by a significant amount of backfiltration of fresh dialysate in the ‘distal’ part. In this way, some of the advantages of haemodiafiltration are maintained with a simpler and easier layout of the technique [43]. Again, the dialysate purity is a key issue in this treatment where bacterial products could be backtransported into the blood together with the reverse flux of water. This may affect the entire concept of biocompatibility of the system. However, synthetic membranes prepared from hydrophilic–hydrophobic blends have been shown to act in contrast to cellulosic materials as an adsorptive barrier against bacterially derived products from the dialysate. Concerning this aspect, great efforts have been made in improving the quality of the polymeric materials to better serve biological requirements [44,45] needed for dialysis membranes and at the same time of the water treatment systems [46,47].

Structure and composition

From basic mass transport equations [48], key structural membrane features affecting convective and diffusive transport of solutes from blood into the dialysate compartment can be identified. The most relevant membrane parameters are pore radius, surface porosity and membrane thickness. Besides these, a number of other parameters control mass transport through the membrane. The sieving coefficients during convective therapies of a membrane are governed substantially by the number of pores, their size and distribution in the innermost selective membrane layer.

Membranes can be divided into different categories, i.e. according to their chemical composition, structural design and pore conformation. The final membrane morphology, their hydraulic and diffusive permeability, sieving characteristics and fluid interaction (at the blood–membrane and dialysate–membrane interface) depend on the manufacturing techniques applied as well as the polymer composition chosen. Nearly all dialysis membranes are prepared by diffusion-induced phase separation. Here the solute sieving coefficients are tailored by the speed/kinetics of the phase separation and the different process parameters, e.g. temperature, polymer composition and precipitation fluid composition. Under different conditions, the geometrical structure of the membrane can become finely sponge-like or finger-type, and the porous structure can become nano- or micro-porous. The membrane formation process also allows creation of different layers in the membrane cross-section with specific functional, and therefore advantageous, clinical properties: (i) the internal skin layer providing a selective sieving barrier for solutes; (ii) the inner structure offering mechanical strength and resistance/stabilization of the pore conformation during sterilization procedures; and (iii) the external layer with barrier characteristics for endotoxin retention/adsorption (Figure 1).

The case of the Polyflux membrane

The Polyflux membrane family represents a series of membranes originally derived from the synthetic polymer polyamide. The ‘parent’ membrane was developed in the late 1970s/early 1980s to serve best
in the requirements for haemofiltration therapy. A strongly asymmetric membrane structure was chosen. In the next step of evolution of the Polyflux membrane family, diffusive transport characteristics were enhanced to enable haemodiafiltration, by blending the hydrophobic polymer with hydrophilic polymer systems [34,49,50]. The challenging problem in manufacturing such membranes was to make reasonable predictions early in development for the selection of efficient technologies to allow high precision and large-scale technology, including full device sterilization after packaging and suitable device designs.

The strategies involved in applied to the membrane optimization include (i) the selection of polymer materials compatible with being blended, and resistant to mechanical stress and sterilization procedures; (ii) definition of surface characteristics providing hydrophilic–hydrophobic domains in the range below 50 nm [51,52] to balance minimal activation of blood components; (iii) a membrane formation process creating an asymmetric three-layer structure enabling a selective functional barrier and maximal permeability; and (iv) the application of specific process technology for precise production and accuracy of the micro- as well as the nano-structure design, i.e. pore size and conformation.

The selection of suitable polymer systems must cope with the increasing clinical requirements, including sterilization methods as alternatives to ETO, i.e. steam and gamma; permeability for middle molecules, but preventing albumin loss for optimized selectivity in high volume exchange therapy modes; limiting complement and subsequent white blood cell activation; and minimal induction of the coagulation cascade.

The Polyflux membrane [34,49,50] is a blend of polyamide [53], which provides endotoxin retention [54,55] due to the hydrophobic sites and improved biocompatibility due to minimal interaction with blood components; polyarylethersulfone, which provides mechanical strength and resistance to heat sterilization; and finally PVP, i.e. polyvinylpyrrolidone frequently applied in pharmaceutical formulations, which

Fig. 1. Scanning electron micrograph of the cross-section of a Polyflux S membrane and further magnifications of the inner selective layer showing the actual granular separation structure. The cross-section of a Polyflux (high-flux) membrane clearly allows identification of its novel three-layer structure. The three layers are defined as follows. (i) Inner selective layer: shows a narrow size distribution and is responsible for the separation of different molecules based on size exclusion. The narrow size distribution is responsible for the selectivity of the separation. This layer has a thickness of ~0.1–0.5 μm. (ii) Support layer: the inner selective layer is supported by a more open membrane structure, which has the function of stabilizing the membrane. This layer has no sieving function and a thickness of ~2–5 μm. (iii) Finger-type structure: layers (i) and (ii) are surrounded by a very open ‘finger-type structure’, which gives additional mechanical stability. Due to the high void fraction of this layer, the diffusive resistance in this part is identical to that in water. This layer has a thickness of ~40–45 μm and presents an external skin with hydrophobic domains.
contributes to the hydrophilic domains in the surface and the enhanced diffusive permeability (Figure 2).

Separation performance of a membrane strongly depends on (i) the structural characteristics of the active separation layer; (ii) the overall morphology of the membrane wall; and (iii) the chemical composition of the membrane, i.e. polymeric materials (blend) used to manufacture the membrane and their distribution across the hollow fibre geometry. To allow optimized mass transport and a high selectivity, a unique structure is required. In this context, the basic design reasoning was to opt for a strongly asymmetric three-layer structure providing the smallest pore size directly at the interface with the blood compartment (Figure 1). For membranes used in extracorporeal devices for blood purification, an additional set of performance characteristics is required, i.e. low protein adsorption as an intrinsic condition to reduce unspecific and unwanted blood–membrane interaction, and enabling high biocompatibility from a general perspective. The Polyflux membrane family, irrespective of whether tailored to high- or low-flux properties, has a typical three-layer structure, as depicted in the scanning electron micrograph in Figure 2, which is designed to allow optimized convective and diffusive mass transport in combination with an excellent biocompatibility.

The membrane formation process allows tailoring of the morphology of the membrane wall, which has an effect on the convective performances of the membrane. In particular, it is important to analyse the specific composition of each layer in relation to the polymeric composition of the blend. If a greater fraction of PVP is present, the hydrophilic nature of the membrane might be enhanced, and so is diffusion. This is indeed the case for the inner skin layer of the Polyflux membrane where a tailored composition contributes to an increased permeability to middle molecular weight solutes and a remarkable selectivity with restriction of the passage of albumin. If polyamide prevails in the studied layer, hydrophobic domains will contribute to the adsorption characteristics and the creation of a functional barrier to endotoxin from the potential bacterial dialysate contamination (Figure 3).

In all these considerations, in fact, one important feature of the membrane is its interaction with water. Original high-flux membranes were almost completely hydrophobic and this caused some unwanted effects in terms of protein interaction and low diffusivity. Modern synthetic membranes have been modified so as to achieve a higher degree of interaction with water and more hydrophilic characteristics. This was achieved by addition of PVP as a strongly hydrophilic
component to the polymeric blend. During the manufacturing process, PVP polymer chains are entangled in the polymeric network and become an integral part of the membrane, and extraction of the single compound becomes almost impossible. In particular, the composition of the membrane at the interface with blood represents the crucial issue for biocompatibility and mass transport efficiency.

From the above observations made during the evolution of this membrane family, it appears evident that the inner layer of the membrane is probably the most important structural component, and its surface governs the interactions with plasmatic and cellular blood components to a major degree. In particular, careful attention has been paid to ensuring the smoothness of the surface and its chemical modification, with creation of hydrophilic–hydrophobic microdomains synergizing to balance minimal activation of blood components.

Direct and indirect methods to characterize chemical heterogeneity of the surface and the microdomain concept have been applied, including selective staining of hydrophilic compounds for backscatter scanning electron microscopy, contact angle hysteresis measurements and atomic force microscopy using different detection modes. The latter is also used in low force tapping mode to study the surface roughness and the porosity/pore distribution of the active separation layer of the membrane. In Figure 4, a typical atomic force micrograph (tapping mode) of the inner surface of a Polyflux high-flux membrane (scan size: $5 \times 5 \mu m$) is demonstrated.

Mathematical integration of the data allows calculation of the difference between the highest and lowest spot (Rz) of the area analysed and two average roughness parameters. The following data were obtained for Polyflux membrane: $Ra = 4.9 \text{ nm}$, $Rq = 6.3 \text{ nm}$ and $Rz = 68 \text{ nm}$. Such roughness analysis has also been carried out for other membranes and previously reported in the literature, and it represents an important means to describe the smoothness of the interface with blood [57].

To study the pore size distribution of nanoporous polymeric membranes, a whole group of analytical techniques are available. However, depending on the technique and the assumptions behind this technique, different sets of data can be obtained. From the analysis conducted using permporometry,
specific statistical distribution curves can be obtained (Figure 5), which finally allow predictions on the impact on hydraulic permeability and sieving coefficients.

Sieving data for single components or sieving curves for mixtures of substances with different molecular weight allow characterization of the width of the pore, size distribution or the sieving properties under defined conditions. Typical sieving curves for the high- and low-flux Polyflux membrane types are shown in Figure 6. However, not only pore size distribution is important for the final membrane performance, but also the density of pores (number per unit of surface), pore length and tortuosity.

Of the different factors determining water permeability and high sieving capacity, pore size has the largest impact. Small increases in pore size have large effects on water permeability. A high degree of membrane porosity is characterized by more pores per unit of surface area and less pore tortuosity.

‘Opening-up’ the membrane structure would increase large solute permeability, but the detoxification process in haemodialysis is based predominantly upon size exclusion (i.e. sieving characteristics of the membrane), and increasing the mean pore size alone is insufficient and possibly harmful (i.e. leakage and loss of useful substances from blood into the dialysate). Basically, a maximal opening of the pores such as to achieve maximal removal of large molecules would be ideal, but this should be obtained in conjunction with a sharp cut-off in the range of molecular weight such as to exclude albumin leakage.

These aspects have been accomplished in the past partially as a result of a specific manufacturing condition particularly related to the choice of the polymer and the composition of the polymeric blend, process conditions, temperature, drying and sterilization. Today, a more accurate and precise control of the innermost layer of the membrane and its porosity and surface can be achieved thanks to the recently emerging and technically applied nano-technologies [57–59]. The application of new technology principles to define, more specifically, the key (pore-related) parameters that influence water and solute permeability is made possible by progress in the understanding and control of the chemical engineering at the nano-scale level. In general, the term ‘nano-technology’ defines the usage of any technology and processes to produce features reproducibly at the nanometre scale, e.g. thin films, fine particles, chemical synthesis on chips with high lateral resolution, advanced micro-lithography, etc. This allows for molecular manufacturing processes, i.e. the creation of a surface and structure modification of the membrane controlling geometry and distribution of the pores of the innermost surface at the nano-scale level. This also includes adaptation of the spinning conditions, improved design of spinning nozzles and finally results in a more homogeneous polymer solution mixing, refined precipitation conditions, change of defined pore structure of the thin inner ‘skin’ region, fibre dimensions (i.e. optimal internal diameter in

Fig. 5. Pore size distribution (schematically) for a low- and high-flux membrane. Hydraulic permeability is governed by the equation described at the top where: $K_f$ is the hydraulic permeability, $n$ is the number of pores, $r$ is the pore radius, $\tau$ is pore tortuosity, $\mu$ is viscosity of the filtrate and $\Delta x$ is the membrane thickness (pore linear length).

Fig. 6. Sieving curve of Polyflux (high- and low-flux) membranes determined using an aqueous polydisperse dextran solution.
relate to wall thickness) and optimized fibre structure for enhanced mass transfer, e.g. ‘wavy’ fibres. A further control is exerted on pore density and tortuosity with reduction of mass transfer resistance and improvement in selectivity of transport characteristics.

All these manufacturing processes controlling structural features on the nano-scale result in fact in a new generation of membranes with high selectivity of mass transport characterized by maximal permeability and minimal albumin losses, and thus actually approaching a remarkable similarity to the functional properties of the glomerular filtration step.

**Membrane function in clinical practice**

The technical and biophysical characteristics of membranes affect the permeability characteristics observed in the clinical setting, although the operational characteristics of the treatment are often the most important variable. In particular, hydraulic permeability and sieving properties of membranes are strongly determined by blood flow conditions and blood composition. Membranes, as they should work as barriers, tend to interact with proteins. However, when low blood flows are present, the protein interaction at the blood–membrane interface tends to be greater. This is due mainly to a lower velocity gradient between blood and the fibre wall (wall shear rate). This lower shear effect will result in thicker boundary layers of proteins and greater concentration polarization. This effect will in turn result in lower hydraulic permeability and lower observed sieving coefficients. Wall shear rates are also affected by blood viscosity, haematocrit and plasma protein concentration. There is, for example, a lower flow velocity in peripheral fibres of a haemodialyser when blood viscosity is higher. All these problems are enhanced when high filtration fractions are obtained in hollow fibre haemodialysers. High filtration fractions result from increased filtration rates at a given plasma flow. This is the case when low blood flows are present in the system and convective therapies are prescribed with excessive ultrafiltration rates. This unphysiological condition is deleterious for the hollow fibre, which becomes progressively clogged and displays a reduction in permeability and sieving coefficients. Considering this, convective therapies should be performed only when blood flows are sufficiently high or in the case of large amounts of pre-dilution.

Haemodialysis membranes do not remove solutes by filtration or diffusion alone. Adsorption is an additional mechanism that may contribute to the final amount of solute removal. The effect of adsorption strongly depends on the nature of the membrane, i.e. materials used to manufacture the membrane. In synthetic membranes, not only can solutes interact with the inner surface of the membrane, but they can be adsorbed onto the supporting external membrane layer. This external component probably does not affect the net solute removal since the adsorbed molecules would have gone in the filtrate anyway. This external membrane structure, however, is responsible for retaining molecules which cannot be found in the filtrate, making the calculation of sieving coefficients or direct dialysate quantification methods worthless in accounting for solute removal. The typical case occurs with β2-microglobulin, in which sieving coefficient measurements are extremely fallacious. Synthetic membranes differ from each other with respect to protein adsorption. New membrane generations prepared from hydrophobic/hydrophilic electrically neutral polymers show very low values for protein adsorption [60, 61].

However, adsorption appears to become an important issue for removing endotoxin and other bacteria-derived products from the dialysate compartment during fluid filtration. This mechanism in fact not only permits avoidance of the dangerous effects of backfiltration with contaminated solutions, but it is also used for repeated filtration of dialysate to obtain ultrapure fluid for reinfusion/substitution. Based on this concept, on-line haemofiltration and haemodiafiltration today are performed with a remarkable degree of safety and clinical tolerance. The problem is mainly that of ensuring a continuous quality control and redundant efficiency so that any accidental rupture or membrane leakage can be overcome by a subsequent stage of dialysate filtration. Further degrees of safety can be provided by an on-line system using a third step filtration in a specific ultrafilter validated for endotoxin and bacterial retention.

**The membrane and the haemodialyser design**

The membrane cannot be considered as a single entity and simply as a biomaterial. It is the barrier for solute separation processes and it may perform very differently depending on the device in which it is employed [62–70].

For this reason, the membrane should be seen as a component in a more complex therapeutic system which includes the blood compartment and the dialysate compartment.

The blood compartment of an ideal haemodialyser should be characterized by the compromise between a low priming volume and a maximal blood–membrane contact surface [60]. The hollow fibre design has certainly contributed to achieving better results compared with the flat sheet configuration. The blood ports, considered for many years simply as arterial and venous ends of the unit, today represent sites of great importance. The arterial port must have a minimal stagnation of flow and it should guarantee a homogeneous distribution of blood flow in all the fibres of the bundle. For this purpose, different types of flow distributors have been proposed (conical, spiral, etc.) with reduced space between the cap and the potting. No dead spaces or irregularities in the internal surface should be present. All these features should be accompanied by an accurate cutting of the fibres to (i) prevent
any collapse or accidental obstruction of the fibre internal lumen and (ii) create a smooth surface to reduce cell activation. The sterilization procedure may be critical in preserving the structure of the polyurethane utilized for the potting.

The length and the number of fibres in a dialysiser characterize the hydraulic resistance of the filter at a given blood flow. In treatments utilizing high rates of convection, filtration pressure equilibrium may occur along the length of the filter. As blood moves through the filter, water is removed by filtration, and haematocrit and plasma protein tend to increase. As a consequence, the oncotic power/pressure of plasma proteins becomes as high as the internal hydrostatic pressure, and filtration ceases. This phenomenon causes possible disturbances/inconvenience in the distal part of the filter where a highly viscous blood is flowing inside the hollow fibres. An accelerated rate of clotting or alteration in flow distribution may occur under such circumstances. Today, with the increased average haematocrit up to 35% due to the broad and common use of erythropoietin to correct anaemia, all dialysers are forced to operate under conditions of highly viscous blood. As a result, the entire system may be affected and it may be likely that peripheral fibres operate with much lower flows compared with the central fibres of the bundle. This results in lower velocity gradients at the blood–membrane interface (low wall shear rates) and less than optimal operational conditions of those fibres, including prolonged contact time, which is thought specifically to cause clot propagation.

To adapt the hydraulic resistance of the haemodialysers to the different operational conditions and the different treatment techniques, hollow fibres with different inner diameters have been designed. In an attempt to reduce the blood compartment resistance, the inner diameter has been increased in some filters from 200 to 250 µm [63]. These filters have been used mostly in arterio-venous circuits, as well as in patients treated with continuous renal replacement therapies. In filters for babies or neonates, the inner diameter has been increased up to 500 or even 1000 µm [64]. The reason for these approaches has been to attempt to reduce the rate of obligatory filtration at a given blood flow. In other words, because of a lower resistance, these filters permit higher blood flows at a given arterio-venous pressure gradient (in arterio-venous circuits) and they present a lower internal pressure drop in the presence of a pumped extracorporeal circuit with a consequent lower rate of obligatory filtration. Obligatory filtration depends on the pressure generated inside the filter: at a constant venous pressure, the higher the resistance of the filter, the higher will be the pressure drop in the filter and the higher will be the pressure at the inlet of the filter. As a consequence, the average pressure in the blood compartment will be higher and so will the filtration rate at a given blood flow and venous pressure [65,66].

The opposite approach has been suggested in an attempt to maintain very high wall shear rates and to increase the obligatory filtration. This has been obtained reducing the internal diameter down to 175–185 µm [67]. In these circumstances, at a similar number of fibres, the cross-sectional area of the filter will be reduced and the average flow velocity per fibre will increase. At the same time, the pressure drop in the blood compartment will significantly increase. With the use of dialysis machines with accurate ultrafiltration control systems, this will result in higher rates of filtration–backfiltration at a given net filtration rate. This will increase the convective component of the transport, without requiring replacement fluid reinfusion as in the case of haemodiafiltration. A similar approach has been proposed recently by placing a constriction ring around the fibre bundle in the mid-segment of the dialysyer, with the aim of increasing the pressure drop both in the blood and in the dialysate compartment [65] (technically not applied yet in regular dialysis). However, from the bio-engineering point of view, it is obvious that membrane configuration and device design can be fine-tuned to optimize performance further.

The design and the construction of the dialysate compartment is of major importance for the performance of a dialysyer. Several attempts have been made in the past to improve the housing design (including dialysate distribution) and the fibre distribution to optimize mass transport. Some modifications have been introduced over the years such as the position of the Hansen connectors in the case (same side or opposite side). Initial studies on solute clearances at different dialysate flows demonstrated that by increasing dialysate flow over a certain limit (600 ml/min) with standard dialysers, the clearance of small molecules could be negatively affected [9]. This effect was attributed to a channelling phenomenon that was creating a preferential flow of dialysate in the region external to the bundle with consequent stagnation in the internal region of the haemodialysyer. The first attempt to reduce this phenomenon was the application of an ‘overflow’ ring internal to the case, to force the dialysate flow into the internal regions of the bundle. Other types of distributors were designed for this purpose, achieving an improved performance of the dialysyer at higher dialysate flow rates. More recently, studies on flow distribution have pointed out the importance of the bundle design per se [68–71]. First of all, the density of the fibres inside the case affects the resistance to dialysate flow and may contribute to a variable distribution of dialysate flow within the fibres. Furthermore, the phenomenon of ‘packing’ of the fibres is responsible for an inhomogeneous distribution of the flow and possible stagnation in various segments of the bundle. The final effect of stagnation may be the reduction of the gradients for diffusion. However, another condition in which the gradient for diffusion is reduced is when high convective rates are utilized in haemodiafiltration. Under such circumstances in fact, ultrafiltrate is transported on the other side of the membrane with a solute concentration similar to that of plasma water. This will result in similar solute...
concentrations on both sides of the membrane, and diffusion ceases. The phenomenon is aggravated further if fresh dialysis solution is not flowing homogeneously on the dialysate side external to the fibres washing away the ultrafiltrate. In these conditions, stagnation will occur and the performance of the haemodialyser will be negatively affected.

To prevent this phenomenon, at least three techniques have been applied [68,71]. The first consists of the placement of space yarns between the fibres to create a better distribution path of the dialysate solution. In the second technique [71], a special fibre crossing with a certain angle is applied during bundle formation to obtain even dialysate distributions. The third method is the creation of the so-called 'Moiré structure' which consists of a waved shape (undulation) of the hollow fibres that prevents the packing of the fibres and maintains the dialysate path open in the entire cross-sectional area of the bundle. In the Polyflux family, waved fibres are additionally crossed and, by combining these two steps, a three-dimensional network guarantees stable and high mass transport rates in the whole bundle (see Figure 7). Not only is a homogeneous distribution of the flow obtained with these approaches, but significant increases in solute clearances can also be achieved.

In conclusion, the membrane structure and material certainly affect the performance of the haemodialysis process. When high convective rates are prescribed, high-flux synthetic membranes must be utilized. Their performances are strongly affected by several factors other than the original material, such as geometry of the haemodialyser and hollow fibre design. Thanks to the improved design and membrane characteristics, newer treatments such as on-line haemofiltration and haemodiafiltration can be easily performed. Higher convection rates will permit us to understand the effective benefit of convection over diffusion, without facing the limitations imposed in the past by the inadequate technology available.

References
The Polysulphone family of synthetic membranes

34. Floege J, Granolleras C, Smeyl B, Goehl H, Koch KM, Shaldon S. Hydrophilic high-flux polysulphone membranes are more efficient for beta-2-microglobulin (b2m) removal than hydrophobic polypamide membranes. *Abstracts ASAIO* 1987; 40
41. Ledebo I. Development to supply endotoxin-free dialysate and substitution fluid. *Artif Org* 1993; 17: 397


70. Ronco C, Bowry SK, Brendolan A et al. Hemodialyzer: from macrodesign to membrane nanostructure; the case of the FX-class of hemodialyzers.