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REVIEW

Review of Membrane Separation Models and Technologies: Processing Complex Food-Based Biomolecular Fractions

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Abstract

There is growing interest in the food industry to develop approaches for large-scale production of bioactive molecules through continuous downstream processing, especially from sustainable sources. Membrane-based separation technologies have the potential to reduce production costs while incorporating versatile multiproduct processing capabilities. This review describes advances in membrane technologies that may facilitate versatile and effective isolation of bioactive compounds. The benefits and drawbacks of pressure-driven membrane cascades, functionalized membranes and electromembrane separation technologies are highlighted, in the context of their applications in the food industry. Examples illustrate the separation of functional macromolecules (peptides, proteins, oligo/polysaccharides, plant secondary metabolites) from complex food-based streams. Theoretical and mechanistic models of membrane flux and fouling are also summarized. Overcoming existing challenges of these technologies will provide the food industry with several attractive options for bioprocessing operations.

Keywords Membrane filtration · Downstream processing · Fouling · Electrodialysis · Ultrafiltration · Bioactive molecules

Abbreviations

BSA	bovine serum albumin
EDR	electrodialysis reversal
EDUF	electrodialysis with ultrafiltration membranes
LCD	limiting current density
NF	nanofiltration
PES	polyethersulfone
UF	ultrafiltration

Introduction

Membrane filtration is a promising technology for process-scale separation and purification of biomolecules in several diverse industries. The replacement of traditional modes of commercial-scale separation such as chromatography with membrane-based approaches has distinct advantages. Not only are membrane approaches amenable to continuous downstream processing of bio-based products, but they can afford lower operational expenses and safer operation at lower pressures (Zydney 2016). Pressure-driven membrane separations including ultrafiltration (UF) and nanofiltration (NF) are key non-destructive approaches for processing in several applications such as water treatment, paper/pulp production, fertilizer, petroleum, textile and food industries. The applications discussed in the present review are limited to food processing.

The ability to generate functional food ingredients from under-utilized natural sources is an attractive, timely and opportune area of research and development, though it still presents challenges to food ingredient manufacturers because of the complex, heterogenous nature of these materials. Biovalorization processing can be accomplished via (i) large-scale pre-treatment of biological materials, (ii) extraction or isolation of compounds of interest, (iii) separation of molecular fractions, (iv) purification of compounds of interest and (v) incorporation into food/nutraceutical product formulation (Galanakis 2015). Membrane filtration can be a valuable tool for these processing steps to target the enrichment of specific compounds from food-based matrices (Galanakis 2015; Pouliot 2008), with multiple therapeutic and nutraceutical applications (Picot et al. 2010). The capacity to separate biomolecular fractions from these feedstocks based on their

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physicochemical properties such as charge, molecular weight or monomer composition can aid in the development of bioactives and functional foods.

Although membrane technologies offer potentially high separation speed and throughput, the accumulation of solute molecules at the membrane surface, termed fouling, is a major hindrance that has limited their widespread application (Song 1998). Fouling is especially concerning for application of membrane separations in complex food-based feed solutions. To overcome this, the present review highlights theoretical models which form the basis of current and potential innovative developments in membrane-based separations to enhance fractionation/purification of complex matrices with relevance to the food industry. Additionally, current use of membrane-based separations is largely limited to fractionation on the basis of molecular weight, restricting selective separation in downstream processing of complex substrates. This review describes several approaches to improve upon these constraints to enhance selectivity and throughput of membrane processing for applications in food-based systems.

Membrane Filtration Vs. Chromatography

Given their high selectivity and versatility, chromatographic approaches are generally favoured at both the analytical and industrial scales for complex separations. Industrial-scale monolithic (Jungbauer and Hahn 2008), counter current (MacKe et al. 2012) and ion exchange (Hahn et al. 2016) chromatography approaches are used extensively in high-valued biopharmaceutical applications involving separation of biomolecules. However, in addition to high capital and operational costs, traditional chromatographic approaches suffer from low diffusion rates (mass transfer) for macromolecules and ultimately provide low throughput. While offering higher selectivity, chromatographic approaches also tend to require additional steps, either pre-separation (solvent evaporation, sample filtration) or post-separation (solvent removal or exchange) which also adds to their drawbacks. Membrane-based separations offer a complementary approach to overcome these limitations. Membrane filtration processes require inherently lower capital costs, and they are relatively insensitive to diffusional resistance of macromolecules and can be easily scaled to high flow rates, affording improved throughput for bulk processes (Lightfoot et al. 2008). Contrasting with the batch form inherent to chromatographic approaches, membrane-based processing also affords the potential for continuous operation (Lightfoot et al. 2008). While it is recognized that even the most efficient filtration unit cannot provide the selective separations inherent to high-efficiency chromatographic columns, enhanced selectivity can be gained by employing multiple membrane separation modules, also known as multistage filtration or membrane cascades. The use of functionalized membranes (e.g. charged or permselective) can also enhance membrane selectivity (Mehta and Zydney 2005). Another approach to improve the selectivity involves electrodialytic separations using UF membranes, which function under an applied electric field to separate compounds based on their charge. Electrodialysis approaches are gaining in popularity, especially in food applications to separate charged species (Firdaous et al. 2009). These and other membrane-based technologies will be discussed in detail in this review, highlighting their potential for efficient separation and recovery of biomolecules from food or natural products.

Membrane Separation Efficacy and Fouling: Mechanisms and Modelling

UF and NF are generally pressure-driven processes by which the desired macromolecular solutes are selectively separated from other impurities through a membrane. Efficiency of these processes is determined by the fraction of material that passes through the membrane, known as permeate flux or flux through the membrane. Various theoretical models have been presented that provide a fundamental understanding of the factors that govern permeate flux across filtration membranes. These models therefore form the basis for designing improved filter-based separation platforms.

Permeate Flux and Solvent Permeability

The hydraulic permeability coefficient (L_p) is a term used to describe the magnitude of the solvent flux (typically water) through a porous membrane. It can be described mathematically as follows:

$$L_p = \frac{\varepsilon r^2}{8\mu\delta_m} \quad (1)$$

where ε is the membrane void fraction (the ratio of volume occupied by open pores in the membrane), δ_m is the membrane thickness, μ is the solvent viscosity and r is the average radius of the membrane pores, which is generally larger when selecting higher molecular weight molecules. Based on this equation, several filtration parameters can be modified to increase permeate flux and thereby improve performance. For example, the permeability coefficient is influenced indirectly by temperature as it, in turn, relates to viscosity. The viscosity of water decreases threefold as temperature increases from 4 to 50 °C (Etzel and Arunkumar 2009). As a consequence, higher membrane performance can be observed at elevated temperatures (35 to 40 °C) (Cissé et al. 2011; Sun et al. 2011). Unfortunately, beyond a threshold (~ 50 °C), higher temperatures are generally unsuitable for biomolecular

processing, as they tend to be thermally labile. The viscosity of high-concentration protein solutions can be decreased by adding co-solutes such as histidine and trehalose (to disrupt intermolecular interactions), which improved permeate flux across UF membranes (Hung et al. 2016). Similarly, thinner membranes (low δ_m) or those with higher pore density (high ε) can improve membrane performance. For instance, the increase in porosity gained from the controlled chemical degradation of a polystyrene membrane (26% weight decrease) was shown to result in a 67% increase in flux across a broad pH range (Shevate et al. 2018).

Solute Behaviour and Gel Polarization

Membrane filtration can be employed with a goal of isolating smaller molecular weight species from the feed as they pass through the membrane and are collected in the permeate. Alternatively, filtration also enables the enrichment and collection of desired macromolecules in the retentate. In both cases, as more feed is processed, the flux through a membrane will be impeded by molecules in the feed solution, particularly at high solute concentrations. During a membrane filtration process, as pressure drives solvent through the membrane pores, a fraction of the permeable (low molecular weight) solute will pass through (C_p). Simultaneously, solute molecules will accumulate on the surface of the membrane as it is a bottleneck (Fig. 1) (Song 1998). Thus, the solute concentration is highest at the wall (C_w), and the concentration decreases with increasing distance from the surface (wall) of the membrane to the bulk (feed) solution concentration (C_b). The distance from the membrane surface, at which the concentration of the solutes reaches that of the bulk feed (C_b), is referred to as boundary layer thickness (δ) (Fig. 1). This change in solute concentration results in the emergence of concentration gradients at the membrane–solvent interface

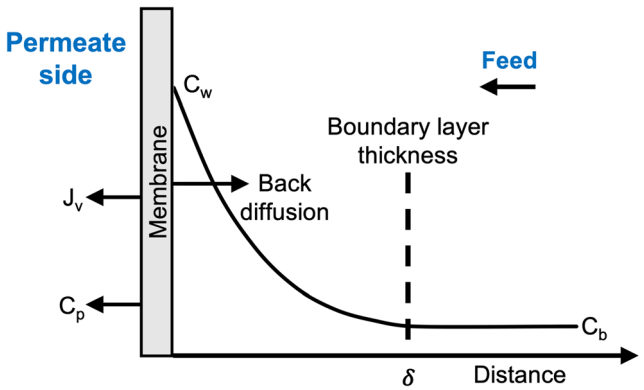

Fig. 1 Schematic diagram of solute transport across a membrane boundary of thickness (δ) via convection and diffusion (adapted with permission from Etzel and Arunkumar 2009, Copyright 2009 [Wiley and Sons]). The x-axis indicates the distance from the membrane surface, and the y-axis indicates the concentration of solute

which is termed concentration polarization or gel polarization. Filtrate flux (J_V) is derived from the stagnant film model (Zydney 1997)

$$J_V = kln\left(\frac{C_w - C_P}{C_b - C_P}\right) \tag{2}$$

where k is the solute mass transfer coefficient, which is the ratio of the diffusion coefficient of solute to the boundary layer thickness ($k = D/\delta$). Based on Eq. (2), flux across the membrane (J_V) can be improved by enhancing the back-diffusion process, i.e. improving the mass transfer between the boundary layer of solute (on the membrane surface) and bulk solution/feed. Hung et al. (2016) were able to use this approach with the help of co-solutes to significantly improve flux across UF membranes for protein solutions. Co-solutes such as histidine and imidazole reduce the attractive protein–protein interactions that hold together the boundary layer of protein on the membrane surface, thereby improving mass transfer between the bulk feed and membrane wall (Hung et al. 2016). Similarly, changing feed pH has been shown to suppress intermolecular interactions and improve permeability (Ma et al. 2016).

Membrane Selectivity

In addition to solvent permeability and solute behaviour, membrane selectivity is a major factor that influences filtration performance. Selectivity of membranes is quantified using sieving coefficients (Mehta and Zydney 2005). The observed sieving coefficient is a fundamental measure of filtration performance and can be defined as

$$S_o = C_p/C_b \tag{3}$$

where C_n refers to solute concentration in the permeate (p) or in the bulk feed (b). Selectivity (ψ) between multiple solutes during membrane separation is the ratio of their sieving coefficients

$$\psi = S_{o1}/S_{o2} \tag{4}$$

where S_{o1} and S_{o2} are the observed sieving coefficients of the less and more retained biomolecular fractions, respectively (Mehta and Zydney 2005). It is important to note that sieving coefficients are not physical properties of the solutes but rather are process-dependent. Therefore, process parameters can be varied to tailor the selectivity of the membrane. Modification of the membrane surface has been shown to increase selectivity (Kasemset et al. 2017). Selectivity has been demonstrated to be inversely correlated to membrane permeability (Kasemset et al. 2017). This selectivity–permeability tradeoff was observed during the separation of bovine serum albumin (BSA) with different membranes (Ma et al. 2016). In this

study, selectivity during separation was successfully tuned by modifying the feed pH, which can modulate interactions between the solute and the membrane surface, along with the solute intermolecular interactions described earlier (Ma et al. 2016). Additionally, membrane selectivity and permeability are affected by the pore structure (Ma et al. 2016). Application of highly porous membranes enabled Shevate et al. (2018) to overcome the traditional permeability–selectivity trade-off.

Membrane Cascades: Improved Selectivity

Gunderson et al. (2007) used a combination of membrane modules called diafiltration units to influence flow conditions of the solvent. Diafiltration is the simplest form of membrane cascade (Fig. 2a) and involves two stages. Solute concentration in the bulk (C_b) and membrane wall was reduced by dilution of the feed stream, thereby increasing global selectivity (via increased S_o values) and enhancing separation (Fig. 2) (Gunderson et al. 2007). The first stage (Fig. 2a (1)) is selectively permeable to low molecular weight solutes, while the second downstream filter (Fig. 2a (2)) is permeable only to the solvent (Gunderson et al. 2007). Diafiltration units can form an important component of a cascade process as a means of removing low molecular weight impurities while simultaneously facilitating solvent recycling. For instance, a two-stage ceramic ultrafiltration cascade was successfully used to recover (~97%) and purify bromelain from crude pineapple wastes (Nor et al. 2016).

In ideal cascades, transmembrane fluxes at each membrane module is distinct as a result of differences in partitioning of the components of the feed solution into permeate and retentate fractions. The number of stages in a membrane cascade relates to enhanced separation efficiency, as does the manner in which the permeate/retentate streams within the cascade are directed (in terms of optimized flow rates, transmembrane pressure) (Caus et al. 2009; Lightfoot et al. 2008; Mayani et al. 2010). Figure 2b describes the flow and partitioning of retentate and permeate fractions at various stages of a three-stage membrane cascade. The feed is partitioned initially (membrane F), and both the retentate and permeate fractions from 'F' are further processed using the W and P membrane modules, respectively (Fig. 2b). Patil et al. (2014) found the ratio of the sieving coefficients (as measured by the concentration solutes in feed and filtrate) in a mixture of solutes to play a major role in influencing yield and purity of solutes. At higher ratios, both yield and purity of solute fractions were found to increase proportionately in a three-stage membrane cascade. In the same study, for a five-stage cascade, the yield and purity became inversely related especially at higher ratios of sieving coefficients; i.e. a decrease in yield was observed for fractions with higher purity (Patil et al. 2014). Rizki et al. (2020a) demonstrated that increased temperature during the operation of a 3-stage cascade for separation of oligosaccharide leads to an increase in the product in the permeate flow along with a higher flux, with no change in product purity (Rizki et al. 2020a). Additional studies from the same group tested multiple configurations and operating parameters of a three-stage cascade to increase purity of the collected fractions (Rizki et al. 2019, 2020b). Therefore, cascade system installation and optimization for various solutes is dependent on modelling the sieving coefficients. Sieving coefficient ratios need to be generally low, for optimal separation and satisfactory yield, at higher stages of cascading.

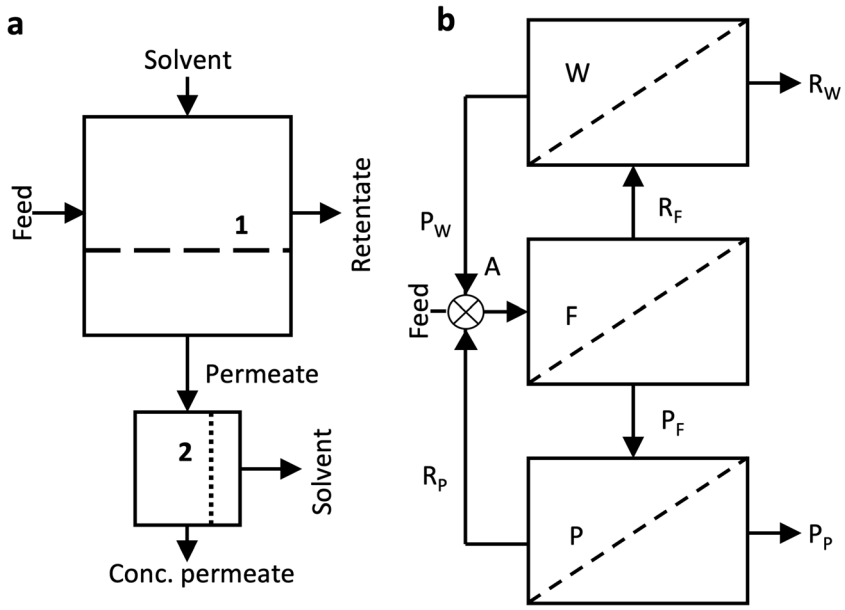

Fig. 2 **a** Schematic diagram of solute transport through a diafiltration system that facilitates concentration of high molecular weight solutes and solvent recycling (modified from Gunderson et al. 2007). **b** An ideal 3-stage membrane cascade with three modules (W, F, P) and Pi and Ri indicating permeate or retentate flux arising from respective membranes. Adapted with permission from Patil et al. (2014) (Copyright 2014 [Elsevier B.V.])

Membrane Fouling: Pressure Limitations

Flux decline is a major factor that has constrained the application of membrane processing, as it necessitates frequent halting for periodic back-flushing to restore flux. Gradual decline of permeate flux is a prevalent phenomenon and occurs primarily as a result of pore blocking and gel layer formation (Song 1998). Figure 3 describes the change in flux in different stages as a result of different chemical mechanisms. The rapid drop of flux in the initial phase of the filtration process is attributed to the membrane pores being blocked by the solute molecules (Fig. 3, I). In phase II, a gradual rate of reduction of permeate flux occurs as a result of formation of the gel layer as the amount of retained solute particles increase on the membrane surface (Fig. 3, II). The retained layer reaches an equilibrium thickness when particles on the membrane surface layer are in equilibrium with particles in the bulk solution, causing the permeate flux to stabilize and reach a steady state (Fig. 3, III). In the steady state, the amount of solute material from the feed (bulk) accumulating at the membrane will be equivalent to solute released from the membrane, either as permeate or through back-diffusion of solute in the direction of the feed (bulk).

A critical pressure threshold dictates the formation of a steady state at any given solute concentration. When the applied pressure exceeds a certain critical pressure, the filtration is in non-equilibrium operation, causing solute to accumulate and expand the thickness of the gel layer, which leads to membrane fouling (Song 1998). There are several models that describe the build-up of solute molecules on membrane surfaces based on the applied pressure (Wijmans et al. 1984; Yazdanshenas et al. 2010). The gel polarization model demonstrates flux decline as a function of the mass transport coefficient of the solute while the osmotic pressure model also takes into account variables such as transmembrane pressure (Wijmans et al. 1984). Wijmans et al. (1984) compared these two models and clearly showed the flux-pressure profile in UF to be a function of the flux-pressure derivative. According to this model, build-up of solute on the wall of the membrane (C_w) generates an osmotic pressure that counteracts the applied pressure (ΔP). The contributions of fouling and gel polarization and their modelling have been described in detail by Yazdanshenas et al. (2010) for clarification of apple juice by an industrial-scale UF module. Identification of flux decline mechanisms is essential for system design and flux enhancement strategies. Additionally, fouling mechanisms vary based on membrane and solute characteristics. Habibi et al. (2020) demonstrated that the same amount of glutathione and BSA accumulated on the membrane surface generates different levels of flux declines that are dependent on the mechanism of fouling (Habibi et al. 2020).

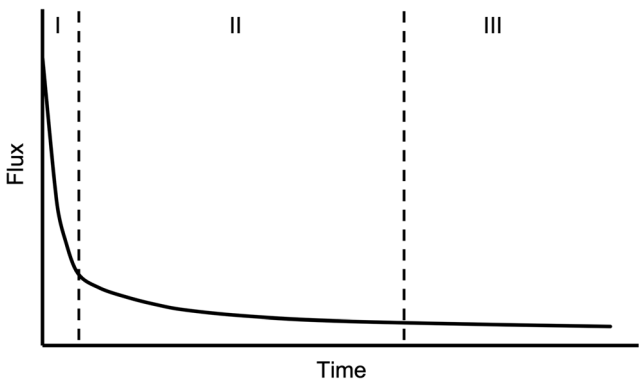

Fig. 3 Schematic diagram of different stages of flux decline (adapted with permission from Song 1998, Copyright 1998 [Elsevier B.V.]). **I** occurs directly as a result of solute molecules causing pore blocking, **II** is a result of solute absorption (cake layer) and **III** is the flux at equilibrium or steady state

As an alternative to dead-end filtration, the crossflow filtration approach places the feed stream flows tangential to the membrane surface and is modelled by a combination of Navier–Stokes and Darcy equations (Hanspal et al. 2009; Nassehi 1998). Studies have demonstrated that crossflow UF with low pressure, low substrate load (feed concentration) and low tangential flow velocity demonstrated the higher efficiency for longer-term operation (Rossignol et al. 1999; Vrouwenvelder et al. 2009). In crossflow filtration, spatiotemporal progression of solute deposition (equilibrium and non-equilibrium region) occurs from the feed end to the retentate end of the membrane during processing. The average permeate flux for the entire membrane surface has been modelled by Song (1998). Crossflow models enable the prediction of steady state and corresponding flux based on the parameters of design and operation of the filtration process (Hanspal et al. 2009; Nassehi 1998). However, studies focused on improving the membrane filtration process for macromolecular solutes by the optimization of parameters (transmembrane pressure, particle size, resistance of the gel layer and cross-flow rates) still rely on the basic understanding of membrane filtration (Binabaji et al. 2015; Gunderson et al. 2007; Hung et al. 2016; Rosenberg et al. 2009). An improved understanding of the chemistry underlying the dynamics of molecules within filtration systems will facilitate fabrication and design of improved filtration systems. Research in this direction is critical for the development of a membrane processing framework for working with feed solutions with multiple solutes and testing the validity of these models.

Functional Modification of Membranes

In addition to processing parameters, fouling on the surface of the membrane varies with surface properties of the membrane such as roughness, hydrophobicity and charge and also depends on the inherent properties and nature of interactions of compounds present in the feed stream. For instance, Persico

et al. (2020) found that peptide fouling resulted from electrostatic interactions over rough surfaces of the membrane. The same study demonstrated that membrane cut-off did not influence the magnitude of fouling for polyethersulfone (PES) membranes, while contrasting results were obtained for polyvinylidene fluoride (PVDF) and polyacrylonitrile (PAN) membranes (Persico et al. 2020). Similarly, skim milk ultrafiltration studies carried out with a variety of different membranes demonstrated that protein adsorption to membrane surfaces increases with an increase in hydrophobicity and polarity of the membrane (Bildyukevich et al. 2020). Modifying membrane surface chemistry and morphology can therefore alter the fouling behaviour of solute. In addition to fouling, membrane modifications also enable us to tailor the membrane properties and enhance separation efficiency. Membranes can be modified to enhance hydrophilic/hydrophobic properties which can decrease membrane fouling that varies with the solutes present in the feed. For instance, charged moieties on the surface of the membrane can transiently bind to water molecules in the feed solution to form hydration layers, which acts both as a physical and energy barrier for macromolecular absorption (Etzel and Arunkumar 2009). Additionally, functionalization contributes to improved selectivity via non-covalent interactions with solute (Ladewig and Al-Shaeli 2017). Increasing hydrophilicity by modifying the membrane surface also reduces bacterial adhesion on membrane surfaces during short contact times (Binahmed et al. 2018).

Membrane functionalization can be accomplished via polymerization (in situ or grafting) or through addition of compounds into the membrane matrix (Ladewig and Al-Shaeli 2017; Shethji and Ritchie 2015; Yogarathinam et al. 2018). For instance, Shethji and Ritchie (2015) demonstrated that sequential cationic polymerization of styrene and substituted styrene monomers on PES membranes is achieved by chemical grafting that used free radical polymerization. Another approach by Yogarathinam et al. (2018) involves the preparation of mixed matrix membranes by incorporating metal oxides into the PES membrane polymer. When used to concentrate whey protein from cheese whey, these modified membranes were found to have higher permeate flux and stabilized flux decline (Yogarathinam et al. 2018). In addition to functionalization at the membrane surface (coating, grafting, etc.) and incorporation of charged moieties (additive modification), tailored chemicals can be directly used in the preparation of membranes. Liu et al. (2017) developed cellulose acetate–based zwitterionic membranes with enhanced hydrophilicity, solvent permeability, flux recovery and fouling resistance to solutions of BSA.

The potential of membrane-based processing can be improved by a combination of functionalized membranes and membrane filtration cascades. Cascades utilizing selectively permeable charged UF membranes can significantly increase the selectivity. Figure 4 presents a hypothetical two-stage filtration system that utilizes charged membrane modules to selectively separate molecules based on molecular size as well as charge. While cascades of regular NF and UF membranes have been used for the separation of biomolecules, functionalized membranes have the potential to add another dimension to this approach. In addition to industrial applications, functionalized membrane coatings have important biomedical applications. For instance, Wang et al. (2013) reported that modified cellulose membranes with zwitterionic brushes demonstrated lower platelet and plasma protein adhesion compared to pristine cellulose, thereby improving blood biocompatibility for biomedical applications (Wang et al. 2013).

The transmission of macromolecules (proteins/peptides) during UF through charged membranes was found by Rohani and Zydney (2010) to be governed primarily by the net charge of molecules, with minimal contribution from the surface charge distribution. Partitioning of charged molecules during UF can be predicted using theoretical models based on pore size, as well as the charge of both the protein (solute) and the membrane (Rohani and Zydney 2010). Functional membrane–based separations have been found to be efficient at low pH (~3) and high pH (~9) (Valiño et al. 2014). The number of charged species in the feed is generally higher at low or high pH, facilitating a larger number of solute molecules to separate across oppositely charged membranes. Unfortunately, maintaining a high or low pH is generally unsuitable in a food industrial setting, as this would potentially impact the palatability of the product. Modulating the ionic strength or pH to improve separation would therefore require follow-up processing (e.g. desalting) of the final product formulation, but this may decrease the economic feasibility of the product.

Electrically Enhanced Membrane Processing

Modification of membrane surface chemistry can significantly increase flux and reduce fouling. However, despite

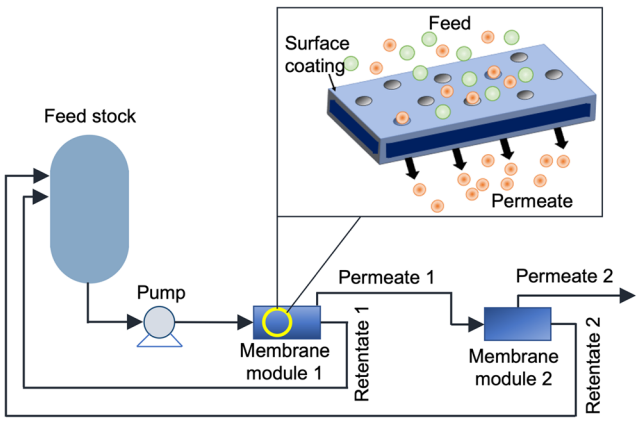

Fig. 4 Schematic diagram of solute transport through a representation of a membrane cascade system with functionalized membrane module

improvements resulting from surface modifications, pressure-driven membrane systems are still limited by the applied transmembrane pressure. To increase flux without having to increase transmembrane pressure, an approach has been developed based on an electrophoretic process for ion selection in tandem with conventional membrane modules (Bargeman et al. 2002; Brisson et al. 2007; Oussedik et al. 2000). This approach, termed electro-ultrafiltration, involves the application of an electric field perpendicular to the surface of the membrane in tandem with pressure-driven tangential flow for the separation of mixtures of charged biomolecules such as proteins/peptides (Bargeman et al. 2002; Brisson et al. 2007; Oussedik et al. 2000). Figure 5a depicts a general schematic of a crossflow electro-ultrafiltration module. The electric field acts as an additional driving force for solute transmission along with applied pressure inside the membrane module (Brisson et al. 2007; Chuang et al. 2008). The electric field also facilitates selective separation based on differences in electrophoretic mobility of the solutes (Rios et al. 1988). Application of an electric field also reduces the protein (solute)–membrane interactions (Rios et al. 1988). A crossflow electro-ultrafiltration module was proposed by Oussedik et al. (2000) to reduce global membrane resistance by combining the turbulence induced by the formation of oxygen bubbles (formed from electrolysis of water at the electrode) near the membrane along with the electrophoretic movement of the proteins or other solutes under an electric field. Application of pulsed electric fields across the membrane results in discontinuous electrophoretic mobilities of the solute molecules that are not in tandem with their convective movement (Robinson et al. 1993). This disrupts the convective accumulation of solute molecules at the membrane surface. Consequently, the boundary layer thickness is lowered, thereby reducing the solute-induced filtration resistance. Similar to the application of electric field, ultrasonication disrupts the boundary layer and leads to increased flux through UF membrane (Teng et al. 2006). However, it is not clear whether these approaches (application of electric field and/or ultrasonication) take into account the changes in temperature (and therefore, viscosity of the solvent) due to localized heating (resistive heating and/or cavitation) that can significantly increase permeate flux.

Electrodialysis is a membrane-based separation process that utilizes an applied electric field to drive ions through ion-selective membranes. It is in contrast to electro-ultrafiltration as hydrodynamic pressure does not play a role in this form of separation. The modern electrodialysis approach was developed in the 1930s and has been employed for industrial-scale desalination, deacidification of fruit juices and demineralization of whey (Houldsworth 1980). It relies on a multicompartment apparatus that has alternating anion and cation exchange membranes. An advancement of the approach integrating UF membranes and termed electrodialysis with ultrafiltration membranes (EDUF), is a patented technology developed by Bazinet and co-workers (2005, WO2005082495A1). The EDUF setup consists of an array of UF and ion exchange membranes stacked together in a conventional electrodialysis cell (Fig. 5b) (Poulin et al. 2006a, b). It facilitates simultaneous separation of positive and negatively charged molecules and has been extensively characterized for protein and peptide separation (Fig. 5b) (Firdaous et al. 2009; Ndiaye et al. 2010; Poulin et al. 2006a; Roblet et al. 2012; Suwal et al. 2014). In addition to charge-based separation, a recent study demonstrated simultaneous separation of different molecular weight fractions by stacking multiple membranes in the electrodialysis system (Henaux et al. 2019). The EDUF technology shows good potential for the food industry, with examples showing several different raw matrices being used for the separation and recovery of bioactive molecular fractions (Doyen et al. 2011; Firdaous et al. 2009). EDUF was able to overcome some of the fouling issues associated with conventional pressure–based processing as solute-based concentration polarization is significantly reduced with electrically driven flow (Firdaous et al. 2009). Both pH (Roblet et al. 2013) and ionic strength (Suwal et al. 2014) were found to have a prominent effect on electrodialytic separation of peptides. In particular, the pH and ionic strength played a significant role in peptide

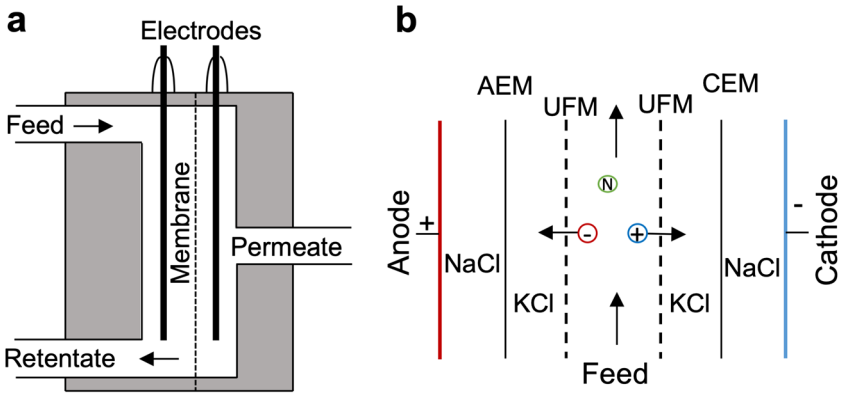

Fig. 5 **a** Schematic diagram of a crossflow electro-ultrafiltration module. **b** Schematic diagram of separation using an EDUF module (stacked anion/cation exchange (AEM and CEM) and ultrafiltration membranes (UFM)) (modified from Poulin et al. 2006a)

selectivity, while little or no effect was observed on peptide migration rate or energy consumption in an EDUF configuration (Roblet et al. 2013; Suwal et al. 2014). Increasing the electric field was shown to enhance the migration rate of the molecules; however, exceeding the limiting current density (LCD, a threshold representing maximum transport of ions through the membrane) resulted in electrolysis of water which changed the pH (Doyen et al. 2013a), although no variation in peptide selectivity was observed by Doyen et al. (2013a) when the applied electric field exceeded the LCD during the fractionation of snow crab protein hydrolysate. As was the case for the application of pulsed electric fields that disrupt the boundary layer, corrugated membrane surfaces improved solute transport during electrodialysis via destabilization of the diffusion boundary layer of solute on the membrane surface (Tadimeti et al. 2016). For the simultaneous production and fractionation of bioactives using a continuous EDUF process, Doyen et al. (2013b) combined enzymatic hydrolysis within the electrodialysis chamber and electromigration of released peptides. EDUF is able to provide higher separation efficiencies while maintaining high recoveries. Ndiaye et al. (2010) isolated β-lactoglobulin (80 kDa protein with immunostimulatory and antimicrobial properties) with efficiency comparable to ion exchange chromatography. Therefore, EDUF could overcome some of the fouling problems observed with conventional pressure–driven processes while also facilitating selective separation under high electric fields. However, EDUF-fractionated products might still require additional cleaning steps to remove salt components (KCl and NaCl, or other electrolytes used during processing) present in the separated fractions.

Downstream Membrane Processing of Complex Matrices

The previous sections described technologies that enable improved membrane separations. These approaches can be incorporated into membrane processing as a non-destructive approach suitable for food matrices. Table 1 highlights the latest developments in various membrane technologies used in food applications. Membrane fractionation is especially attractive for larger molecules, such as proteins, or for heat labile compounds, such as plant secondary metabolites (polyphenols, flavonoids, etc.). Separation and recovery of the latter group of compounds should be designed based on their physicochemical properties. Another consideration to be taken account for scale-up of processing is the relative energy consumption of various approaches for separation of a given mass of material. In contrast to selectivity which increases with lower feed concentration as described earlier, relative energy consumption decreases with higher feed concentration (Henaux et al. 2019). The following sections describe additional parameters as that should be taken into account for processing of a heterogeneous mixture of compounds from complex streams (food materials, tissue extracts, etc.).

Electrodialytic Separation: Food-Based Matrices

EDUF has been successfully used to concentrate/fractionate bioactives from complex matrices such as whey protein (Kravtsov et al. 2019; Mohan et al. 2018), snow crab protein isolate (Doyen et al. 2011), fish (herring, salmon) protein hydrolysate (Durand et al. 2019; Henaux et al. 2019) and alfalfa protein hydrolysate (Firdaous et al. 2009). In addition to fractionation or separation of bioactive molecules, EDUF has also been successfully utilized to enrich biomolecules in consumable products, for instance anthocyanin enrichment from cranberry juice (Husson et al. 2013). Sarapulova et al. (2018) studied the progressive fouling of anion exchange membranes during electrodialysis of wine and demonstrated that polyphenols along with polysaccharides form colloidal aggregates that deposited on the surface of the membrane (Sarapulova et al. 2018). π–π (stacking) interactions between phenol rings of polyphenols and aromatic groups of membrane matrix were suggested to be primarily responsible for the adsorptive layer on the membrane. Electrodialytic membrane separation, although possessing higher fouling resistance, will still present challenges when processing complex biomatrices. Mineral salts including $CaCO_3$, $Mg(OH)_2$ and $Ca(OH)_2$ present in complex samples such as dairy products can precipitate at the membrane interface during electrodialysis (Cifuentes-Araya et al. 2012). Protein, peptide and amino acid fouling and its characterization during electrodialysis have been reviewed by Suwal et al. (2015).

Pulsed electric fields disrupt the solute molecules accumulated at the membrane surface to reduce fouling (Robinson et al. 1993). Another approach called electrodialysis reversal (EDR) simultaneously changes the electrode polarity and the flow direction to influence concentration polarization at the membrane, thereby slowing down the accumulation of solute on the membrane surface. Persico and Bazinet (2018) utilized permselective membranes to reduce solute accumulation via a strong hydration layer on the membrane surface. Permselective membranes are made of charged resin and are covered by a very thin and highly cross-linked oppositely charged layer on its surface. Pulsed electric field (Robinson et al. 1993), electrodialysis reversal (Katz 1979) and permselective membranes (Persico and Bazinet 2018) have been described as possible solutions to the fouling problem in electrodialysis. Ion exchange membrane fouling during electromembrane approaches is proposed to occur in the inaccessible, interstitial spaces of the membrane (Suwal et al. 2015), which makes it challenging for cleaning process as well as experimental characterization of fouling process.

Table 1 A summary of membrane technologies relevant to food applications that have been published since 2018

Sl. no.	Membrane technology	Area of application	Description of study	References
1	EDUF	Membrane regeneration, juice and wine processing	Anion exchange membrane fouled by wine components results in increased electrical resistivity and thickness due to formation of colloidal particles at the membrane pores. Treatment of the membranes with NaCl results in salting out of the colloidal particles, with higher concentration resulting in improved regeneration of membranes	(Nevakshenova et al. 2019)
			Treatment with H_2SO_4-acidified water–ethanol mixtures was more effective than NaCl solutions for regeneration of membranes	(Bdiri et al. 2018, 2019)
2	EDUF	Whey protein hydrolysate processing	Simultaneous separation of cationic and anionic peptides from whey protein hydrolysate	(Mohan et al. 2018)
3	EDUF	Fish protein hydrolysate separation	Simultaneous separation of salmon frame protein hydrolysate with 3 different molecular weight cut-off membranes stacked in an electrodialysis system	(Henaux et al. 2019)
			Cationic and anionic fractions with different molecular weight profiles were obtained as a result	
			Double fractionation of anionic and cationic peptides, resulting in 4 fractions	(Durand et al. 2019)
4	EDUF	Corn by-product: bioethanol production	Separation of acetic acid from lignocellulosic materials	(Suwal et al. 2018)
5	Electrodialysis with bipolar membranes	Deacidification of whey	Increased energy efficiency of acid whey deacidification with electrodialysis with bipolar membranes was possible through a preliminary demineralization step with conventional electrodialysis	(Kravtsov et al. 2019)
6	Membrane cascade	Oligosaccharide separation	Described the impact of temperature on yield and purity of fructooligosaccharide separation with a single-stage and 3-stage membrane cascade	(Rizki et al. 2020a)
			Optimizing separation of 3 different fractions of fructooligosaccharides by using multiple membrane cascade configurations and operating parameters (pressure, membrane size) which improved the fractionation and purity	(Rizki et al. 2019, 2020b)
7	Functional membranes	Processing cheese whey	Preparation of mixed matrix membranes that incorporated metal oxides for processing cheese whey effluent, which resulted in higher flux and lower fouling	(Yogarathinam et al. 2018)
8	Ultrafiltration	Skim milk	Membrane processing at higher temperatures resulted in higher rates and magnitudes of irreversible fouling despite higher flux	(Ng et al. 2018)
			Membranes with higher hydrophobicity and polarity results in increased susceptibility to protein adsorption to the surface	(Bildyukevich et al. 2020)
9	Ultrafiltration	Whey protein hydrolysate	Peptide fouling was evaluated on 15 different membranes. Membrane roughness contributed significantly to fouling	(Persico et al. 2020)

Conventional Filtration: Food-Based Matrices

Comprehensive examination of processing parameters and fouling behaviour is essential for membrane processing of complex matrices. For instance, skim milk ultrafiltration at higher temperatures resulted in higher magnitudes and rates of irreversible fouling despite the higher flux that is associated with increased permeability (Ng et al. 2018). When applied to isolate polysaccharides from plant extract, UF demonstrated the highest separation performance relative to those obtained through gel permeation chromatography or ethanol precipitation (Xie et al. 2014). Optimization of transmembrane pressure, flow rates and cut-off/pore size to maximize permeate fluxes of plant extracts is the routinely used approach (Sun et al. 2011; Xie et al. 2014). Alternatively, several studies report the filtration performance and optimization as applied to rather simple protein/oligosaccharide mixtures (binary/multiplexed) (Brisson et al. 2007; Córdova et al. 2017; Pruksasri et al. 2015). Binary or multiplexed mixtures (proteins or oligosaccharides) are consistently used to understand the basis for fractionation of complex matrices (such as cheese whey from dairy industries), rather than complex extracts (Brisson et al. 2007). More studies are necessary where process optimization and characterization for membrane filtration are carried out with samples representative of the complexity of these streams. The dairy industry is a prime example for pioneering the development of membrane technologies. Multistage filtration systems are designed in dairy processing based on the target application, whether it will be developing cheese from unfiltered milk or fractionating whey protein concentrates to derive functionally important molecules such as lactoferrin (Valiño et al. 2014). An additional processing step is the utilization of NF modules for separation of lactose, which also has an application in fermentation procedures as a carbon source. As mentioned earlier, demineralization of whey protein concentrate can also be carried out using electrodialysis (Rektor and Vatai 2004). These applications demonstrate that membrane processing can be designed for complex matrices based on the demands of yield and purity.

Biofouling, Cleaning and Regeneration of Membranes

Membrane processing of by-products from industries such as dairy and beverages (fruit juices) or fish processing, biofilm formation and the resulting fouling are also a major concern (Chamberland et al. 2017). As mentioned earlier, reduced bacterial cell adhesion was observed in functionally modified membranes with increased hydrophilicity. However, increased contact times result in increased cell adhesion even on the modified membranes (Binahmed et al. 2018). Protein unfolding (bacterial cell surface proteins) at the membrane surface and stabilization as a result of hydrophobic interactions with the membrane matrix were determined to be the primary basis of cell adhesion (Binahmed et al. 2018). The biofilms are resistant to cleaning cycles and can form irrespective of membrane type or surface chemistry (Chamberland et al. 2017). Suwarno et al. (2018) carried out in situ, on-line determination of the thickness and strength of biofilm formed on PES membranes by fluid dynamic gauging (Suwarno et al. 2018). Physical parameters such as smoothness of the membrane and flow velocities have been demonstrated to mitigate this problem (Chamberland et al. 2017). Composite membranes incorporating silver nanoparticles have been developed to reduce biofilm formation for membrane applications in waste water treatment (Wang et al. 2019), and similar approaches have not been carried out in the literature for food processing approaches. Complex bioprocessing approaches should incorporate provisional measures to tackle fouling and the eventual changes of membrane properties that are experienced with continued use (Lightfoot 2005). A variety of physical and chemical changes, along with membrane performance, has been attributed to membrane ageing. Additionally, chemical cleaning especially with sodium hypochlorite solutions can also lead to deterioration of polymeric membranes such as PES membranes (Malczewska and Żak 2019). These changes depend on the chemistries of different membrane surfaces and feed materials. It can only be comprehensively addressed by considering performance factors such as membrane resistance, fouling rate, cleaning (concentration and exposure) and deterioration of membrane housing (Robinson et al. 2016). Several milder, in situ, sustainable methods of membrane regeneration have been recently in development. Sodium chloride solutions have been successful in the regeneration of stacked anion membranes (AEMs) fouled by wine components during EDUF (Nevakshenova et al. 2019). H_2SO_4-acidified water–ethanol mixtures were found to be relatively more effective than NaCl solutions for regeneration of both AEMs and CEMs (Bdiri et al. 2018, 2019).

Industrial filtration modules for size-based separation tend to use ceramic/stainless steel filtration systems rather than polymeric membrane–based filters for enhanced lifetime due to better chemical resistance and higher-pressure tolerance. However, membrane filters remain important in fractionation of macromolecular solutes, and especially for narrow molecular weight ranges for enhanced fractionation of biomolecules such as oligosaccharides and proteins.

Conclusive Remarks and Future Perspectives

Downstream processing of food-based substrates in its current form is a complex separation process which dominates production costs of bioactive compounds. Limitations of conventional separation processes have hampered the development of

economically viable food products that are accessible to the general consumer. Innovations in downstream processing can lower production costs of new food products or ingredients while enabling the development of novel bioactives, nutraceuticals and functional foods. Developments in technologies, such as membrane cascades, functional membranes and electrofiltration systems and their application in tandem, have the potential to enable the effective separation of macromolecular solutes present in complex feed systems. Food membrane processing poses unique challenges resulting from high-foulant feed streams and target biomolecular fractions which sets it apart from membrane applications in the environmental technology sector and water treatment. These technologies are leading towards multistage downstream processes that operate at high throughput in a continuous manner to facilitate the fractionation and purification of molecules of interest from complex substrates at scale with high recoveries. Managing membrane fouling and degradation while improving upon current methods of membrane cleaning and regeneration is essential for feasible applications of this technology in an industrial setting. Additionally, modifying operation parameters such as applied electric fields, pressure, temperature, feed flow and pH along with developments in novel charged membranes has the potential to improve upon currently available membrane technologies to reduce fouling while improving selectivity. Models that predict the behaviour of various components and factors during membrane processing enable widespread and rapid optimization to facilitate tailored separation of compounds based on properties such as size and charge using these technologies from a variety feedstocks.

Food-based bioproduct development is an area which can benefit immensely from adapting membrane technologies to suit different matrices and separate a wide variety of biomolecules. Additionally, evaluation of separation technologies needs to be carried out with complex samples that are representative of real-world heterogeneity in addition to model biomolecule solutions or mixtures. Future trends in adapting and utilizing membranes in food and bioproducts are predicted to revolve around the innovations that contribute towards the development of true continuous downstream processing approaches that can lower costs and enhance recovery, selectivity and throughput.

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