Chapter

Introductory Chapter: An Overview of Recent Advances in Membrane Technologies

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1. Introduction

Environmental changes, global warming, and inappropriate planning are two sides of the worldwide water shortage coin [1–3]. **Figure 1** shows the status of different countries based on water-stressed scenario [4]. Based on United Nations report, more than 2 billion people will experience water scarcity by 2050 [4]. All the previous projections show the vitality of drinking water production and desalination technologies. Currently, there exist two main commercial water-treatment process classes including thermal-based processes (including multistage flash distillation (MSF), vapor compression (VC), and multieffect distillation (MED)) and membrane filtration processes (including reverse osmosis (RO), nanofiltration (NF), and related energy recovery devices (ERD)). Thermal processes were more common previously. However, membrane technologies are outweighing the older processes. Main reasons for RO desalination process growth have mentioned to be rapid technical advances along with its simplicity and elegance [5–9].

Despite all advances in the field, fouling in its different types (colloidal matters, organic fouling of natural and synthetic chemicals, inorganic fouling (scaling), and biological fouling (biofouling)) is the remaining issue of industrial membrane processes [9, 10]. Various types of fouling will result in feed pressure increment and higher operational costs, more frequent requirement of chemical cleaning of the modules and shortened lifetime of the membranes. Fouling types happen simultaneously and could affect each other. This is while biofouling is identified as the critical issue as it is imposed to the membrane surface by living and dynamic microbiological cells and viruses. As the biological attachment, division of the cells and colonization on the surface occurs, the microbiological species and the exopolymeric substance produced by them, create resistance to antimicrobial treatments and the resulted biofouling starts to impose bio-corrosion and lowering the performance of the system [11]. Exposure of the membrane systems to feed's biological contamination highly depends on the environmental factors of the feed itself (nutrient content, available biological species, temperature, light, turbidity, and currents (tides and waves)) [12]. Items under feed water and microorganism classes are related to the microorganism proliferation and conditions supporting their existence. This is while main efforts over process enhancement and modification of membranes are attributed to the membrane-specific properties such as composition and surface structure-characteristics (classified under the title of membrane properties). Apparently, the issue of biofouling could own various levels of severity in different locations. Biofouling is mentioned to be responsible for 45% of the overall fouling that occurred in nanofiltration (NF) and RO plants [13–16].

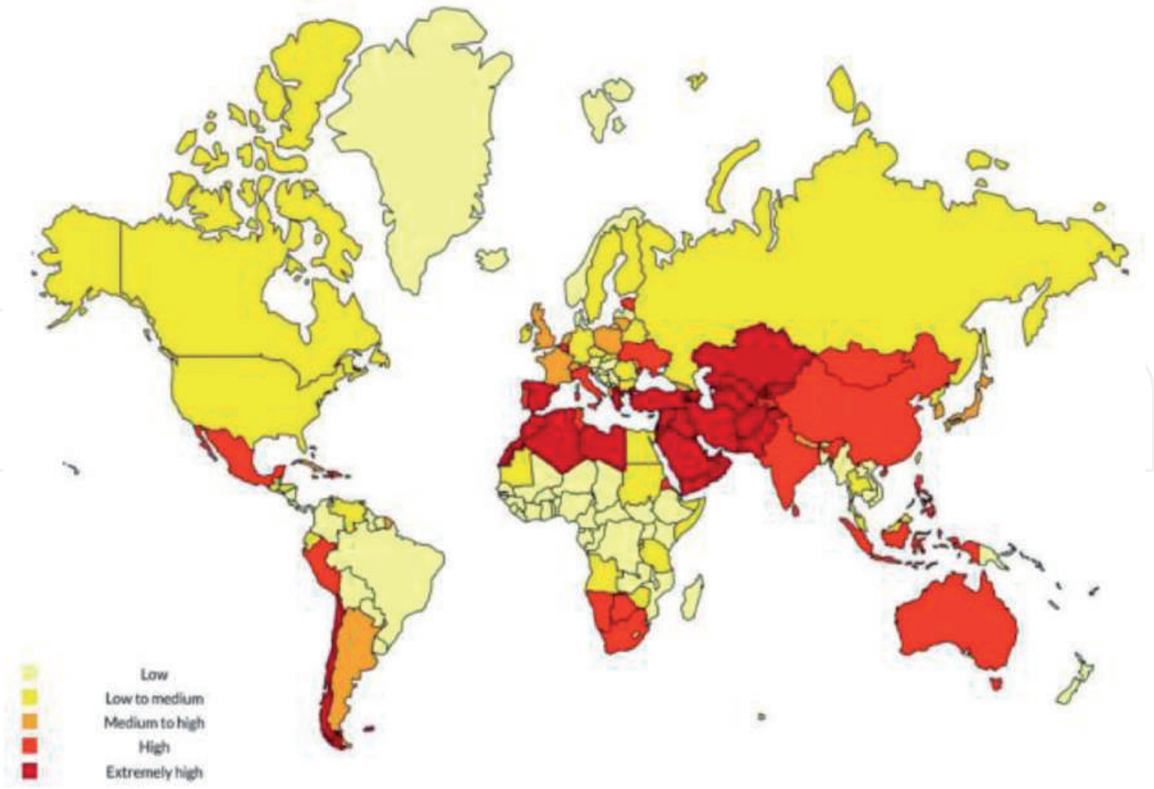

Figure 1.
Classification of water-stressed countries (based on water maps issued in [8]).

This is while FO processes as another prospective water treatment process, due to its inherent distinctions from pressure driven membranes processes, owns different fouling and biofouling profiles [17]. There have been several reviews covering different aspects of the process from material, technological, process, modeling, and economics aspects [18–30].

Another aspect of membrane-based water desalination technologies is their sustainability. Energy consumption optimization and recovery along with controlling footprint of the desalination plants have been focused more recently to further improve the technology [5]. Energy consumption in RO plants is mostly due to high-pressure pumps (more than 50% (**Figure 2**)) (energy consumption profiles in various plants might differ as water resource specifications are not identical). Groundwater resources are easier to treat and desalt in general as they are more restricted and less polluted [31]. Minimizing this energy input by using high-tech pumps, developing highly permeable membranes, eliminating fouling and biofouling issues on membrane surfaces and using energy recovery devices (ERD) [6, 32]. Another aspect, which has received more attention, is renewable energy-assisted water desalination renewable energy desalination (RED). Coupling desalination processes with clean renewable energy resources such as hydropower, wind, solar photovoltaic, geothermal, wave and tidal, etc. is an essential step in further improving the technology due to the high-energy demand of the processes [33, 34]. While RED plants are meant to be renewable energy dependent, they are commonly connected to the power distribution grid due to techno-economical limitations. Desalination plant capacity and renewable energy resource type could affect the final costs within these approaches. Several combination of renewable source and desalination technologies are considered individually and in a combined cycle. These combinations could be practical and promising depending on their scale, geographical characteristics of the installation, available technical infrastructures in the region, plant's remoteness, and access to electrical grid. Efforts for finding hybrid and newly developed low-cost processes have been addressed as a concern for sustainable water production [35].

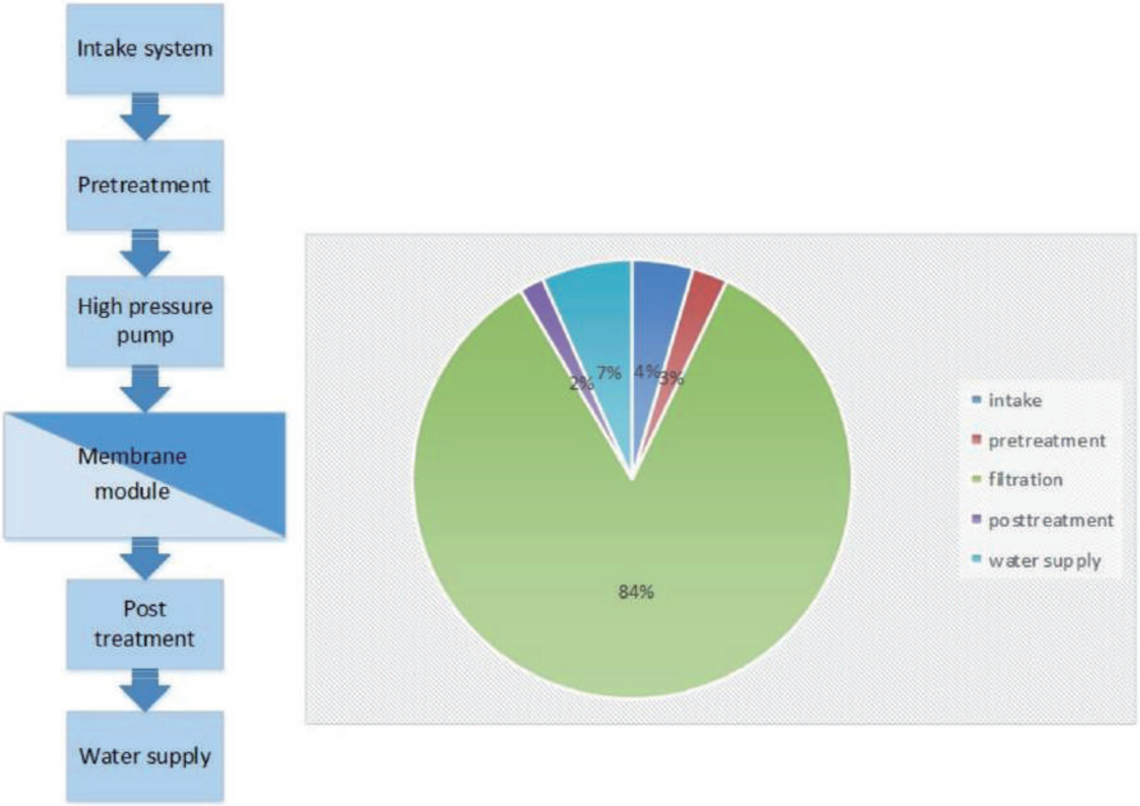

Figure 2.
Reverse osmosis process plant component and for energy consumption shares of total production cost.

While various advances in membrane technology are being reported, the only commercialized ones are polyamide (PA) thin-film composites and the rest are in fundamental development stage [36]. One of the emerging membrane technology candidates is forward osmosis (FO) also introduced as "direct osmosis," [37] "manipulated osmosis" [38], or "engineered osmosis" [39]. Despite the fact that it was introduced back in 1970s [40], the process has recently gained more attention. This is proved by grown number of publications since 2006–2016, with a total number of 1700 papers covering FO topics [17].

FO is based on a natural driving force, there is no need for external energy sources (rather than a small pressure) (around 2–3 bar to eliminate the frictional resistance on two sides of the membrane). This also means that less intense fouling occurs one the membrane surface in comparison with pressure-driven RO membranes [23]. Moreover, lower operating pressure means lower operating and capital cost due to less-pressure vessel incorporation in the plant [41]. Several proven applications of the process, such as concentration and dehydration, are efficiently put into practice. This is while the application of FO as a desalination process is not economical since it requires further purification step when it comes to water desalination [42].

In case of desalination, it is reported that the energy cost comprises 20–35% (with statistically higher reported values) of the final cost of the produced water, and this will change based on the size of the plant and the energy and electricity costs in each region [43]. Lower operation pressure and lower fouling profile in FO process have turned the process into an interesting membrane process, yet it cannot be considered as an alternative to RO in majority of applications. FO, in theoretical studies, is economical in comparison with pressure driven membrane processes if draw solution regeneration would not be needed. Yet, there is no practical justification to support theoretical studies at this time. Accordingly, process development researches must target such applications [44].

Rather than water treatment, academic researches over FO applications are reported in waste water treatment and recycling (municipal [45, 46], hospital [47, 48], landfill leachates [49, 50], pharmaceuticals [51, 52], industrial [53, 54]) salinity gradient based or pressure-retarded osmosis (PRO) power production [55, 56], trace organic treatment (pharmaceutical) [57–59], drink processing [60–62], and agriculture industries [63].

Rather than PRO process (which was failed practically in its only ongoing project), several other areas of energy production are taking advantages of membrane technologies, of which, most important ones are fuel cells [64] and biofuel production and purification [65]. Ion exchange membranes are subject of many intensive researches and the field has been improved intensively thanks to the engineering enhancement and material development for fuels cells [66–68]. Fuel processing and bio-based hydrocarbon production and purification areas are also taking advantages of membrane process. Rather than simple applications of oily waste waters resulted from the industry and filtration separation (complementary application of membranes [69, 70]), membrane-based process integration and intensifications have resulted in higher productivity. An instance of this would be transesterification membrane reactors for biodiesel production, which offers an ecofriendly, high quality product, low cost and small foot print fuel production path [71–73].

Integration and intensification or processes using membranes are a significantly highlighted section of the field. These include several concepts such as using simple and nonreactive membranes in a reactor as an extractor-contactor to remove one of the products in reaction environment so that the yield could be enhanced in an equilibrium reaction. Beside this, functionalized membranes (on the surface or within their structures) could act as catalysts and separated filters simultaneously [74]. Membrane-based process intensifications could result in lower consumption of energy, lower environmental footprint, lower required area, and higher efficiencies. This could finally result in a cheaper product such as processed fuels, purified, desalinated water, etc. [75–77]. **Table 1** offers different application of membranes in reactors as instances of process intensification opportunities for membranes.

Mutual application of membranes and nanoparticles is result in a new field of separation science entitled as mixed matric membranes (MMM) [78, 79]. More specifically, inorganic nanomaterials with specific properties such as antibacterially [11, 80], antifouling [81], photocatalytic behavior [82, 83], specific functional groups [84] for detailed purposes such as providing active binding sites for functionalization, etc. As nanomaterials could be synthesized with different and adjustable properties, MMMs could be tailor-made for specific target in gas-separation processes [85], thin-film-composite-assisted water desalination [86], forward-osmosis-assisted water desalination [87, 88], integrated waste water treatment and water desalination processes [89], fuel-cell-based energy production [90], valuable species recovery [91, 92], etc. Separation mechanisms could also be tunable as the MMMs would be governed by both solution-diffusion and sieving-sorption mechanisms [93]. More importantly, mechanical properties and stability of MMMs are generally improved as the structures are reinforced due to presence of inorganic phase [94]. **Table 1** offers a comparison between polymeric, inorganic, and mixed matrix membranes.

Membranes are also being intensively used in the area of biomedical applications and more specifically blood purification. Since its emerge back in 1960s, membranes were used as a main component of dialyzers in hemodialysis (HD) process [96]. Modules, membrane modalities, and membrane materials in HD have experienced a huge improvement so far [97–101]. All modifications have targeted more efficient clearance of uremic toxins and controlling body originated mediators

Membranes	Advantages	Disadvantages
Polymeric membranes*	Easy synthesis and fabrication Low production cost Good mechanical stability Easy for upscaling and making variations in module form Separation mechanism: Solution diffusion	Low chemical and thermal stability Plasticization Pore size not controllable Follows the trade-off between permeability and selectivity
Inorganic membranes*	Superior chemical, mechanical, and thermal stability Tunable pore size Moderate trade-off between permeability and selectivity Operate at harsh conditions Separation mechanism: molecular sieving (<6 Å), surface diffusion (<10–20 Å), capillary condensation (<30 Å), and Knudsen diffusion (<0.1 μm)	Brittle Expensive Difficulty in scale up
Mixed matrix membranes*	Enhanced mechanical and thermal stability Reduced plasticization Lower energy requirement Compacting at high pressure Surpasses the trade-off between permeability and selectivity Enhanced separation performance over native polymer membranes Separation mechanism: combined polymeric and inorganic membrane principle	Brittle at high fraction of fillers in polymeric matrix Chemical and thermal stabilities depend on the polymeric matrix

**Polymeric membranes: microfiltration, ultrafiltration, nanofiltration, and reverse osmosis filters, which are fabricated only from organic monomers or polymers; ceramic membranes: all filters fabricated from inorganic materials, mixed matrix membranes: are membrane filters fabricated from both organic and inorganic materials.*

Table 1.
Characteristics of different membranes [95] (with permission from publisher).

as a result of defensive system activations. Currently, medium cut-off membranes (60 kDa) are candidates of higher performance with acceptable clearance and low nutrient loss [73, 102]. After many years of development, zwitterionized membranes are most recent generation of hemocompatible dialyzers [96–99].

Rather than FO applications in food industries (as previously mentioned early in the same chapter), the area takes advantages of several other membrane-based processes. Main known applications are beer, beverage and juice concentrations [103–105], and protein recovery from waste streams [104, 106]. More importantly, justification of minerals in dairy streams (milk) to offer value-added products is an interesting application of membranes in food industry [107]. Protein purification (more specifically whey) was conventionally performed by chromatography-based processes. Membrane separation technologies, however, are out weighting those industrial processes due to higher yield and lower energy consumptions [108]. Since nutrition substances own molecular weight and size with different ranges, various membrane processes with different pore size distributions are applied for each specific separation, concentration, or recovery target [109]. Since the technology is one of the main ones in food industries for at least two decades, many integrated processes are now being used for better productions, such as enzymatic hydrolysis ultrafiltration [110]. While the applications might differ from what academic areas have gone through for desalination and water treatment, barriers and accordingly research targets are similar. These include antifouling and antibacterial membrane surfaces, narrow molecular weight cut-off and pore size distribution for higher separation efficiencies, and more stable membranes regarding to their structural and mechanical properties [111–114].

2. Outlook

For past few decades, different aspects of membrane technology application have grown to different extents. The most significant application share of the technology is devoted to water treatment, to both pre- and posttreatments, water desalination, and wastewater treatment. Different aspects of these processes, however, are still being intensively worked on to enhance the economic aspects to minimize the power consumption and environmental aspects (controlling brained streams side effects) of water treatment. Other areas such as cosmetics, pharmaceutical, fuel processing, and production and food industries are all taking benefits from various range of membrane processes. Yet, as the applications are more limited and the processes are fairly complicated, the growth rate is not comparable to water treatment industry. More specific application of thin-film filters in association with biomedical areas (artificial organs) are also experiencing continuous improvements. This is while the issues in these specific areas are focused more on hemocompatibility, biocompatibility, and life-sustaining ability of the technologies rather than on the financial aspects.

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Chapter

Organic-Inorganic Hybrid Membranes for Agricultural Wastewater Treatment

Katrina Jose, Fadi Layyous Gedeon and Chil-Hung Cheng

Abstract

The global agricultural sector consumes a large amount of fresh water for irrigation. Less than half of agricultural wastewater is properly treated before discharging to environment or recycling. Treatment of agricultural wastewater for reuse in irrigation can alleviate burden on water resources as well as protect the environment from detrimental effects caused by various organics, pesticides, and soluble ions in the wastewater stream. This work reviews several current membrane technologies that are applied at removing the pollutants in agricultural wastewater. Subsequently, several strategies to further improve membranes' performance are highlighted. The advancement of materials science at the nanometer scale can assist the fabrication of membranes with higher selectivity of pollutant removal, higher permeate flux, and lower membrane fouling.

Keywords: agricultural wastewater, mixed-matrix membranes, membrane filtration, osmosis, membrane distillation, metal-organic frameworks, zeolites, nanofillers

1. Introduction

The agricultural sector is the biggest freshwater user, which accounts for over 70% of world's total freshwater consumption. This specific usage varies depending on geographical locations, as shown in **Figure 1** [1]. For example, Asia and Africa both show about 81% of total withdrawal water is used by the agricultural sector, with the volumes of 2069×10^9 and 184×10^9 m^3/year, respectively. In North America, as of 2010, about 34% of total freshwater withdrawal is used by the agricultural sector [2]. For instance, estimated 4.75×10^9 m^3/year freshwater was withdrawn by the agricultural sector in Canada during the period of 2008–2012. The demand of freshwater generates a heavy burden on water resources management globally. In addition, surface run off which is one of hydrological cycle mechanisms, brings rotting plants, pesticides, fertilizers, and contaminations into watersheds. These contaminants, nitrates, phosphates, and others cause algae blooms in waters. The growth of algae results in hypoxic conditions with low biochemical oxygen demand (BOD). This significantly impacts the livestock and aesthetics of aqua systems. Moreover, some of the aforementioned contaminants with biological activity would alter the endocrine system of aquatic organisms (endocrine disrupters, EDs), when presenting excessively in aqua systems. Some EDs might trigger hormonal changes in some aquatic species. Thus, if EDs enter water sources for human consumption, it poses huge adverse impacts on human health [3]. Hence, reuse of wastewater for the agricultural sector is an alternative resolution to alleviate the demand on freshwater.

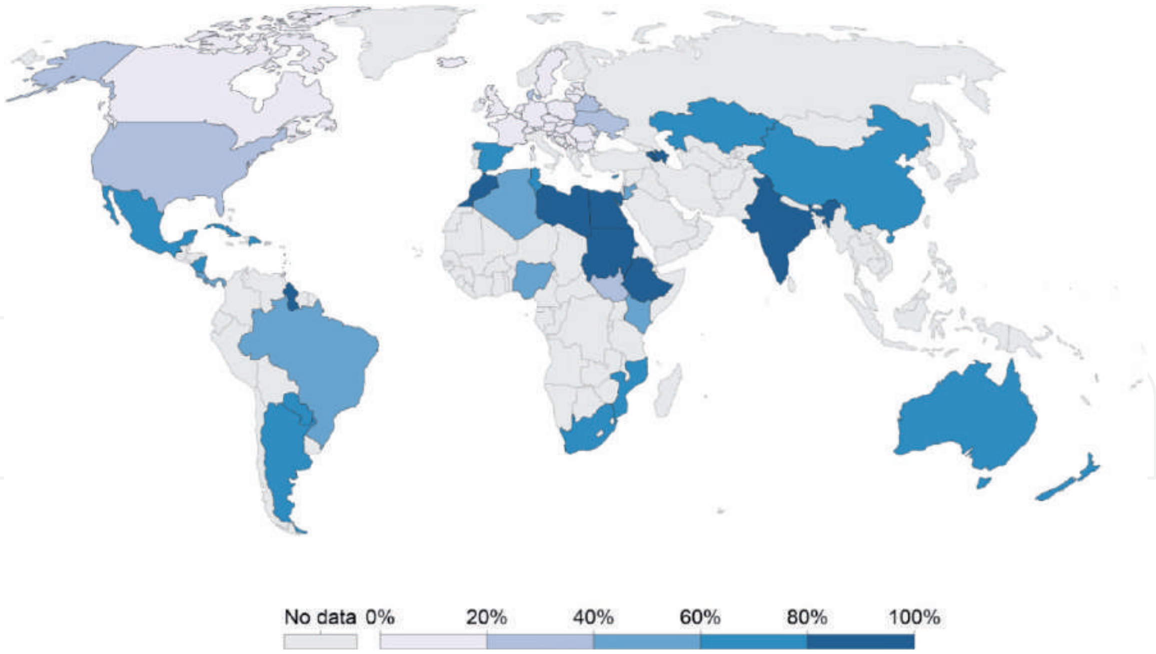

Figure 1.
In 2015, the percentage of agricultural water in the total water withdrawals which is the total water used for agriculture, industry, and domestic purposes [1]. Agricultural water is defined as the annual quantity of self-supplied water withdrawn for irrigation, livestock, and aquaculture usage.

Geographical location	North America[1]	Latin America[2]	Europe[3]	The Russian Federation[4]	Middle East and North Africa[5]	Sub-Saharan Africa[6]	Oceania[7]	Asia[8]
Estimated yearly volume of generated wastewater (km^3)	85	29.8	52.4	27.48	22.3	3.7	2.1	133.3
Percentage of generated wastewater that was treated	71%	20%	71%	51%	51%	n/a	84%	32%
Percentage of treated wastewater for agriculture	45%	n/a	n/a	n/a	51%	n/a	n/a	1%

Time period of collected data in Ref. [7].
[1] *2004 and 2010.*
[2] *1996–2002.*
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Table 1.
Statistics of generated wastewater and wastewater treated [7].

Reuse of wastewater for agricultural usages not only alleviate the demand of fresh water, but also have several benefits through the ripple effect of water conservation: energy saving on the cost of re-surfacing ground water [3], improvement of crop yield [4], increase of soil quality, expansion of agricultural border, as well as reduction of fertilizers usage and expenses [5, 6]. As summarized in **Table 1**, the volume of yearly-generated wastewater and the percentage of treated wastewater vary dramatically depending on geography, possibly due to the economy level and industrialization. In general, the percentage of generated wastewater that receive appropriate treatment before reuse or discharge is about 50%. However, it is noteworthy that less than half of the appropriately-treated wastewater is reused in agriculture sectors in most of continents. This low usage of treated wastewater implies that there exist a great opportunity to maximize the portion of treated wastewater, such that it can alleviate the loads on fresh water resources.

2. Status quo of agricultural wastewater treatment

In nature, one of wastewater treatment processes that occur spontaneously is where bacteria or other micro-organisms in the wastewater stream digest the sewage and other organic matters, yielding new micro-organisms, carbon dioxide and others [8]. In community, wastewater treatment plant is to speed up the natural processes from which the water is purified. Firstly, the wastewater from communities flows through screens, and grit chambers to remove large particulate pollutants, such as sand, debris, and floating objects. The stream subsequently passes through a sedimentation tank to remove suspended solids. This is categorized as the primary treatment. In order to meet more stringent environment regulations, the effluent from the primary treatment flows through a trickling filter and/or an activated sludge process, with the main purpose to remove organic matters. The effluent from the process is sent to another sedimentation tank to remove excess bacteria. At the end, the exit stream from the sedimentation tank is disinfected with chlorine before being discharged into environment. This is the secondary treatment. More advanced waste treatment techniques are applied after the secondary treatment, in order to produce more usable treated water for discharging or for reuse. These techniques include filtration, distillation, and reverse osmosis. The following lists techniques that are used for agricultural wastewater treatment:

2.1 Constructed wetland (CW)

Wetlands are midway areas between land and lakes or oceans, such as swamps or tidal wetlands. Commonly, wetlands are featured with the flow of surface or near-surface shallow water, and saturated substrates. The saturated substrates are usually under oxygen-poor conditions that support the growth of anaerobic microorganisms community. The near-surface shallow water flow can maximum the mass transfer rate and interfacial area between gas and water. The synergic effect from complex mechanisms in wetlands can breakdown or transform various organic and inorganic substances or compounds. A constructed wetland (CW) consists of a properly-designed basin that contains water, a substrate and vascular plants [9]. A schematic diagram is shown in **Figure 2** [10, 11]. Generally, CWs can improve water quality, can serve as a buffer zone to desynchronize storm rainfall and surface runoff, as well as to recycle nutrients from wastewater stream. A recent survey on performances of 25 full-scale CWs across Eastern Canada and Northeastern USA, indicated that CWs effectively reduce various agricultural wastewaters, based on indices of five-day biochemical oxygen demand (BOD_5, 81%), total suspended solids (TSS, 83%), *E. coli* (log reduction, 1.63), fecal coliforms (log reduction, 1.93), total Kjeldahl nitrogen (TKN, 75%), ammonia-ammonium-N ($NH_3^+NH_4^+$-N, 76%), nitrate-nitrogen (NO_3^-N, 42%), and total phosphorous (TP, 64%) [12]. It is noteworthy

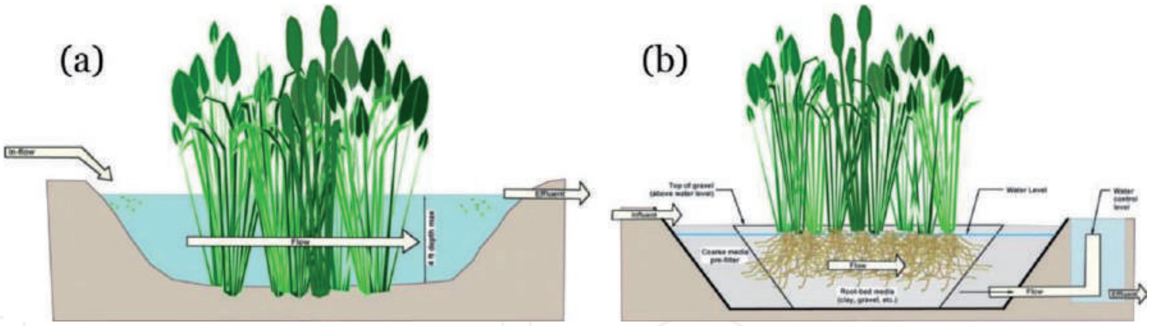

Figure 2.
A schematic diagram of (a) surface flow wetland and (b) subsurface flow wetland designed for treatment of agricultural wastewater [10].

that subsurface flow CWs exhibit higher performance than surface flow CWs. This is possibly because the subsurface flow CWs are capable of insulating micro-organisms from cold winter air temperatures during winter of surveyed regions.

CWs are a comparably economical, low-maintenance, and low operational cost option for treating large variety of wastewater types of wastewaters that include farmyard runoff, dairy spillover, aquaculture wastewater, and abattoir wastewater among others [4]. In addition, CWs can buffer fluctuations of surface water or subsurface water flowrate, as well as to enhance the water reuse/recycling. On the other hand, CWs also inherit naturally some limitations, such as the requirement of large land that makes CWs more practical in rural areas, the seasonally-dependent performance that effluent quality may not meet the environment standards all the times, the environmentally-sensitive micro-organisms that may not survive under toxic conditions.

The effluent from the secondary treatment still contains suspended particles, organic pathogens, and nutrients that can pose potential adverse effects on downstream water distribution systems, and elevate health and environment risks, for example, pipe clogging, and cancer [13, 14]. Thus, the effluent from the secondary treatment is not suitable for agricultural reuse in irrigation application, and requires a tertiary treatment in order to achieve the quality standards for agricultural water. The standards are assessed using salinity level or sodium adsorption ratio (SAR), which is defined as follows [15]:

$$SAR = \frac{Na^{+}}{\sqrt{\frac{Ca^{2+} + Mg^{2+}}{2}}} \quad (1)$$

According to standards of Food and Agriculture Organization (FAO), reclaimed water after tertiary treatment that can be reused in agricultural irrigation, should contain 0–400 and 0–61 mg/L for calcium and magnesium, respectively.

2.2 Membrane filtration

The tertiary treatments involve salt removals using membranes in nanofiltration (NF), microfiltration (MF)/ultrafiltration (UF), reverse osmosis (RO), forward osmosis (FO), and membrane distillation (MD) [16, 17]. The classification of these treatments depends on the sieving effect posed by the pore diameter within their membranes through which eluents are pressurized to flow, i.e., the pore diameter of NF membranes ranges from 1 to 10μm. NF and RO demonstrate the capability of removing diverse monovalent ions from wastewater streams. However, the low-sodium treated water is not appropriate for reuse in agricultural irrigation, as some divalent ions (Ca^{2+} or Mg^{2+}) are essential nutrients for crops growth. Furthermore, most organic matters, like pesticides, in the effluents from the secondary treatment cause severe fouling to NF and RO membranes, which shortens the membrane lifetime, and increases the operation costs [15, 18]. MF is suitable for removal of suspended solids and micro-organisms. UF is mainly applied to remove viruses and organics whose size down to 20 nm [19]. Thus, MF/UF are strategically applied as the pretreatment step prior to NF-RO process. The energy cost of wastewater reuse using the MF/UF-NF/RO scheme was estimated 0.8–1.2 kWh/m^3, which is slightly higher than that of the conventional surface water treatment of 0.15–0.3 kWh/m^3. However, the MF/UF-NF/RO scheme demonstrated a much better energy cost than desalination of brackish water or seawater [18]. Furthermore, the salt rejection rate of MF/UF-NF/RO scheme increased to 98.2–98.8%, compared to that of RO-alone scheme (94.3–97%) [20].

FO is a naturally-occurring separation process that can draw water from a low concentration environment (feed solution) to a high concentration one (draw solution), due to the inequality of chemical potentials across the FO membranes [15]. FO can be utilized in combination with RO (FO-RO) or as a standalone process (FO-only) to retain some nutrients in agricultural wastewater, such that the quality of treated water from FO-RO process can meet irrigation water regulations, compared to the single RO system. A schematic diagram of FO-RO integrated system is shown in **Figure 3**. For a total system operated at a recovery of 70%, the FO-RO process demonstrated about 30% of energy consumption (kWh/m^3), compared to the RO-alone system [21]. It is also noteworthy that the rejections of ammonium and phosphate of FO-RO integrated system were >92.1 and >99.8%, respectively; whilst, the rejections of ammonium and phosphate of FO-along system were 50–80 and >90%, individually [22, 23].

The aforementioned wastewater treatment technologies are based on pressure-driven membrane processes. On contrary, there are thermally-driven membrane processes that are suitable to treat wastewater with high salinity and toxic contaminants. Membrane distillation (MD) is one of promising technologies in this category. MD utilizes low-grade or waste heat as the driving force at creating the vapor pressure difference across a microporous hydrophobic membrane which is permeable for volatile compounds from the feed side. In principle, the volatile compounds of wastewater at the feed side can be fully collected at the permeate side of the membrane, separated from the nonvolatile compounds, and solids in the

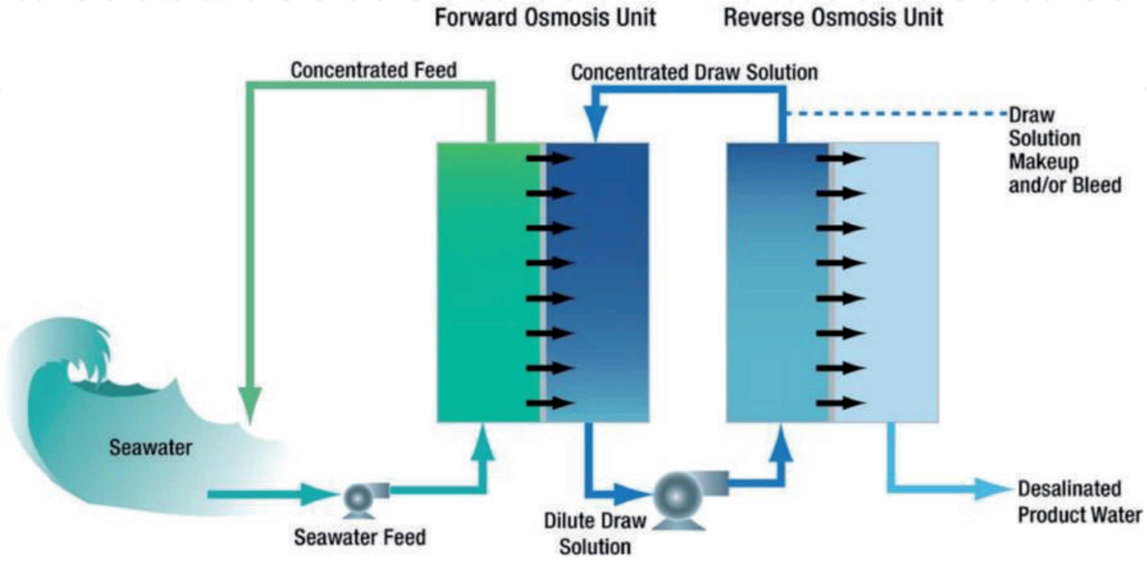

Figure 3.
Schematic diagram of FO-RO integrated system for seawater treatment for agricultural uses [21].

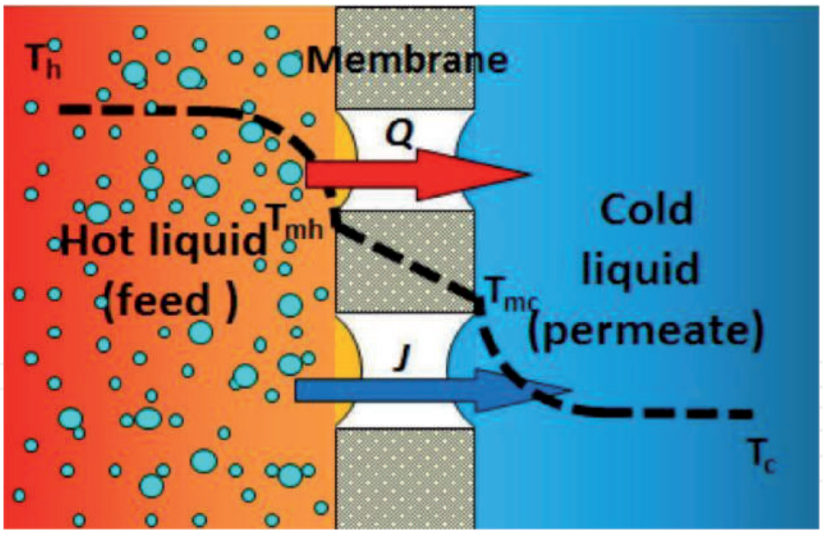

Figure 4.
Schematic diagram of MD for wastewater treatment for agricultural uses [25]. Q is the heat flux across the membrane due to the temperature gradient between the feed and permeate. J is the mass flux of permeable vapor across the membrane due to the pressure gradient between the feed and permeate, created by the temperature gradient.

wastewater [15, 24]. A MD schematic diagram is illustrated in **Figure 4**. A functionable MD membrane should demonstrate the following features simultaneously: (1) hydrophobic micropores for high liquid entry pressure (LEP); (2) thin membrane thickness for high mass transfer rate of volatile compounds; (3) low thermal conductivity for maintaining high vapor pressure graduate across the membrane; (4) high chemical resistance for maintaining the sieving effect of the membrane.

Compared with those pressure-driven membrane technologies, MD exhibits several advantage edges, such as lower operation pressure at the feed side, cost-effective, less propensity of membrane fouling, as well as generating high purity of treated permeate. However, the last advantage can be a potential MD shortfall in its application in agricultural irrigation due to the low or zero ion concentration. In addition, not many membrane materials can meet those criteria of successful MD membrane. This becomes a big hurdle at commercializing MD process in industry. Thus, it is projected that MD processes might be more suitable as the pre-treatment step for RO, in order to improve water recovery and minimize the permeate disposal.

3. General aspects of membrane technologies

As mentioned in previous section, MF and UF technologies are adopted to remove suspended particulates and organic matters in wastewater stream. Given that the pore size of semipermeable membranes in MF and UF are in the range of 0.1–10 and 0.01–0.1 μm, respectively [19, 26]. MF membranes are commonly made from polymer materials, such as polysulfone (PS), polyether sulfone (PES), polyvinylidene fluoride (PVDF), polypropylene (PP), polyethylene (PE), polytetrafluoroethylene (PTFE), cellulose acetate (CA), ceramic metal or metal oxides [27]. The organic membranes are usually prepared via phase inversion technique, and the ceramic metal oxides membranes are most prepared via sol-gel technique. Organic MF/UF membranes are prepared by controlling several operational and compositional synthesis variables in the phase inversion reaction, such as the volatility of solvent [28]; while inorganic MF/UF membranes are tailored by controlling heat treatment conditions, pore forming additives, and sol-gel precursors [29].

Index	Unit	MF	UF	MF-UF
TOC	mg/L	71.9 (94.1%)	25.9 (97.9%)	trace (100%)
TDS	mg/L	1154 (27.7%)	424 (27.7%)	8.4 (99.4%)
TSS	mg/L	9 (97.4%)	5 (98.5%)	trace (100%)
Oil and grease	mg/L	21.5 (99.4)	1.5 (99.4)	trace (100%)

The percentages in the parenthesis are the extent of reduction in each assessment index [30].

Table 2.
Several indices for evaluation of MF, UF, and MF-UF membrane's performance.

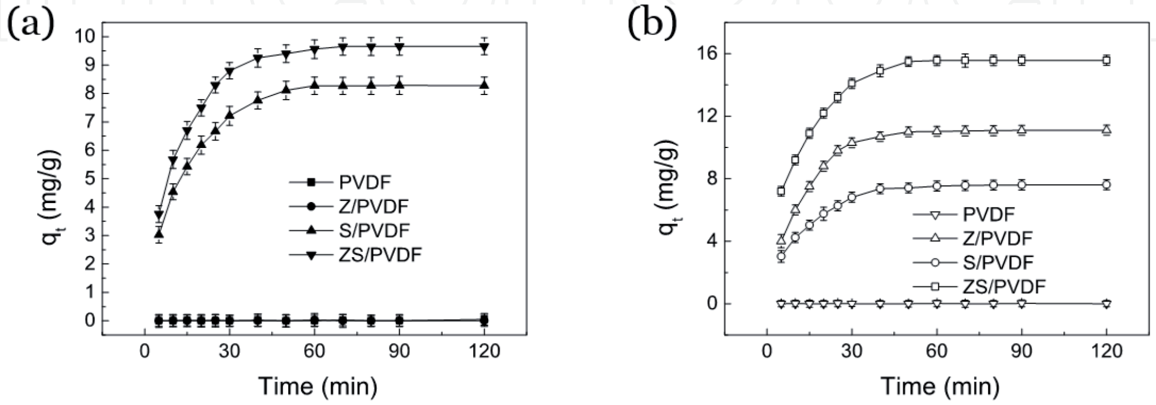

Figure 5.
(a) Nitrate adsorption with an initial concentration of 20 mg-N/L; (b) phosphate adsorption with an initial concentration of 20 mg-P/L. Z: Functional layer of PVDF membrane made of zirconium hydroxide. S: Functional layer of PVDF membrane made of SDMOAC. It is clearly elucidated that pristine PVDF (UF) membrane has no adsorption selectivity and capacity towards nitrate and phosphate [31].

A recent study on the performance of MF, UF, and MF-UF membrane processes, respectively, in oily wastewater treatment was carried out on PES, and PVDF membranes [30]. Total organic carbon (TOC), total dissolved solids (TDS), total suspended solids (TSS), and oil-and-grease content, are applied as indexes to access the membranes' performance which follows the order of MF-UF > UF > MF, as shown in **Table 2** [30]. The results clearly indicated that the combined MF-UF technique was better than individual MF, and UF techniques, in terms of the solid removal rate. It is also noted that the operation conditions of membrane techniques, such as transmembrane pressure (TMP), cross-flow velocity and oil concentration at the feed side, affect each membrane technique greatly. Other studies also indicate that the rejection of phosphate, nitrate, and ammonium ions using MF or UF processes is too low, such that the effluent from these treatment cannot meet the environment standards prior to discharging to the aquatic environment [31] (**Figure 5**).

Nanofiltration (NF) processes are an advanced separation technology applied to remove pesticides, ammonium ions from wastewater stream [32]. The pore size of NF membranes is in the range of 1–10 nm [19, 26]. NF membranes are commonly made from polymer materials, such as polysulfone (PS), polyether sulfone (PES), polyaniline (PAN), polyether ether ketone (PEEK), polyimide (PI), and polyamide (PA) via phase inversion technique [33, 34]. Alternatively, inorganic ceramic membranes are adopted in NF, such as zeolites, carbon nanotubes, graphene, metal oxides, and metal-organic frameworks among others [20, 34]. Given the pore size range falls in between atomic and molecular levels, the separation mechanism of constituents in the feed solution is based on the diffusivity of pollutants across the membrane (Knudsen diffusion). In addition, NF membranes usually carry positive or negative surface charges, due to the dissociation of surface sulfonated or carboxyl groups. The electrical field of surface charges alter the permeability of ions in the wastewater stream accordingly. Thus, NF membranes exhibits higher selectivity of salt rejection towards most divalent cations and some monovalent cations than MF and UF, while the operation pressure and energy consumption are lower than those of RO. Polymeric NF membranes are most fabricated via the phase inversion technique during the interfacial polymerization reaction [33].

A study using a commercial NF membrane (polypiperazine-amide thin-film composite) was conducted to investigate the nitrate removal efficiency from a real groundwater. The nitrate rejection was about 55.1–62.2%, due to the adsorption competition of sulfate with nitrate [35]. However, the membrane demonstrated a complete removal of phosphate [36]. The treated water would require another post-treatment process, such as RO, in order to meet the environment standards [35].

RO processes are a tertiary wastewater treatment technology applied to remove monovalent ions from wastewater stream [32]. The pore size of RO membranes is in the range of 0.1–1 nm [19, 26]. RO membranes are mainly made from polyamide thin film composite (TFC) via interfacial polymerization from two monomers, an amine, and an acid chloride [37]. The thin polyamide layer deposits on a microporous hydrophilic polysulfone membrane as a mechanical support to polyamide. The polysulfone layer is sandwiched between polyamide and mesoporous polyester. Given these small pore diameters, the separation of different components from the feed solution side is based on the solubility and diffusivity of each component into the polymer membrane matrix.

As shown in **Figure 6**, RO membrane displayed high removal of divalent ions (>99%), and had comparable monovalent ions rejection as published results. Overall, the RO process had better total dissolved solute (TDS) rejection than the NF process. Furthermore, the performance of both NF and RO processes declined after 3 years operation. It is noteworthy that the Cl^- rejection of RO process (94.4%) declined to 43.9% after 3 years operation. The declination rate is more significant than that of NF process. In addition, the SO_4^{2-} and Ca^{2+} rejections of NF process decreased more than those of RO process. The former declined performance was suspected to the vulnerability of RO membranes to chloride ions. The latter declined rejection was possibly due to the membrane fouling [38].

Although most of RO membranes demonstrate very high salt rejection (>99%), it is also widely recognized that RO membranes suffer two major drawbacks: (i) membrane fouling to all matters in the feed stream, (ii) sensitive to the presence of chlorine or chloride ions, due to the electrophilic nature of amide nitrogen and aromatic rings of polyamide in RO membranes [39]. To overcome these drawbacks, several strategies can be adopted (i) pretreatment of feed stream prior to RO processes, (ii) surface modification using physical adsorption of hydrophilic polymers or chemical grafting of hydrophilic functional groups [39].

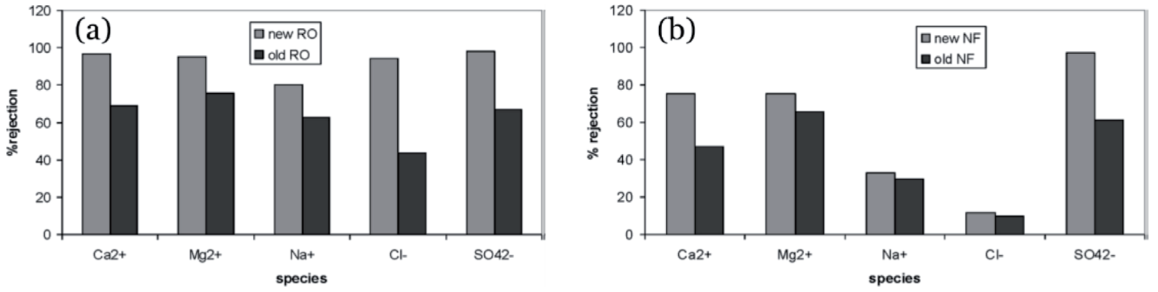

Figure 6.
Performance comparisons of (a) RO process and (b) NF process. New means the beginning of the operation using new membranes. Old means the membranes after 3 years of operation [38].

4. Promising technologies of membranes for agricultural wastewater treatment

It is widely recognized that membrane-based processes are the most energy-efficient, compact, and high throughput technology for agricultural wastewater treatment. There are several strategies to further improve the performance of membranes in each type of processes, such that the most cost-effective system can be applied at industrial scale:

4.1 Combination of various membrane filtration processes

Wastewater nutrient recovery is a promising strategy to recycle nutrients and pesticides while minimizing or avoiding the energy penalty for removing those nutrients in wastewater treatment facilities. It was estimated that 30% of nitrogen and 16% of phosphorus from fertilizers exist in wastewater. Thus, wastewater nutrient recovery can minimize the usage of fertilizer for crop production [17, 40]. For example, combining NF-RO processes together can generate water for agricultural irrigation application [41]. The NF step in this integrated process is to concentrate divalent ions at the retentate side, while the RO step is to produce high purity recycled water with low SAR at the permeate side. Combining the concentrated divalent ions stream from NF, with the purified recycled water stream from RO can prepare the quality of treated water to meet the standards for agricultural irrigation. As shown in **Table 3**, UF is perfect for the removal of suspended solids (TSS) as well as pathogens (BOD, COD, and TOC). However, RO is an ultimate treatment processes to remove most of soluble ions [13]. It is expected that membrane fouling would be severe at the UF process.

When searching for a low fouling technology, FO processes stand up by its nature of separation mechanism. An interesting study was conducted using a pilot scale FO-RO hybrid process to treat a synthetic wastewater. The salt rejection (NaCl) is about 95–97% which is lower than that of RO process only [42]. However, the nutrients rejection performance of the hybrid system was superior than each individual process, shown in **Table 4**. The treated water quality was better than EPA primary drinking water standards. It is also noticeable that the membrane fouling was observed in the spiral wound FO membrane, although the fouling was mostly reversible. This contributed to the restored water flux after membrane cleaning.

Performance index	UF rejection (%)	UF + RO rejection (%)
BOD	94.5	96.0
COD	92.0	98.0
TOC	41.0	95.6
TSS	99.3	100.0
Cl	2.3	81.1
Na	10.7	85.0
K	3.7	51.4
Ca	12.2	88.3
Mg	2.4	88.1
N-NH_4	20.6	80.5
PO_4	12.0	93.4

Table 3.
Performance of UF-RO integrated systems at agricultural wastewater treatment [13].

Performance index	FO-only	RO-only	FO-RO
Phosphate rejection (%)	99.6	99.6	>99.99
Nitrate rejection (%)	76.7	83.2	95.8
Dissolved organic carbon (DOC, %)	98.6	99.8	>99.99

Table 4.
Comparison of nutrients rejection of FO-only, RO-only, and FO-RO [42].

Similarly, a FO-NF hybrid process was applied to treat real wastewater with a salinity of 3–5 mS cm^{-1} for 480 days [43]. It was found that when magnesium chloride solution was used the draw solutions of FO, the membrane fouling became reversible and less extent. The permeate of the FO-NF hybrid process can meet the agricultural irrigation standards without further adjustment. The only disadvantage of FO-NF process is its cost of treated water higher than that of FO-RO technology, owing to higher energy consumption (40%) and the chemical loss of draw solution.

4.2 Modification of membrane surface properties via grafting or blending

FO processes are the best candidate to remove ammonium ions in wastewater, among the pressure-driven and temperature-driven membrane separation techniques. However, the ammonium rejection rate is low, around 48% [44]. The poor performance can be attributed to the small molecular weight and diffusivity of ammonium ions, which are comparable to the solvent molecules [45]. One of strategies to enhance the ammonium rejection rate is to change the membrane surface to become more positively-charged and hydrophilic, such that the FO membranes can retard the permeability of ammonium ions via Donnan exclusion effect. For example, a latest development is to modify a polyamide (PA) membrane surface to form amine-functionalized membranes, via a cross-linking agent (N,N′-dicyclohexylcarbodiimide) followed by a nucleophilic attack from polyethylenimine (PEI), shown in **Figure 7**. The zeta potential of amine-functionalized PA membrane is largely increased compared with the pristine PA membrane, indicating the presence of positive surface charges on the modified membranes. The ammonium rejection of amine-functionalized PA membrane exhibited higher performance then the pristine PA membrane (100 vs. 97% for synthetic ammonium solution, and 89.3 vs. 75.5% for a real wastewater correspondingly) [45].

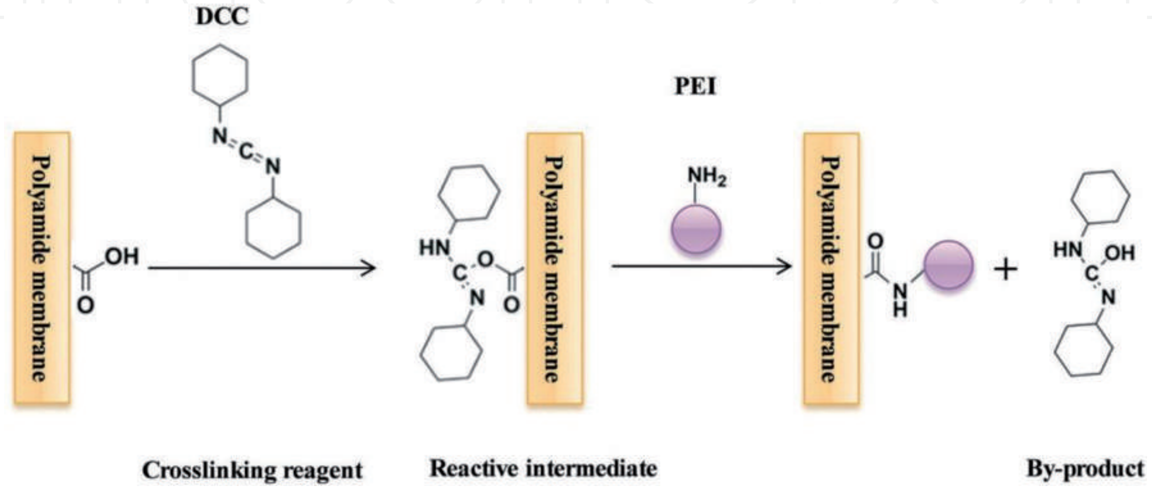

Figure 7.
Schematic diagram of surface modification of RO membrane via grafting [45].

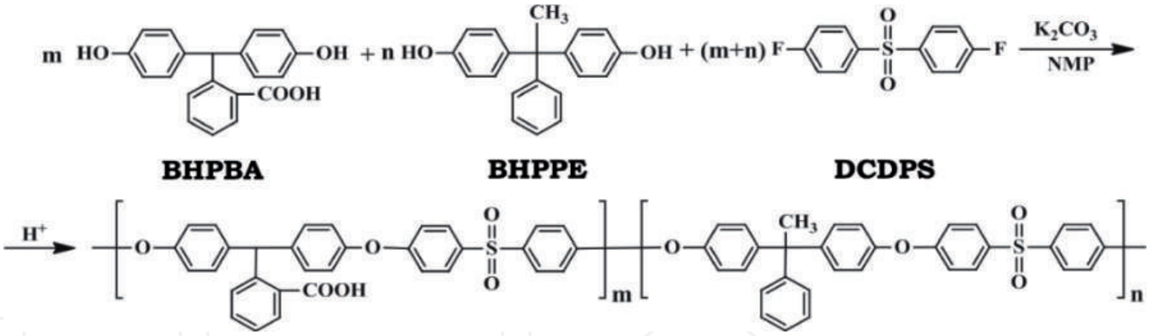

Figure 8.
Synthesis of hydrophilic NF membranes via copolymerization [46].

The modification of membrane surface properties via grafting is not applicable to a few commercial polymers. In addition, the introduction of functional group via grafting yields functionalized membranes with lower thermal resistance and mechanical strength. An alternative approach to functionalize membrane surface or matrix is to introduce the hydrophilic groups (carboxylic or sulfonic acids) via co-polymerization reaction of strategically selected monomer containing designated functional groups, with polymer membranes. For instance, Zhang' group fabricated hydrophilic NF membranes by copolymerization of 2-(bis(4-hydroxyphenyl)methyl) benzoic acid (BHPBA), 1,1-bis(4-hydroxylphenyl)-1-phenylethane (BHPPE) and 4,4′-dichlorodiphenyl sulfone (DCDPS). The schematic diagram is shown in **Figure 8** [46]. The resulted NF membranes with adjusted COOH contents exhibit high glass transition temperatures (T_g), ranging from 184 to 246°C, that are comparable or superior than pristine PES membrane. This is due to the high benzene ring content in each monomer. In addition, the carboxyl groups introduced into the NF membranes are located on the pendent benzene ring of PHPBA, instead of being located on the backbone of the polymer. This will enhance the thermal stability of copolymer.

The dye rejection of the fabricated NF membranes via copolymerization increased along with the content of carboxylic groups (>90% for RB2 dye, and >74% for RO16 dye), due to the smaller membrane pore size by incorporating the functional groups. The salt rejection of the investigated NF membranes showed the following order: Na_2SO_4 (84%) > NaCl (19%) > $MgSO_4$ (11%) > $MgCl_2$ (6.6%). Furthermore, the fouling resistance ratios of the investigated NF membranes increased along with the content of carboxylic groups. This is due the electrostatic force interaction between the soluble microbial products (BSA and humic acid) and the functional groups of membranes [46].

4.3 Incorporation of nanofillers in polymeric membranes

Membrane bioreactor (MBR) processes are a hybrid wastewater treatment technology, combining biological wastewater treatment and MF-UF processes simultaneously. MBR processes are usually considered as a pre-treatment step for NF and RO processes, because they exhibit high tolerance at total suspended solids of influent composition variation, and production of high effluent quality (**Table 3** in Refs. [47, 48]) However, the membrane fouling is a major hurdle on applying MBR processes at larger scale. An approach to circumvent this hurdle is to increase the membranes' hydrophilicity via incorporating inorganic nanocrystals (nanofillers) in polymeric membranes, also named organic-inorganic mix-matrixed membranes (MMM) [49]. The benefits of applying MMMs in MBR processes include: (i) energy saving due to lower transmembrane pressure (TMPs), which are reduced 31.38 (Z4-MBR) to 40.45% (Z8-MBR) upon the incorporation of zeolite nanofillers in MMMs compared with the bare polymer membrane; (ii) higher throughput due to

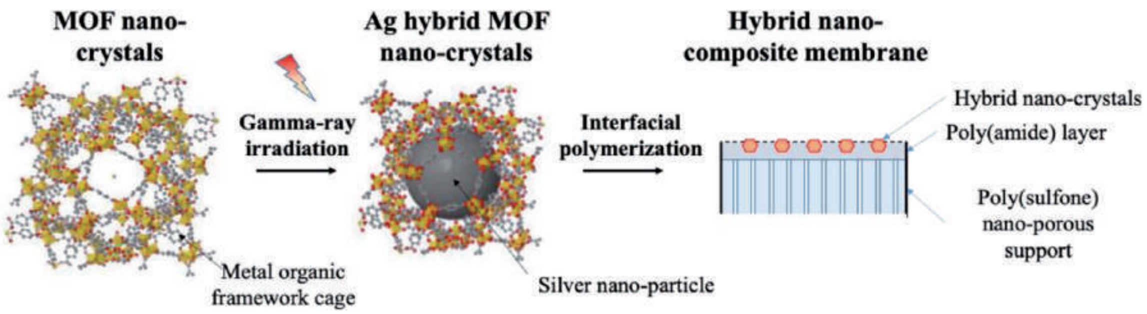

Figure 9.
Schematic diagram of hierarchically-nanostructured mix-matrixed membranes in RO processes [52].

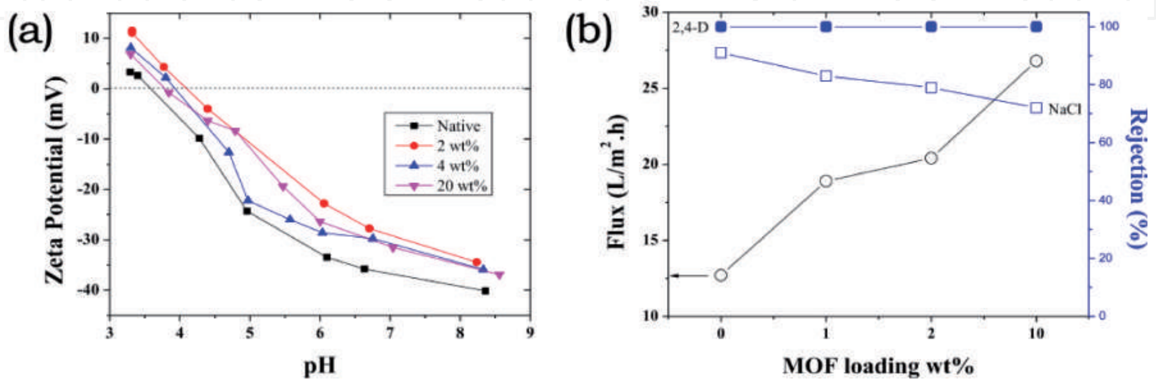

Figure 10.
(a) Zeta potentials of hierarchically-nanostructured Ag-MOF nanocrystals in PA; (b) the membrane performance of Ag-MOF nanocrystals in PA using 2,4-dicholorophenoxyacetic acid as the model compound in a simulated wastewater. The numbers in the legend of part (a) indicate the content of MOF nanocrystals in membranes [52].

lower membrane fouling. The zeta potentials of MMMs were enhanced to −7.7 mV (Z4-MBR) to −5.35 mV (Z8-MBR) compared to that of bare polymer membrane (−14.3 mV). The more hydrophilic MMMs reduce the soluble microbial products (SMPs) by 18.94 (Z4-MBR) and 42.11% (Z8-MBR) respectively, via the direct adsorption of SMPs on zeolite nanofillers in MMMs. This yields a lower propensity of membrane fouling.

In parallel with MBR processes that use the physical adsorption/molecular sieving mechanism at wastewater treatment, catalytic membrane reactors (CMR) has shown their potentials in degradation and destruction of pesticides and pathogens (catalytic reaction), and purification of the degraded wastewater through pores within membranes (physical adsorption/molecular sieving) simultaneously [50]. To CMR processes, mixed-matrixed membranes are fabricated to have both functionalities, by incorporating catalytic nanoparticles in microporous polymeric membranes. Long-term stability of MMMs in CMR, and homogeneous dispersion of catalytic nanoparticles in polymer matrix are vital factors at their applications at large scale [51]. A recent design of hierarchical nanostructure MMMs was achieved to address the aforementioned issues, by incorporating catalytic metal nanoparticles inside the cavities of metal organic frameworks (MOFs) nanocrystals. The metal-incorporated MOFs nanocrystals were subsequently imbedded into polyamide (PA) RO membranes via interfacial polymerization. The schematic diagram is illustrated in **Figure 9** [52].

The zeta potentials of hierarchically-nanostructured mix-matrixed membranes increased with the content of MOF nanocrystals, exhibiting more hydrophilic feature upon incorporating nanocrystals compared with the pristine PA membrane. This contributed to higher permeate flux from 12.5 kg m^{-2} h^{-1} of pristine PA membrane to 27 kg m^{-2} h^{-1} of 20 wt% MOF incorporated membrane. However, the salt rejection capability decreased by 20%, due to the presence of interfacial spaces between MOF nanocrystals and PA matrix. It is noteworthy that the organic compound rejection of 100% was exhibited, no matter if nondegraded or degraded organic compounds presented, shown in **Figure 10**.

5. Outlook

Membrane technologies are considered as the feasible solution to address the water reuse and nutrients recovery in agricultural sectors [15]. The efficiency of pollutant rejection and permeate productivity are the major factors to maximize membrane processes at a larger scale. This depends on the membranes' ability to maintain its selectivity towards retaining pollutants as well as their ability to minimize the membrane fouling, while keeping its fabrication cost-effective. Several approaches are developing to address these issues. For example, the concept of nutrients recovery from wastewater stream leads to develop hybrid membrane processes such as NF-RO [41], FO-RO [21], and FO-MD [53]. FO is a low membrane fouling technology and relative low pressure compared with RO. MD is also a low membrane fouling technology to concentrate volatile organic matters in wastewater stream.

Alternative approach is to modify the membrane surface hydrophilicity via grafting hydrophilic monomers on membrane matrix and/or incorporating inorganic nanoparticles in polymeric membranes. The modified membranes can exhibit less propensity of membrane fouling. For instance, a nanofiltration PVDF membrane was modified with tannic acid (TA), polyethylenimine (PEI), and halloysite nanotubes (HNTs). The modified membrane exhibited higher dye removal (92.5%), heavy metal rejections (54.6% for Cu^{2+}, 47.9% for Cd^{2+}, 61.6% for Fe^{3+}), and permeate flux (42 L m^{-2} h^{-1}), compared with pristine PVDF membrane, shown in **Figure 11** [54]. Similarly, ultrafiltration membrane PS can have a higher nitrate removal (41.4%), higher permeate flux (43.3 L m^{-2} h^{-1}), and less membrane fouling (flux recovery ratio, 81.2%) when graphene oxide (GO) nanocrystals were blended in the polymeric matrix, compared with those of pristine PS membrane (15.50%, 17.84 L m^{-2} h^{-1}, and 30.56% respectively) [55].

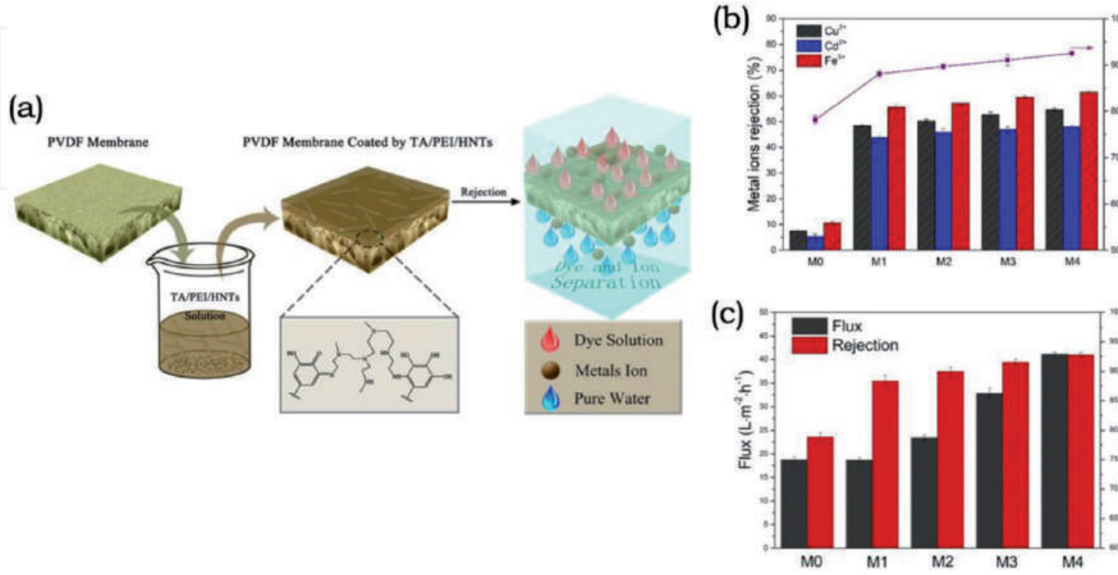

Figure 11.
Modification of nanofiltration membrane towards antifouling. (a) Schematic diagram of modified membrane preparation, (b) performance of heavy metal rejection, (c) performance of dye rejection (direct red).M0: Pristine PVDF membrane. M1: PVDF + TA + PEI. M2: PVDF + TA + PEI + HNTs (1 mg/mL). M3: PVDF + TA + PEI + HNTs (2 mg/mL). M4: PVDF + TA + PEI + HNTs (3 mg/mL) [54].

6. DDD

When we consider the irrigation water quality published by Food and Agriculture Organization, and the recycling the nutrients (pesticides, and some divalent ions) in agricultural wastewater, membrane technologies such as NF, RO, FO, or MD would emerge themselves from others, in terms of selectivity of pollutant removal and productivity of water reclamation for agricultural reuse. The energy cost of operating membrane processes replies on membranes' performance in the wastewater treatment processes, such as high salt rejection, low membrane fouling, high permeate flux, high mechanical strength and high long-term stability. While current membranes exhibit most of the aforementioned features, the membrane fouling is inexorable in most of the pressure-driven membrane separation processes. Membrane surface modifications can tailor the membrane surface hydrophilicity to alleviate the fouling extent. The strategies include copolymerization of hydrophilic monomers in polymer membranes, grafting hydrophilic functional groups on membranes, incorporating novel nanofillers (GO, MOFs, zeolites, metal oxides) in polymer membranes, and depositing hydrophilic thin film on membranes. These strategies usually create some challenges towards how to balance the membranes performance with permeate flux declination, as well as how stable these modified membranes are at the operation conditions. Being able to address both concerns can broaden membrane technology applications.

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Chapter

Membrane and Bioseparation

Yaghoub Mansourpanah and Farideh Emamian

Abstract

Although one of the strongest methods of purification is chromatography, the major problem of porous bed chromatography is that purification takes place using the diffusion. This will prolong the purification process and bring down the efficiency. In recent years, membrane methods have greatly overcome this limitation due to low membrane thickness, low pressure drop, and convective flow, and they are a great alternative to chromatography columns. Unfortunately, the membranes have a low surface area. For solving such problem, membrane modification with polymeric brushes and layer-by-layer adsorption in polyelectrolyte films can be attractive. Accordingly, in this chapter we introduce types of biomolecule purification methods, the best purification method, membrane modification techniques, and their limitations and assets. Also, we introduce the membrane as an attractive tool for selective purification and separation of biomolecules.

Keywords: membrane, polyelectrolyte multilayers, polymeric brushes, biomolecules, layer-by-layer adsorption

1. Introduction

The rapid development of biotechnology needs more reliable and effective methods for isolation and purification of bio-products (proteins, enzymes, peptides, or nucleic acids). Since the introduction of recombinant insulin as a therapeutic agent in 1982, the global protein therapeutic market is rapidly expanding with the continuous growth of biotechnology. However, due to the complexity of protein mixtures, the purification of proteins remains a problem in their production. Since purification and recycling are then about half the costs of producing cell-derived drugs, high fecal separation techniques and high recyclability are fundamental to produce the essential therapeutic proteins.

The therapeutic proteins currently constitute a very effective pharmaceutical industry, predicting that they would expect their sales to reach 165 billion dollars [1]. So far more than 100 proteins have been accepted as therapists, many are undergoing therapeutic testing. Recombinant therapeutic proteins, drug-antibody mixed, vaccines, enzymes, recombinant/normal cytokines, interferons, monoclonal antibodies, growth hormones, and coagulation factors are known as biochemical therapists. They have been proven effective in the treatment of many potentially fatal diseases, such as cancer, diabetes, and cardiac disorders [2]. Protein purification is essential for basic protein research and the production of therapist antibodies [3–5], and the expansion of the need for pure protein [6] is challenging the existing purification methods [7]. Separating a protein is especially important to reduce degradation, to remove impurities that can interfere with protein function, and to remove toxicity from proteins that are used in therapy [8].

Packed columns have been the primary tools for protein isolation and analysis for decades. However, it has a number of problems such as compressibility of the beads, plugging and fouling, and especially the slow flow speed through the column.

Membrane chromatography is able to overcome the mentioned problem of packing column and minimize it. Because it provides a higher flow rate, much lower pressure drops, and illustrates greater productivities per unit time. In comparison with the bead-packed column, flow through pores of the membrane (convective transport) quickly brings protein to binding sites. However, despite their potential, a major disadvantage of the membrane absorbers is low internal surface area that leads to a relatively low binding capacity. To overcome this problem, membrane modification, especially with two methods of coating and grafting polymerization, can be efficient, in such a way that membranes with multiple binding sites and specific functional groups for the capture of different biomolecules are achieved.

A wide range of polymeric and porous inorganic supports have been used in order to develop protein adsorbing membranes with high protein binding capacities and selectivity. Functional groups containing carboxylic acid, epoxide, $-SO_3H$, $-NH_2$, and $-CH_2OH$ are particularly interested for membrane modification. Based on the various interactions between the groups mentioned on the membrane and biomolecules, various types of ion exchange membranes, hydrophobic interactions, covalent bonding, affinity, etc., for the separation and purification of enzymes, proteins, and antibodies from various sources, have been developed. In this regard, our goal is to introduce the membrane as an excellent tool for the selective separation and purification of biomolecules with high binding capacities as well as the introduction of the best membrane modification methods to improve membrane performance in this area.

2. Types of macromolecular purification methods

Because an organ contains thousands of proteins and their amounts can change over a wide range, isolating a target protein is often challenging. To overcome this challenge, scientists often attach an affinity tag to recombinant proteins. **Figure 1** shows the overall schematics of the production and isolation of the recombinant proteins that the special binding of the marked protein (tagged) is the strongest level in the purification of the protein [9, 10]. When this technique is performed in a column, it is often called “affinity chromatography.”

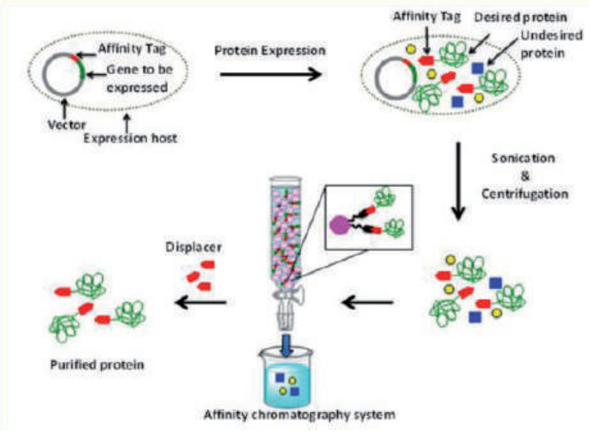

Figure 1.
Expression and purification of a recombinant protein [11].

Several methods for purifying the protein are available [3, 4, 6, 10, 12, 13], and the methods of chromatography are the most powerful and versatile methods. In these techniques, stationary functional groups such as ion exchange groups [14], hydrophobic molecules, or affinity ligands [15] capture the desired proteins.

Reversed-phase chromatography is relatively selective and separates proteins based on their relative hydrophobicity on a large scale. But this method requires an organic solvent mobile phase, which certainly denatures a number of proteins and eliminates the operation [12]. Ion exchange chromatography [12] separates proteins based on their charge density (**Figure 2a**), although gel filtration chromatography (size-exclusion chromatography) separates these molecules based on their size and is useful for the condensation of protein samples [16] (**Figure 2b**). In affinity purification, the scientist designs an affinity tag on recombinant proteins, and this special tag acts as a facilitator for the desired protein separation from the protein mixture (**Figure 2c**) [15, 17].

Affinity chromatography due to its high selectivity is the most robust method to isolate a single target protein from complex biological fluids (probably, affinity adsorption is a better name for this technique, which usually occurs in a batch mode). This isolation relies on the interaction between the functional groups (ligands bound to a solid surface) and the inserted tag in the protein. Some examples of affinity interactions include the interaction between antigens and antibodies, the binding of the histidine tags to the ion-metal complexes [18, 19], adsorption of maltose tags to carbohydrate matrices [20], the binding glutathione-S-transferase to glutathione [21], and the binding of streptavidin to biotin [22].

2.1 Immobilized metal affinity chromatography (IMAC) for His-tagged protein purification

IMAC is a very versatile and powerful way to purify the protein based on the tendency of specific amino acids to the variable metal ions attached to a solid support. Porath et al. introduced IMAC in the mid-1970s [23–26]. In this way, metal ions such as Ni^{2+}, Zn^{2+}, Co^{2+}, or Cu^{2+} are attached to ligands (e.g., iminodiacetic acid (IDA) or nitrilotriacetic acid (NTA)) that are fixed on a support (**Figures 1–5**). A wide range of solid supports are available to immobilization of metal chelates, and polymer materials with hydroxyl groups are particularly common [25]. Usually in protein purification, the interaction of various metal ions with proteins, depending on the metal ion complex, is carried out through histidine, tryptophan, or cysteine residues [23, 25, 27]. For metal ion complexes that are especially attached

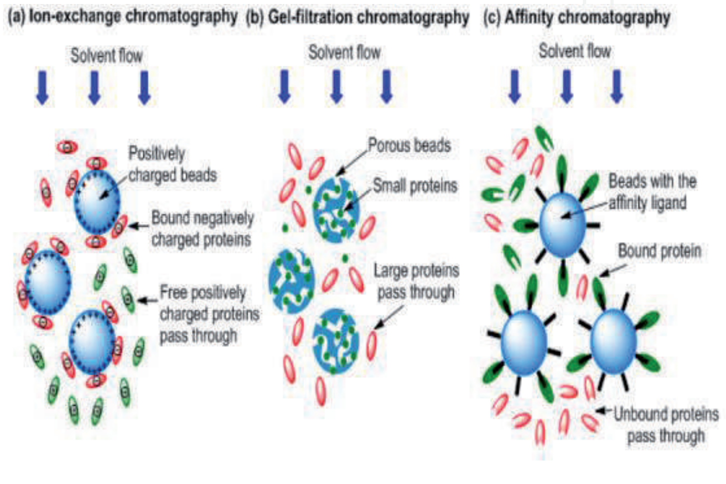

Figure 2.
Different types of chromatographic methods for protein purification [11].

to imidazole, the number and relative position of the available histidine residues determine the binding of protein. Therefore, in the expression of recombinant proteins in bacterial cells, to add a short sequence of histidine residues to each of the terminals C or N of the recombinant protein (typically 6), a short sequence of DNA binds to the desired gene. This histidine tag strongly binds to Ni^{2+}, Co^{2+}, or Cu^{2+} complexes (**Figure 3**) [26]. Because most proteins contain one or a relatively large number of histidine residues, the selected metal ion complex to capture the proteins labeled with histidine should not have very strong interactions with imidazole or many of the various proteins that will be attached to the support. For this reason, Ni^{2+} and Co^{2+} complexes are more commonly used to purify the proteins labeled with histidine than the Cu^{2+} complex [25, 28, 29].

The most common metal ion ligands, IDA and NTA, occupy three or four of the metal ion coordination sites, respectively; in this case, at least two of the coordination sites remain free [30].Therefore, the proteins His-tagged coordinate to the metal ion complex during the purification process (**Figure 3**). However, most proteins contain one or more histidine residues, which can cause non-specific binding and reduce the purity of the protein. Selection of Ni^{2+} as a coordinating ion leads to relatively weak complexes with single histidine residues and low non-specific adsorption [11]. In contrast, the hexa-histidine tag forms very strong complexes with immobilized Ni^{2+} [31, 32] to effectively capture the tagged protein. Replacement agents (usually free imidazole) that bind to immobilized metal ions can specifically eluate the proteins His-tagged; other elution methods include pH changes and ionic strength [28].

IMAC has many advantages: Low cost, high specificity (selectivity), simplicity, and mild elution condition. In addition, the binding site can be rearranged several times without loss of performance, and selectivity can be controlled by selecting different metal ions and change physical properties such as pH, ionic strength, and temperature [30, 33]. This technique can quickly isolate polyhistidine-tagged proteins with 100-fold enrichment in a single purification step, and purity can increase by more than 95% [34]. However, the non-specific binding of proteins due to histidine or cysteine clusters creates an important challenge in purification; adding low concentrations of a competitive agent (such as imidazole) to the loading environment can help to overcome this challenge, but it often reduces protein binding capacity [32, 34]. Also, exact selection of the phase for IMAC is important to get high yield and low production cost.

Among the many methods available for the purification of biomolecules, salt deposition, dialysis, electrophoresis, etc., chromatographic methods are

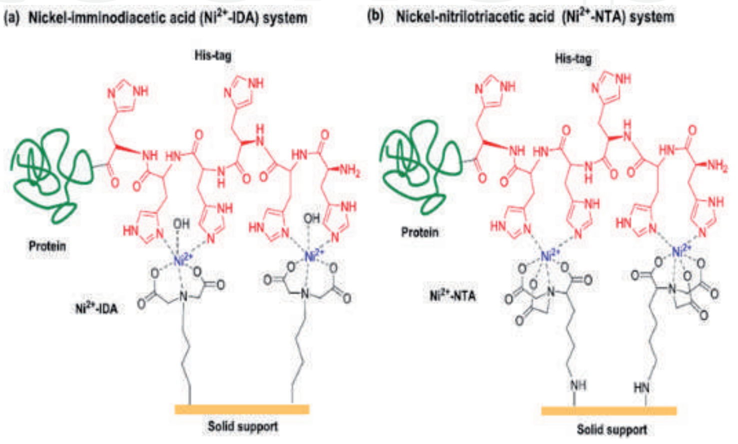

Figure 3.
Models of interaction between the polyhistidine affinity tags and two stationary metal ion-ligand complexes. (a) Ni^{2+}, imminodiacetate (Ni^{2+}-IDA), and (b) Ni^{2+}, nitrilotriacetate (Ni^{2+}-NTA) [27].

remarkable because of their selectivity and particular. Also, the mentioned methods cause impurities in the process of separation as well as more stages of separation. Membrane-based chromatography because of its superiority over conventional chromatography columns is a very good alternative to these columns. Membranes are economically more affordable than stacked columns. It can be remarked that the membrane's superior advantage over packed columns is passing the convection flow through the membrane pores, which speeds up the purification and separation process. In the next section, these two are closely compared.

3. Common phases for IMAC and their advantages and limitations

The most popular IMAC template uses packed-bead columns (**Figure 4a**). Packed-bead columns have been used for decades as the main means of purifying proteins for both analytical and preparation needs [35]. In a chromatographic separation based on column, the solution that contains the target molecule is loaded onto a chromatographic matrix, and moving phase separates the components, so the goal is apparent in a group elution of the column [36, 37]. In comparison, with a column based on affinity, the target selectively binds to the ligand, while other compounds along with the moving phase pass through the column [35]. The subsequent washings with the buffer will remove the remaining impurities, and in the final stage the target protein, as soon as the surface is replaced by a competitive factor, denatured or other mechanism in a pure form, is eluated of the column [26]. The main limitation of the most bead-packed columns is the transfer limited by the slow diffusion of proteins into the bed pores, which leads to a long separation and low productivity; this limitation also refers to large amounts of eluate and the need for analyte concentration after separation [38–41]. In addition, stacked bed phases create a high pressure drop across the stacked bed, and the same packing of large-scale columns is difficult [4, 38, 42, 43].

The development of homogeneous nonporous chromatography may overcome diffusion constraints, but these systems are relatively expensive, due to the low surface area having a low binding capacity, and also create high pressure drop [44, 45].

The porous membranes are forming as an attractive solid support for IMAC, and various studies discuss the progress of membrane adsorbents over packed columns for protein purification [3, 8, 46–48].

Compared to the bead-packed columns, the flow through the membrane pores (convective transfer) brings the proteins to the binding sites (**Figure 4b**). Convection transfer minimizes the constraints caused by the diffusional mass transfer resistance [10]. In addition, the membranes are thinner than the packed

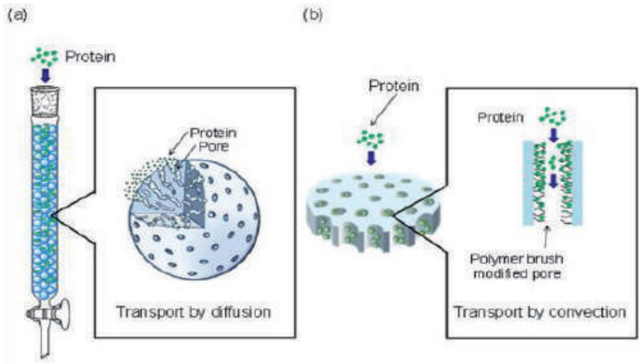

Figure 4.
Transfer of protein to binding sites. (a) Diffusion in nano-porous beads. (b) Convection flow in membrane pores [10].

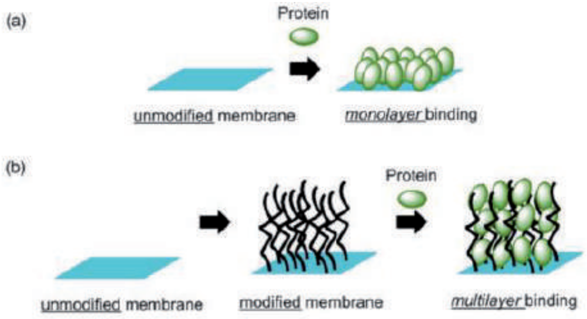

Figure 5.
Capture of (a) a single layer of protein on the unmodified membrane surface and (b) a multilayered protein on the surface of a membrane modified by a polymeric brush [51].

substrates, so the pressure drop across the membrane is significantly lower than that of a packed column. These advantages make membrane purification systems copacetic for very fast and large-scale protein purification. Although membrane adsorbents are very interesting for purification, due to the low surface area, they suffer from lower binding capacities [49, 50]. Membrane modification is a very effective method for providing the desired functional groups as well as increasing the surface area of the membrane. Usually, the unmodified membranes only have a surface area of $10m^2/g$ [51], and they mainly bind less than one layer of protein in their pores. Grafting of polymer chains in membrane pores is a common approach to increase biomolecule capture (especially proteins); more detailed explanations of this method are given in the next section.

In 1990 Müller et al. suggested the use of polymer brushes containing ion exchange sites to capture protein multilayers in membrane pores [52]. The membrane pores are modified with polymer chains binding several layers of protein (**Figure 5**) [51].

4. Surface modification techniques to increase bonding capacity

The surface modification should be such that, in addition to the availability of desirable and appropriate functional groups, there is no conflict with the purpose of the membrane process and separation, but in line with it and contributing to this goal [53–64]. Among the membrane modification methods, two methods involving grafting polymerization through appropriate initiator and coatings are more significant. In this section two methods include layer-to-layer adsorption of polyelectrolyte films and the growth of polymer brushes (**Figure 6**), the first is one of the coating methods and the other is one of the polymerization methods, for membrane modification and the provision of multiple binding sites in membrane pores have been discussed.

In most membrane-based processes, hydrophilicity is one of the most important factors. Also, in the separation of biomolecules using membranes, this factor is important to prevent non-specific surface adsorption. The diameter of the membrane is also one of the important factors in the separation process, and, based on the purpose of separation, a suitable diameter membrane can be prepared. To improve the membrane's hydrophilicity, even a hydrophobic polymer as a base membrane (such as polyether sulfone) can be grafted with a hydrophilic moiety. Therefore, in membrane preparation for separation processes, the base membrane should be prepared in such a way that, in addition to having a sufficient density of suitable functional groups, be hydrophilic, and its pores diameter be appropriate for maintaining the flow velocity. In this regard, it can be concluded that, in general,

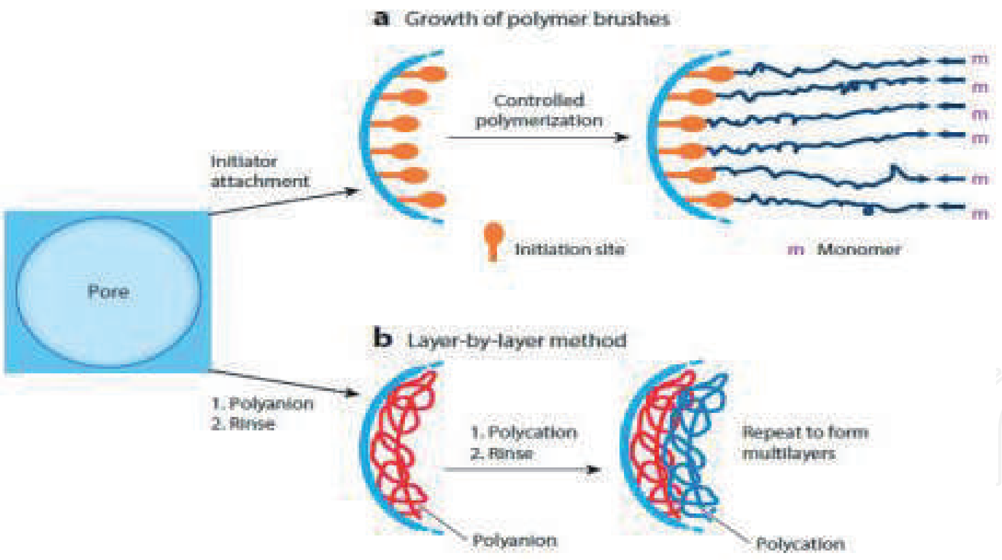

Figure 6.
Schematic diagram of (a) growth of polymer brushes and (b) layer-by-layer adsorption to form films that may capture proteins in membrane pores [65].

the diameter of the membrane pores, the hydrophilicity, and thickness are the main factors governing the process of separation; here the factors are also considered.

4.1 Modification of surfaces with polymer brushes

Polymer brushes are assemblies of polymer chains with one end attached to the surface and one end extended of the surface (**Figure 8**) [66]. These brushes are very moving and attractive to binding several layers of protein in many substrates such as membrane pores. Such brushes, when appropriately derived from the ligand, can capture several layers of protein through metal ion complexes (**Figure 7**).

4.1.1 Methods of growth of polymer brushes on surfaces

There are two main methods for the growth of polymer brushes on solid surfaces, physical absorption [68, 69] (**Figure 8a**) and covalent bonding [70] (**Figure 8**).

In the physical adsorption, one end of a block copolymer strongly adsorbed to the surface. A covalent bonding can be made through either "grafting-to" [71, 72] or "grafting-from" methods [73]. In the "grafting-to" method, polymers with end-functional groups to form polymer brushes react with a suitable functional group on the substrate. Alternatively, by "grafting-from" method the polymer chains grow directly through initiators that are covalently attached to the surface. These two covalent techniques provide different densities of polymer brushes [11]. In the

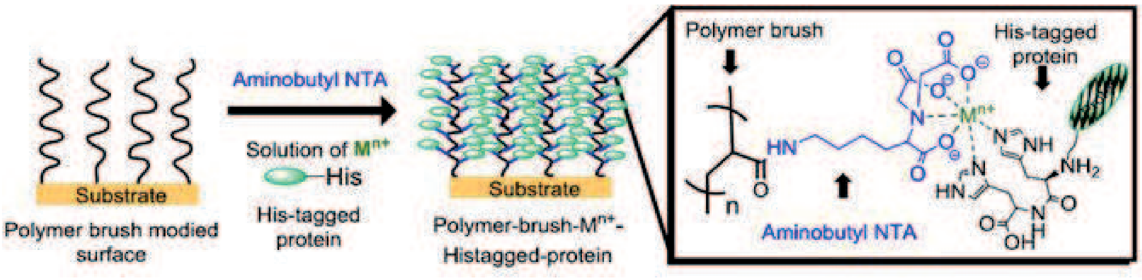

Figure 7.
Multilayer binding of the His-tagged protein to an acrylic acid brush derived with aminobutyl NTA [67].

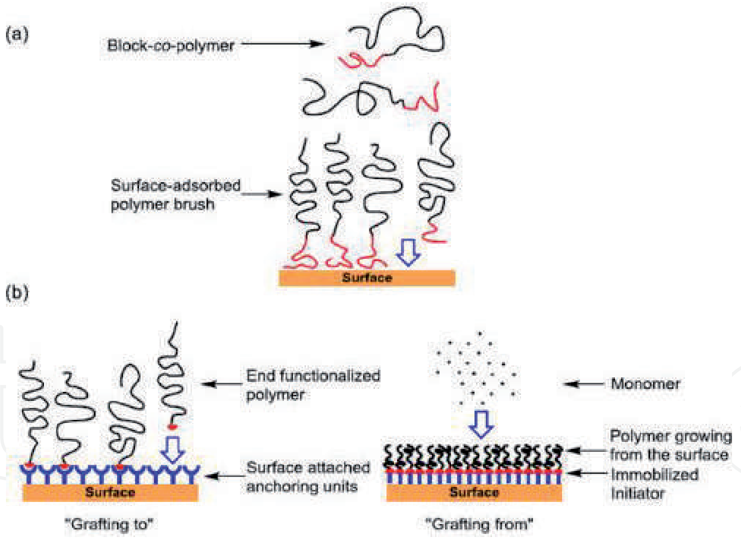

Figure 8.
Formation of a polymeric brush through (a) the physical adsorption of a block copolymer and (b) covalent bonding through "grafting-to" and "grafting-from" methods [11].

"grafting-to" method, the limitations of surface access for the incoming polymeric chains are referred to relatively low thickness and bond densities; in contrast, the "grafting-from" method uses small monomers, which, to provide relatively high bond densities, easily reach the surface growing reactive [11]. Controlled polymerization through the surfaces can create polymeric chains with adjustable lengths.

Polymerization methods used to synthesize polymer brushes include cationic polymerization [70], anionic [74], atomic transfer radical polymerization (ATRP) [75], ring-opening polymerization, and TEMPO-mediated radical [76].

4.1.2 Immobilization of biomolecules on polymer brushes

Several groups successfully made polymer brushes for biomolecule immobilization [12, 77, 78]. However, most designs require a separate derivative process to introduce a special functional group, for applications such as protein staining (**Figure 7**). Polymer brushes with hydroxyl groups, carboxylic acid, and epoxide are the most commonly used choices for simple derivation, among these, poly(acrylic acid) brushes are also more attractive, because these brushes in water multiply their initial thickness swells.

The membrane modification can be done through the growth of the brush by initiators located in the membrane pores (**Figure 9a**). Membrane modification with brushes usually employs polymerization from surfaces to achieve high polymer-chain areal densities [17, 18, 79]. Thus, brush synthesis typically includes initiator attachment to the membrane and polymer growth from these immobilized initiators [18, 79]. Among many techniques for brush growth, surface-initiated atom transfer radical polymerization (SI-ATRP) is particularly useful because ATRP offers controlled polymerization of a wide range of monomers under mild conditions and uses readily available catalysts and initiators [19–22]. Several groups modified a variety of membranes using ATRP from immobilized initiators, and binding capacities of such membranes often exceed 100 mg of protein per milliliter of membrane [42, 80–83]. The amount of protein binding in polymer brushes varies with polymer-chain areal density; low-chain densities yield few binding sites and minimal protein capture, whereas high densities may result in steric hindrance to protein entry into the brush [65]. Hence, an intermediate chain areal density will likely lead to the most protein binding [65]. Chain density depends in part on the density of initiation sites anchored to membrane surfaces, and anchoring typically occurs through surface functionalities such as hydroxyl groups [84] and carboxylic acids [85]. However, some membranes have low densities of such surface functional group.

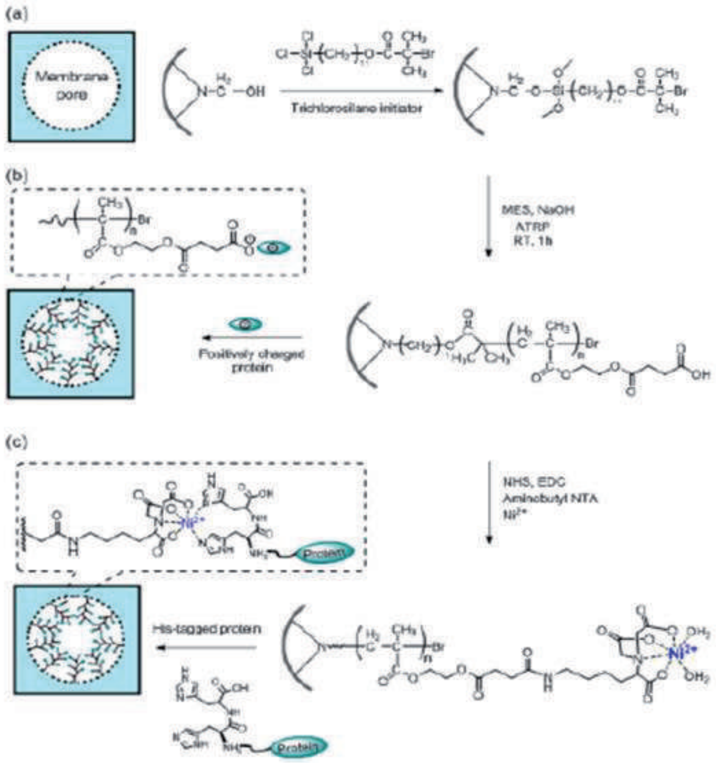

Figure 9.
Functionalization of membrane pores with poly(HEMA) brushes, activation (PHEMA) for forming poly(MES), and binding of His-tagged protein to a PMES-NTA-Ni2+ brush in a membrane pore. (a) Membrane modification though brush growth from initiators immoilized in membrane pores. (b) Protein capture in brush_modified membrane pores via ion_exchange. (c) Further functionalization of brushes for more selective purification of tegged protein [73].

In one study [80], to solve this problem, layer-by-layer adsorption of a macroinitiator was performed on a polyethersulfone membrane, and then the membrane was successfully modified using the ATRP from this macroinitiator. In protein capture through ion exchange, the brush-modified membranes show a significant protein binding capacity of 80–130 mg per cm^{3}of membrane (**Figure 9b**) [42, 48, 76, 86].

Further functionalization (**Figure 9c**) enables brushes to selectively purify the protein tagged. Alumina membranes with PHEMA-NTA-Ni^{2+} bind 120 mg His-tagged ubiquitin (His U) per cubic centimeter of membranes [87]. Also, nylon membranes with PMES-NTA-Ni^{2+} are functionalized. These membranes had larger pores than alumina membranes but still absorb 85 mg His U per cubic centimeter of membrane [88]. In addition, these membranes selectively bind His-tagged retinaldehyde binding protein from a cellular extract in less than 10 minutes. In general, the ability of polymer brushes to increase the binding capacity of the protein in the membrane depends on the type of polymer brush and the geometric shape of the membrane.

Even though the MES polymerization is carried out in water, attachment of the trichlorosilane initiator to the membranes is done in tetrahydrofuran (THF), which is sometimes incompatible with polymer membranes. To overcome this problem, Anuraj et al. utilized aqueous immobilization of a macroinitiator that was absorbed to the membrane through the hydrophobic interactions [89]. The subsequent polymerization of MES requires less than 5 minutes, and after functionalization with NTA - Ni^{2+}, these membranes provide the protein binding capacity as high as those after 1 hour of polymerization through modified membranes using the trichlorosilane initiator.

The main problem of the membrane modification with polymer brushes is the complexity and inefficiency of brush synthesis and derivation. Usually, the growth of brushes involves at least two steps: initiator attachment and polymerization under anaerobic conditions [67, 82]. In addition, often the monomer growth in brush does not end, and controlling the density of the initiator and the polymerization conditions for optimization of the binding is challenging [90]. Derivation is also inefficient. To develop more simple ways to modify the membranes, the Bruening group began a layer-by-layer adsorption study, which is described in the next section in detail about this method.

4.2 Modification of surfaces with polyelectrolyte multilayers (PEMs)

Polyelectrolytes are formed through alternating (layer-by-layer) adsorption of polyanion and polycation. These films can bind proteins and multilayers through electrostatic interactions or, when they contain appropriate ligands, may capture special proteins (**Figure 10**). Such films are versatile materials for binding several layers of protein on surfaces, including membrane pores.

4.2.1 Growth mechanisms and structure of polyelectrolyte films

In 1990, Hong and Decher [91, 92] demonstrated the basic principles of layer-by-layer (LbL) polyelectrolyte adsorption by exposure to a charged substrate with alternating solutions of polyanions and polycations (**Figure 11**). After adsorption of each polyelectrolyte, the surface (location) takes reverse charge, and one quasi-equilibrium adsorption requires only a few minutes.

Although the polyelectrolyte spray provides a quick way to form them [93], the absorption from the solution is the most common method for making these films [91]. Also, among many methods for forming thin films such as dip and spin coating or single-layer adsorption, layer-by-layer deposition of the complementary polymers has emerged as a technique, especially for controlling the thickness and performance of the film (**Figure 11**). **Figure 11** shows the most common layer-by-layer method indicates the alternating (continuous) absorption of polyanions and polycations. Currently, this method, by simply immersing a substrate selected in polyanion and polycation solutions, is performed with rinsing to remove excess polymer after each deposition step.

Polyanions used to deposit these films include poly(acrylic acid) [94], poly(styrene sulfonate) [95], poly(vinyl sulfonic acid) [96], hyaluronic acid (HA), and so on. However most polycations contain ammonium groups of type IV [97, 98] or protonated amines [99, 100]. **Figure 12** shows a number of these polyelectrolytes. The layer-by-layer method can also employ a wide range of charged components including proteins [101, 102], viruses [16], nanoparticles [103–105], and flaky minerals [106, 107]. A number of layer-by-layer methods employ interactions such as hydrogen bond [16, 108–111] or covalent bond [112–115].

The PE adsorption depends on the charge density and polymer structure. Polyelectrolytes with constant positive charge, such as poly(sodium styrene sulfonate) (PSS) and poly(dialyldimethyl ammonium chloride) (PDADMAC),

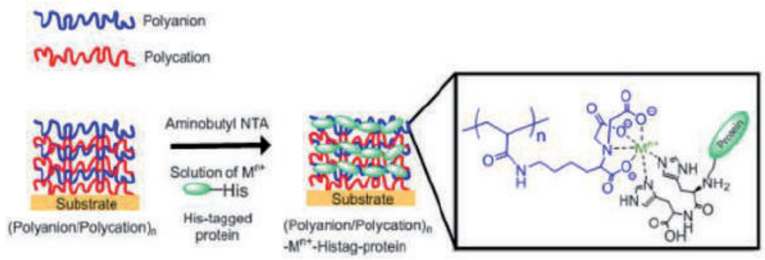

Figure 10.
Multilayer protein binding in a PEM derived with NTA-Mn^+ complexes [11].

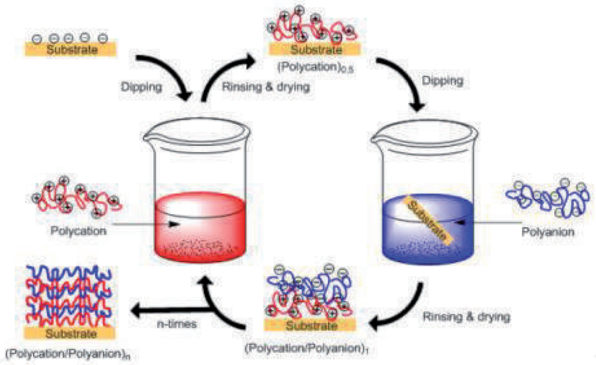

Figure 11.
Layer-to-layer absorption of polyelectrolyte multilayer [11].

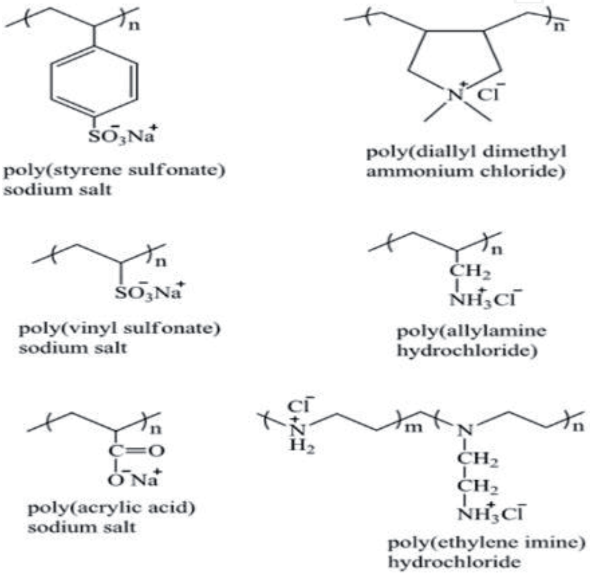

Figure 12.
The structure of conventional polyelectrolytes used in the manufacture of multilayers [116].

are called strong polyelectrolytes [117]. In comparison, for weak polyelectrolytes such as poly(vinyl amine) (PVA), poly(L-lysine) (PLL), poly(acrylic acid) (PAA), poly(allylamine hydrochloride) (PAH), and linear poly(ethylene imine) (LPEI), the charge depends on the pH and ionic strength [116]. Since both the density of charge and the PE conformation change with pH and ionic strength, these deposition parameters can dramatically alter the thickness and film conformation [116]. Typically, the thickness of PEM increases with increasing ionic strength of the sedimentation solution, because of the separation of the charge and the formation of loops and trains [118]. For weak polyelectrolytes, usually the thickest films are formed at pH values where polyelectrolyte has a low density of charge [119].

The binding and release of a protein, or other macromolecules, in a PEM greatly depends on the porosity and size of the mesh pores in the film (**Figure 13**) [120, 121]. In addition, film properties such as hydrophilicity-hydrophobicity balance and network charge complicate the binding and release of protein.

LBL films are often similar to a network structure (**Figure 13**), which includes cross-links caused by electrostatic interactions of polyanions and polycations.

The main factor governing the porosity of the network is the density of electrostatic complexation sites. A low-density cross-link refers to more open films and wider protein binding, but such films may be unstable. The change in polyelectrolytes, ionic strength, pH, or temperature can change the cross-link intensity and the protein binding as well as the film's stability and thickness.

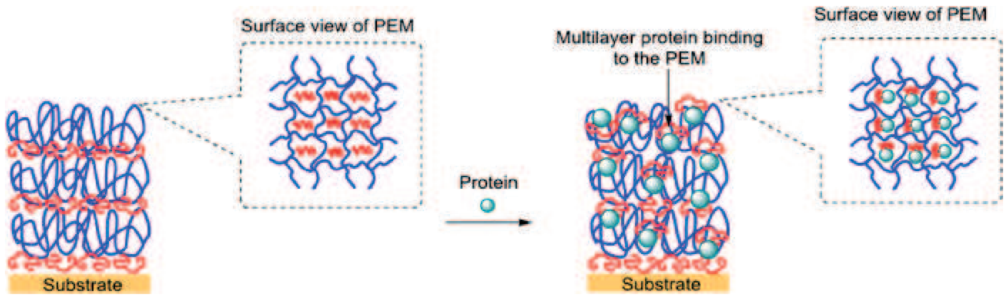

Figure 13.
Schematic representation of polyelectrolyte matrices designed for widespread protein binding [11].

4.2.2 Factors that change the growth of the film during layer-to-layer polyelectrolyte adsorption

In the addition of the selected polyelectrolyte for deposition, a series of adsorption parameters such as concentration and composition of support electrolytes [122–133], the molecular weight of polyelectrolytes [134–142], pH of polyelectrolyte solutions [143–150], adsorption time [122, 151–156], and temperature [157–159] affect the amount of polyelectrolyte deposited in layer-by-layer methods. Understanding the mechanisms of polyelectrolyte multilayer formation and the role of process parameters on determining the thicknesses and interfacial properties of multilayer films is essential for future film applications. Below we discuss the effects of a number of these variables on the growth of the film layer by layer.

4.2.2.1 The effect of electrolyte support

A number of studies investigated the importance of electrolyte support on the growth of polyelectrolyte films [122–126]. In the absence of salt added, polyelectrolytes, to maximize the intervals between charged repeating units (monomers) of polymers, are very broad [116]. Under these conditions, the adsorbed layers are thin, and the charge compensation of the surface is done only slightly (**Figure 14**) [160].

Excess salt may separate charges on polymeric chains and allows them to spiral and form thicker layers (**Figure 14**). Additionally, charge separation may require more polyelectrolyte adsorption to compensate for the opposite charge in a previously adsorbed film [116]. However, very high salt concentrations may lead to film lamination [161].

In addition to the electrolyte support concentration, the support electrolyte identity also changes the thickness of the film. Less hydrated cations [162] offer an increase in thicker polyelectrolyte films.

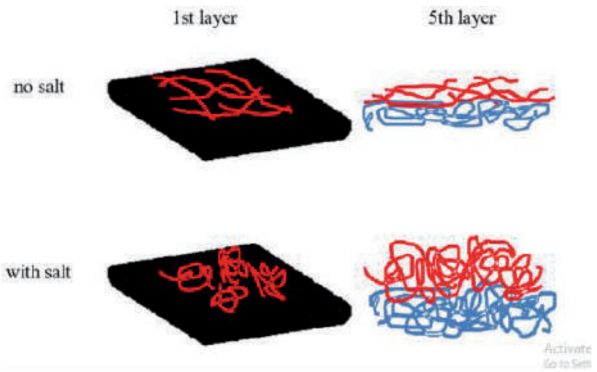

Figure 14.
The design of adsorbed polyelectrolyte layers in the presence and absence of salt. The lack of salt leads to thin layers of widespread polyelectrolytes, although in high ionic strength (salt presence), the coiled polymers form thicker layers [116].

Several other studies have tested that salt support in polyelectrolyte solutions changes the growth of films [163–165]. In these studies, the support electrolytes are all sodium salts, but the type of anion changes along the Hofmeister series from the cosmotropic anions to the chaotropic (F^-, $HCOO^-$, BrO_3^-, Cl^-, ClO_3^-, Br^-, NO_3^-, ClO_4^-) [165,]. Cosmotropic anions are strongly bound to water molecules and induce a number of structures in solution which leads to the deposition of molecules such as proteins; such anions increase the power (ability) of a hydrogen bond between water molecules to reduce the freedom of movement [116]. Chaotropic anions, due to their low electronegativity, high polarizability, and their weak electrostatic fields, destabilize the hydrogen bond between ions and solvent molecules to increase the solubility of a number of molecules [166]. Chaotropic anions strongly bind to polycations, thus reducing the density of the charge on the polyelectrolyte [116]. This refers to the formation of a coil structure, which increases the thickness of the layer.

4.2.2.2 Polyelectrolyte effect on multilayer adsorption

A number of polyelectrolyte properties, including chemical structure, molecular weight, concentration, and degree of ionization, affect the growth layer by layer of the polyelectrolyte layers. In this section, we will briefly explain the effects of these properties.

Studies showed that polyelectrolytes with different molecular weights have different effects on film thickness [91, 97]. Based on all these studies, it can be concluded that it is hard to predict how the thickness of the film will change with molecular weight.

The effect of concentration of polyelectrolyte solution is greater for strong polyelectrolytes. In high polyelectrolyte concentrations, many polyelectrolyte chains interact with the interface at the same time, and each one can only absorb on a small number of binding sites, which leads to relatively thick films. Inversely, in lower polyelectrolyte concentrations, polyelectrolytes interact with many binding sites at the surface to produce thinner films [167, 168].

The results of a number of studies show that increasing the concentration of polyelectrolyte to a certain extent can increase the thickness of the film. On this basis, it can be concluded that there is a saturation limit to increase the thickness and adsorption of the film, preferably similar to an adsorption isotherm [116].

4.2.2.3 The effect of deposition pH (or polyelectrolyte ionization degree) on the growth of polyelectrolyte multilayers containing weak polyelectrolytes

The effect of this parameter on weak polyelectrolytes is observed. The pH of the weak polyelectrolyte deposition solutions greatly affects the thickness of the film, as well as its permeability and morphology [143–147]. In weak polyelectrolytes, the ionization of groups such as amines and carboxylic acids, and therefore the density of the polymer charge, is a strong function of pH [116]. Increasing the density of the charge over the polyelectrolyte will result in the formation of thinner films and a decrease in thickness; however, increasing the density of charge on previously adsorbed polyelectrolytes will help to form thicker films [116]. However, it should be noted that extreme pH values can be completely prevented by film growth with the aid of desorption [149]. Changes in the charge density due to differences in pH are specifically dependent on the polyelectrolyte system; in lower charge densities, due to less electrostatic repulsion between repetitive units (monomers), weak polyelectrolytes will form more coil conformations [116]. In addition, a weaker electrostatic repulsion between adsorption polyelectrolyte molecules should help to form thicker films [150].

4.2.2.4 The effect of temperature on the growth of polyelectrolyte multilayers

The effect of this parameter appears more in strong polyelectrolytes. Increasing the deposition temperatures significantly increases the thickness of the polyelectrolyte films. Polyelectrolytes tend to precipitate at higher temperatures, which leads to the formation of thick and rough layers [159]. Secondary interactions such as hydrogen bonding and hydrophobic and van der Waal's forces, which depend on temperature, also change the thickness of polyelectrolyte multilayer films [169].

It seems that the time parameter effect is less than the other parameters mentioned. Available studies on polyelectrolyte multilayers show a wide range of time estimates (seconds to hours) needed to form a layer [122, 151–156]. This widespread range of times may be due to differences in structure, molecular weights, and deposition pH amounts of polyelectrolytes used to form multilayered films [116].

5. Membrane modification and its application in biotechnology

5.1 Protein purification

Membrane-based processes are beginning to play crucial roles in the separation and purification of biotechnological products. Polyelectrolyte films and polymer brushes in porous support can be used as new membranes for biomolecule isolation and purification. Many studies investigated the interaction of proteins with LBL films [170, 171], In some cases, films can be used as protein storage with high binding capacity of proteins [172]. However, no theory has foreseen the insertion or loading of biomolecules in films, this is often due to the lack of experimental tools for accurately analyzing the molecular distribution and mobility [11].

LBL adsorption of polymer films and subsequent derivation were used to construct PEM-modified membranes, which easily capture the His-tag protein [173]. PEI/PAA multilayers selectively attach a protein from a mixture of concanavalin A and lysozyme. At pH 7/3, $(PEI/PAA)_3$ preferably adsorbed positive-charged lysozyme, and $(PEI/PAA)_2$ PEI adsorbed negative-charged concanavalin A [174]. Polyelectrolyte multilayer films formed in membrane pores that are terminated to a polyanion have cation exchange sites, as shown in (**Figure 15**).

Adsorption of proteins depends on the surface charge, protein charge, and the thickness of the polyelectrolyte film [175]. Generally, protein binding in LBL films depends on the size of the membrane pore, hydrophobicity, and surface charge [65].

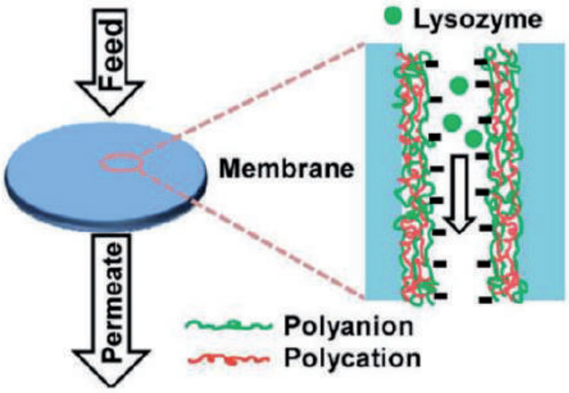

Figure 15.
Showing a schematic diagram of positive-charged lysozyme binding to a polyelectrolyte film terminated to the polyanion (the charges have been marked only for the end layer) [116].

Membranes containing film PAA/BPEI/PAA bind 100 mg/ml lysozyme through ion exchange [11], which is about twice the capacity binding of the commercial ion exchange membranes. So that, the Mustang S exchange membranes represent the binding capacity of lysozyme only 45-50 mg/cm^3 of membrane [133]. Also, after further modification of these layers with metal ion- NTA complexes (**Figure 16**), the membranes bind 70 mg/ml concanavalin A (ConA) (a 25-kDa protein) and 97 mg/ml of His-U (a 10-kDa protein). Interestingly, these membranes are selective, so that, optionaly,capture His-tagged COP9 (His-tagged COP9 signalsome complex sub unit 8) from a cell lysate with a purity of >95% [11]. More interestingly, and most importantly, the entire purification process takes less than 30 minutes from the beginning to the end of the process.

When the protein is captured from the cell extract, the size of the pores greater than 1 μm prevents the blocking of pores, and to maintain the flow speed is important [65].

Despite the successes mentioned in the membrane modification using polyelectrolyte multilayer films, because the derivation of these films is done using NTA ligand, which is an expensive ligand, the derivation of these films is costly, and also, only a small fraction of aminobutyl NTA is bound to the membrane; in addition, only one small portion of aminobutyl NTA attaches to the membrane. To overcome this problem, direct adsorption of metal ion binding polymers was performed without the need for further derivation with the NTA ligand [11].

Most purification processes employ a tool and method that, in addition to being inexpensive and productive in terms of time, are also consuming. Membrane-based purification processes are fast due to the fact that flow through membrane pores rapidly brings biomolecules to the binding sites. But despite this advantage, the biggest defect in the membrane is the lower surface area than the beds containing nanoparticles, which ultimately leads to lower binding capacity. In this regard, attempts to increase the membrane binding capacity and membrane modification methods should be advanced in a way that all these benefits are provided together. The advantage of polymeric film and brush-based modification techniques is that these polymers in water can swell several times their initial thickness and make the entry of biomolecules to the binding sites more rather easier and ultimately provide high

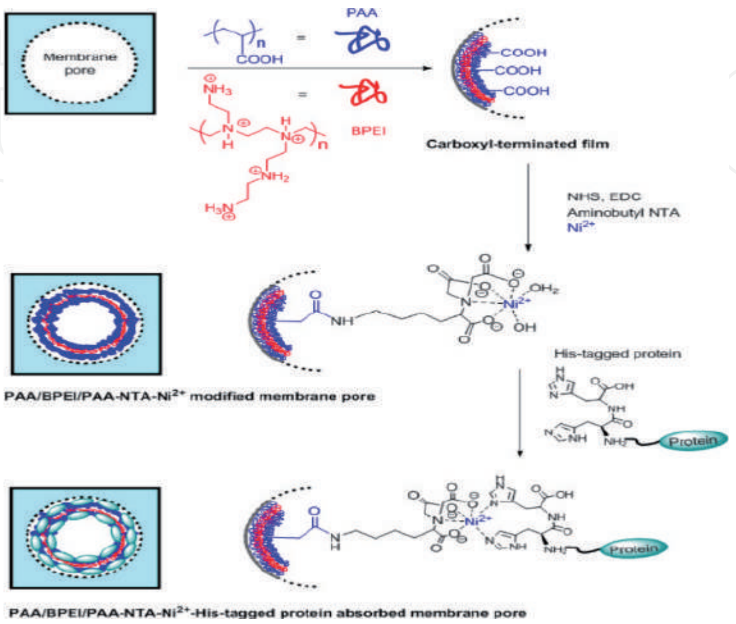

Figure 16.
The display of adsorption schematic (PAH/PAA)$_n$ in a membrane pore, functionalization with NTA-Ni^{2+}, and multilayer His-tagged protein binding [11].

binding capacity. Polymer films should have enough thickness and swelling to achieve high binding capacity and, on the other hand, do not block the membrane pore. In this regard, in most studies, three or lower layers are adsorbed in the membrane pores.

5.2 Antibody purification

Membrane purification processes are also used to purify and isolate antibodies. Common antibody purification processes using columns that contain immobilized protein A and G are costing.

Microporous membranes containing PAA/PEI films [176] were modified with small peptides and antibodies and then used to purify antibodies and proteins. Also, membranes containing small peptide, K19, selectively capture Herceptin from human plasma (**Figure 17**). And, the membrane modified with antibodies were successfully used to capture protein from cell lysate (Anti- (hemagglutinin A) (HA) antibodies captured HA-tagged regulator G-protein signaling2 (HA-RGS2) from cell lysate) (**Figure 20**).

Small peptides were immobilized to the membrane pores using the activation of the last PAA by NHS/EDC (**Figure 18**), and then the antibody was purified.

Although antibodies are important biotechnological therapists, their purification is highly costly; on the other hand, purification techniques that based on the column are long [176]. Therefore, trying to find the appropriate purification procedure for these therapists is essential. Membrane-based methods are promising candidates for this goal.

In this case, to purify the protein by immobilization of antibodies in membrane pores, there is the fact that the immobilization of antibodies by electrostatic is unstable, but provides high binding capacity (**Figure 19**). (A) In contrast, covalent immobilization provides stable binding to membrane pores but provides lower binding capacity (**Figure 19**). (B) In contrast, a two-step immobilization method [176], comprising electrostatic immobilization followed by a covalent linking (**Figure 19**) (C), maintains both the high capacity of electrostatic immobilization and the stability of covalent binding.

Tagged-protein selectively was captured using modified membranes with immobilized antibodies in membrane pores, which were immobilization with two-step immobilization method (**Figure 20**).

5.3 Phosphopeptide enrichment using TiO_2 nanoparticles containing membranes

Due to the relatively low abundance of phosphorylated proteins, detection and identification phosphorylation sites are challenging even with recent advances in

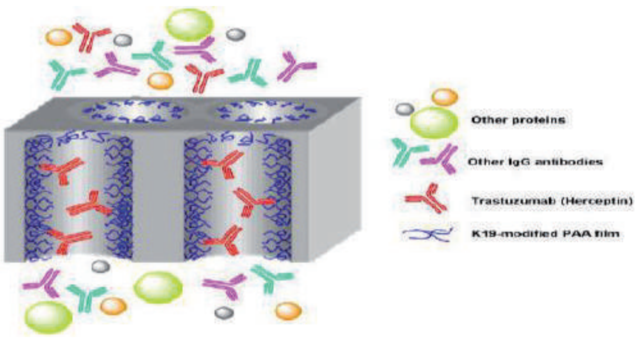

Figure 17.
Illustration of selective Herceptin capture in membranes modified with K19 peptide. K19 selectively binds Herceptin in the presence of other IgG antibodies [176].

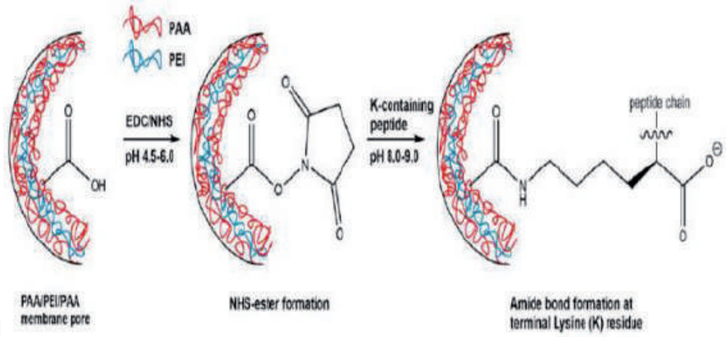

Figure 18.
Peptide/protein immobilization via EDC/NHS mediated coupling. For peptide in this research, a terminal lysine couples to PAA carboxyl groups. Proteins present surface amines for the coupling reaction [176].

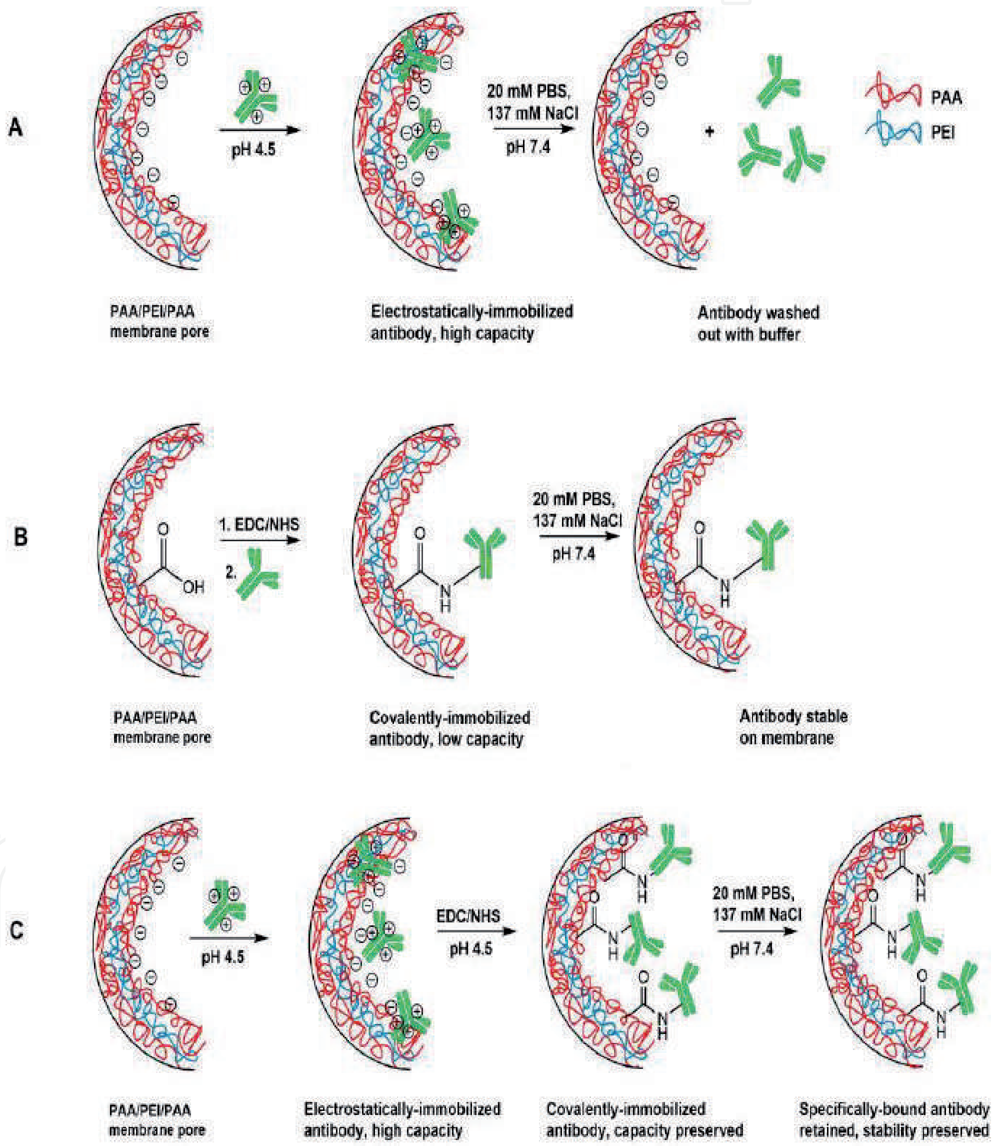

Figure 19.
(A) Electrostatic immobilization of antibodies yields high capacity, but the antibody elutes from the membrane in salt solutions. (B) Direct covalent immobilization does not yield the high capture capacity of electrostatic immobilization, but it does increase the stability of antibody on the membrane. (C) The two-step antibody immobilization of antibody first uses electrostatic capture to attain a high capacity and then covalently links the antibody to the membrane to increase stability [176].

MS [177]. The adsorption of nanoparticles in membrane pores is another way to provide selective binding sites. Phosphopeptide capture can be done through selective adsorption on ZrO_2 or TiO_2 columns or on matrix-assisted laser desorption/

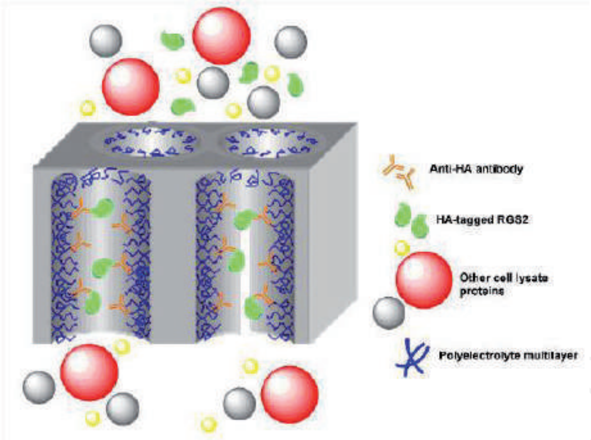

Figure 20.
Illustration of membrane-based selective capture of HA-tagged RGS2 from cell lysate. The capture employs immobilized antibodies [176].

ionization (MALDI) plates containing TiO_2 nanoparticles [178, 179]. Membranes are modified with sequential adsorption of poly(sodium styrene sulfonate) (PSS) and TiO_2 nanoparticles in membrane pores [180] (**Figure 21**). The membranes are attractive for the immobilization of TiO_2 nanoparticles [181–183], which are very small for column formats. These nanoparticles have a high surface area and can exhibit different and more binding capacities than larger particles. The binding capacities obtained in this way are less than the binding capacities of the brush-modified membranes, because the nanoparticle adsorption cannot provide films with high thickness and swelling.

5.4 Protease-containing membranes for controlled protein digestion before mass spectrometry analysis

By using existing methods for immobilization of protein in membrane, the Bruening group began employing enzyme-modified membranes as controlled reactors for protein digestion prior to analysis MS. MS is the most common and powerful technique for detecting proteins and their posttranslational modifications [184]. Although peptides, in comparison to proteins, are more capable of MS and liquid chromatography MS analysis [65]. Therefore, digestion is usually a critical initial step for analyzing MS proteins; digestion usually occurs after a protease such as trypsin is mixed with substrate proteins in solution [65]. Although this method requires low enzyme concentrations to restrict self-digestion of protease, digestion times are generally 1 hour or more [185]. To overcome this problem and

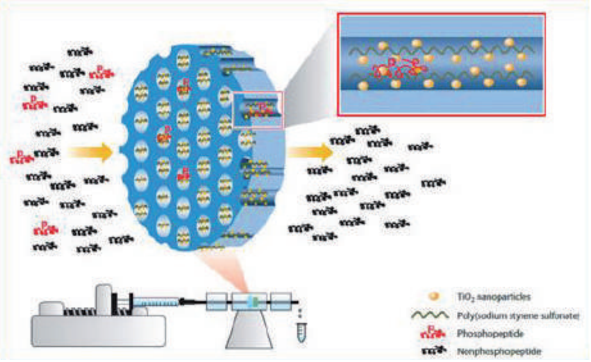

Figure 21.
Schematic of selective phosphopeptide capture in a membrane containing TiO_2 nano particles. A small holder attached to a syringe pump enables phosphopeptide elution in as little as 10 microliters of solution [65].

make it easier to analyze MS online, several research groups developed reactors with proteases immobilized on solid supports including monoliths [186, 187], membranes [188, 189], polymeric microfluidic channels [188, 190], and resins [191, 192]. With a thickness of only 10–200 micrometers, membranes provide excellent surface for controlling protein digestion [65]. Perhaps the biggest advantage of membrane digestion is controlling of peptide size afforded by varying residence times down to the millisecond level [65]. Little residence times should yield big peptides as a result of missed cleavage site, as a result of greater sequence coverage; larger peptides should enhance recognition of posttranslational modifications [65]. The purpose of current studies is to use large peptides to activate antibody sequences [65]. Limited digestion can also help reveal the presence of flexible regions in proteins because proteolytic sites are more accessible in these areas [193, 194]. (**Figure 22**) shows schematically preferred digestion in a protein flexible, accessible region, recognition of such regions is important for selecting shorted protein sequences to express for crystallization [65].

5.5 Isolation of enantiomer in racemic mixtures by membrane

Most of the drugs used today are racemic. An enantiomer may have the same effect as another enantiomer or even a harmful and different effect. Therefore, there is a need for tools and methods to detect and isolate enantiomers. The membrane's advantages over other separation methods in the previous sections are discussed in detail. As a new result of the use of membranes in the separation of racemic mixtures, modifying the regenerated cellulose membrane with chiral L-proline-copper complexes [195] through an intermediate epoxy-silane surface functionalization reaction for various times is a good example (**Figure 23**).

This chiral copper complex has various powers of coordination interactions with different enantiomers based on their space chemistry (stereochemistry) [195]. In this work, the ligand exchange chemistry is used to create membranes capable of separating the mixture of amino acids and potentially other drug substances that have functional groups capable to ligating with the metal complex. Such technique is simple, inexpensive, and scalable; also the method applied for membrane modification is very simple. The resulting membranes were evaluated in single component diffusion experiments with D- or L-phenylalanine (Phe), which showed much higher permeability for D-Phe than L-Phe. The high amount of Peclet number obtained (~400) [195] during the filtration process, combined with the complete fractionation of the enantiomer, shows that such system is very attractive and excellent as a competitor for chiral chromatography.

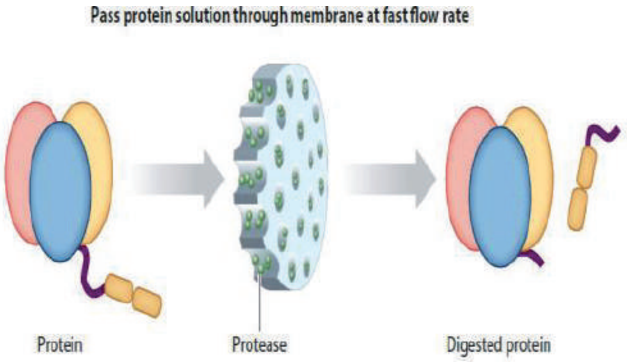

Figure 22.
Limited digestion at the most flexible and accessible site of a protein during rapid passage through a protease containing membrane (protein not drawn to scale, as it is much smaller than the membrane pores) [65].

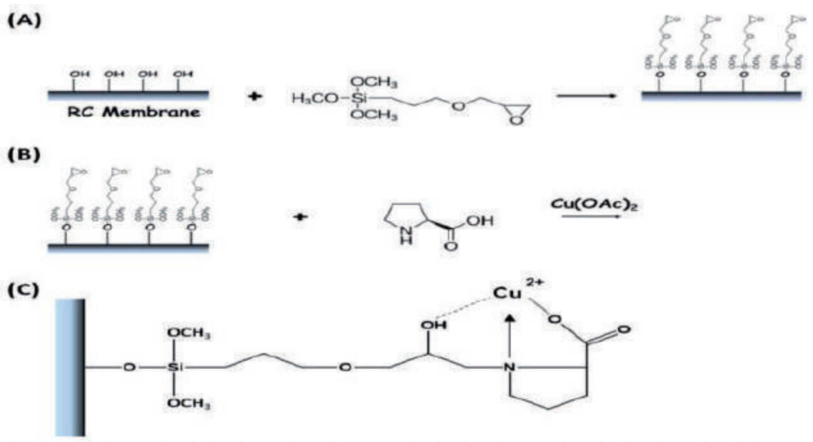

Figure 23.
Chemistry of ligand exchange. (A) Functionalization of RC membrane surface with the epoxy-silane. (B) Grafting of L-proline to membrane surface followed by immersion in aqueous copper acetate solution. (C) Resultant complex of grafted L-proline with copper [195].

6. Conclusion

Given that biomolecules now cover many areas of human life (most importantly the therapeutic area), identifying purification methods and isolating these materials and finding the right and most appropriate method are essential. Due to the constraints of column-based isolation and purification methods, the membranes provide the possibility of purification and rapid separation of biomolecules and, as a result, are excellent and unmatched substitutes and rivals for compacted bed-based chromatography systems. Membrane modification with polymer brushes provides three-dimensional and swelling structures for separation and purification of biomolecules with high-capacity binding. In terms of hard conditions, anaerobic conditions, initiator density control and their synthesis hard conditions, layer-by-layer adsorption of polyelectrolytes is a good alternative instead for brush synthesis, which is also explained in the brush section. In this way, with this simple modification method, membranes with binding capacities higher than conventional commercial membranes and as much as polymer brushes can be obtained. By controlling the thickness of the polymer films and also controlling the density of the polymer brushes,In addition to obtaining a high binding capacity, can maintain the flow rate through the membrane pores. The use of membranes in various fields of biotechnology indicates membrane's success in this area. In this regard, it can be said that the membranes will find great positions in the future of life.

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Chapter

Membrane Distillation: Basics, Advances, and Applications

Mohammad Reza Shirzad Kebria and Ahmad Rahimpour

Abstract

Membrane technology as an emerging separation process has become competitive with other separation techniques in recent decades. Among pressure-driven and isothermal membrane processes, membrane distillation (MD) as a thermally driven process has come out to put an end to hardships of such processes like distillation. MD process can be used in a wide variety of applications such as desalination and wastewater treatment. Generally, MD is a process which water is a main component of the feed solution and only water vapor can pass through a hydrophobic membrane pores. With four main configurations different from each other by their condensation procedure, the performance of MD process is limited due to the lack of appropriate module, membrane, and energy consumption rate. In recent years, many experiments have been carried out to find well-suited membrane type and module. Also, applying solar or waste heat as heat source and the capability of coupling with other processes like forward osmosis and osmotic distillation distinguish MD process from other membrane processes. This chapter addresses membrane characteristics, MD applications, transport mechanisms, and process challenges.

Keywords: separation process, membrane distillation, desalination, hydrophobic membrane

1. Introduction to history and fundamentals of membrane distillation (MD)

1.1 Brief introduction to history

When the term membrane distillation (MD) is the subject of discussion, traditional thermal distillation process comes to mind, unconsciously. In fact, MD and thermal distillation are temperature-dependent processes in which work is based on vapor-liquid equilibrium (VLE) and needs heat source to be supplied to attain the requisite latent heat of vaporization of the feed solution. To avoid misapprehensions, a workshop was held in Rome on May 5, 1986, in order to find a unique name for a process previously known by different names such as transmembrane distillation, thermo-pervaporation (PV), and membrane evaporation. Terminology committee consisted of six different members including V. Calabro (Universita della Calabria, Calabria, Italy), A.C.M. Franken (Twente University of Technology, Enschede, Netherlands), S. Kimura (University of Tokyo, Tokyo, Japan), S. Ripperger (Enka Membrana, Wuppertal, Germany), G. Sarti (Universita di

Bologna, Bologna, Italy), and R. Schofield (University of New South Wales, Kensington, Australia) who chose membrane distillation term for a distillation process in which two sides of membrane (liquid and gas phases) are detached by a porous membrane [1]. Generally, MD must be referred for nonisothermal membrane separation process in which the driving force is partial pressure difference induced by temperature gradient across the membrane that fulfills the following properties: (i) high porosity, (ii) high wetting resistance, (iii) does not change the VLE of the species, (iv) separates liquid and gas phases, and (v) condensation must not occur in membrane pores.

For the first time, on June 3, 1963, MD process was defined by Bodell to which he filed US patent describing an apparatus producing potable water from impotable aqueous mixture [2]. He invented an apparatus which was impermeable to water molecules but permeable to water vapor molecules. After Bodell's invention, on 1967, new findings were reported by Weyl (filed on May 14, 1964) to which he recorded a US patent describing an improved apparatus for recovery of water from impotable salty water [3]. Unlike Bodell who used silicon rubber as membrane (0.64 mm outer diameter and 0.30 mm inner diameter), Weyl used a polytetrafluoroethylene (PTFE) membrane (average pore size of 9 mm) to produce potable water. He also stated other hydrophobic polymers such as polyethylene (PE) and polyvinyl chloride (PVC), and also hydrophilic polymers coated by hydrophobic materials can be applicable for fabrication of MD membranes. After recording of the first MD patent, it took 4 years to publish the first MD paper by Findley on 1967 in the international journal *Industrial & Engineering Chemistry Process Design Development* [4]. Findley used different types of materials to fabricate MD membrane such as gumwood, aluminum foil, cellophane, and glass fibers. He also used silicone and Teflon to make the membranes more hydrophobic. According to the MD experimental results, some of the membranes fabricated by Findley had intra-pore condensation or intra-layer moisture adsorption. Based on his experimental

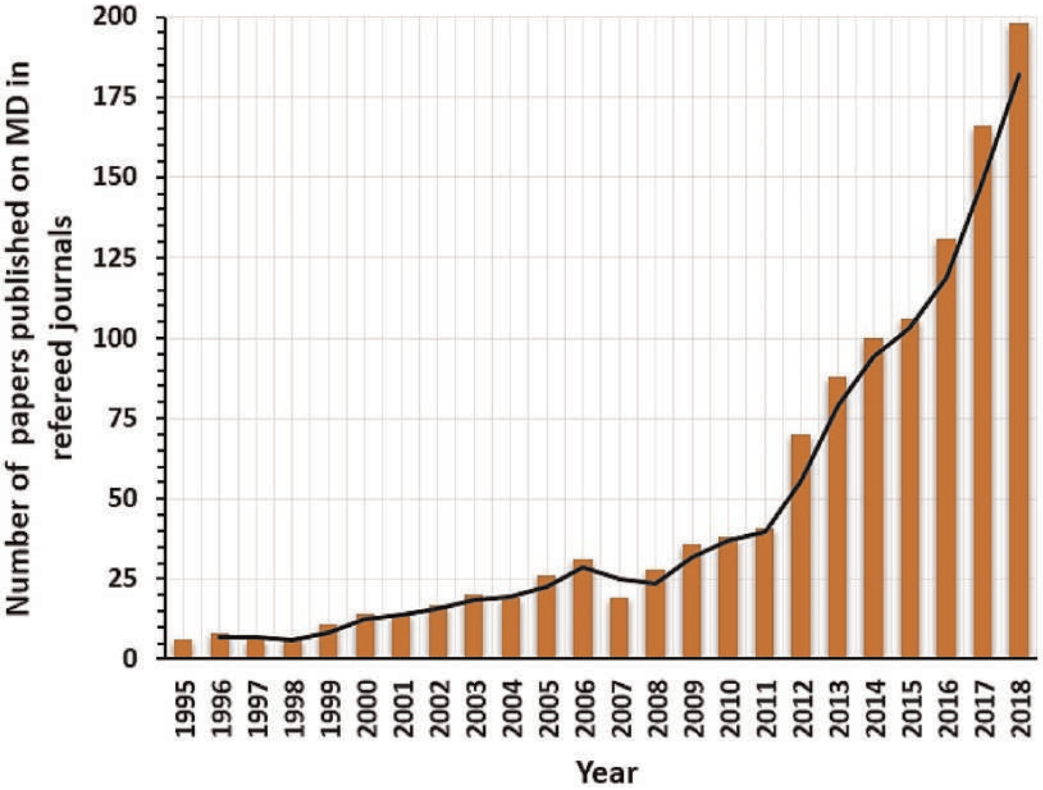

Figure 1.
Research interest on membrane distillation up to December 31, 2018, represented as a plot of number of papers published in refereed journals per year.

findings, Findley stated the highest efficiency will be achieved on high temperatures along with using low-cost membranes. After short couple of years, research interest on MD decreased unexpectedly due to lower obtained MD flux than other separation methods such as reverse osmosis (RO). After staying in shadows for several years, MD garnered attention once again in the early 1980s due to advances in membrane manufacturing techniques. Gore and Associated Co. [5], the Swedish National Development Co. [6, 7], and Enka AG [8–10] were the first to commercialize developed generation of MD membranes. Esato et al. developed a biologically inert membrane oxygenator which is later commercialized under the name Gore-Tex membrane distillation as spiral wound module [11]. Also, plate and frame membrane module was used by the Swedish National Development Co. in air gap membrane distillation (AGMD). In 1984 during the holding of Europe-Japan Joint Congress on Membranes and Membrane Processes, Enka presented the results of their direct contact membrane distillation (DCMD) experiments applying polypropylene (PP) hollow fiber membranes [12].

From an industrial viewpoint, MD has attracted little attention, yet, due to its rate of productivity which is not competitive enough compared with other industrial technologies. On the contrary, research interest in MD has grown considerably within the academic community. The number of MD publications in referred journals has increased almost 40 times in 2018 since 1995. **Figure 1** shows growth rate of MD publications from 1995 to 2018.

1.2 Fundamental of MD

MD is a well-suited technology for separation processes in which water is the major component of the feed solution. In MD, at least one side of a microporous hydrophobic membrane is in direct contact with an aqueous solution. Partial pressure difference induced by temperature gradient between two sides of membrane causes mass transfer through membrane pores. During MD process, liquid molecules are not allowed to infiltrate due to the hydrophobicity of the membrane, and only water vapor molecules are able to pass through the membrane walls. Based on partial pressure difference, evaporation of volatile compounds occurs; the vapor molecules pass across the pores and are condensed/evacuated on the permeate side of the membrane. Various MD configurations are applied to maintain the driving force on two sides of the membrane [13]. However these configurations can only be distinguished by their condensation procedure (**Figure 2**).

i. A condensing fluid (usually pure water) colder than feed stream flows across the permeate side of the membrane by means of circulating pump. At the time, the volatile component (water or volatile organic compounds) evaporates at the hot liquid/vapor interface, passes through the pores, and condense in the condensing fluid inside the MD cell. This type of configuration is known as direct contact membrane distillation due to direct contact between condensing fluid and the membrane surface. Among various MD configurations, DCMD is the most extensively investigated due to its ease of setup in laboratory scale and higher permeate flux than other configurations. Generally, DCMD is an appropriate method for desalination or production of fruit juice in which water is the main permeate component [14].

ii. In this configuration, vacuum is applied in the permeate side of the module by vacuum pumps in which vapor molecules are sucked out through membrane pores. To maintain driving force, the applied vacuum pressure must be lower than the saturation pressure of volatile components separating from the hot

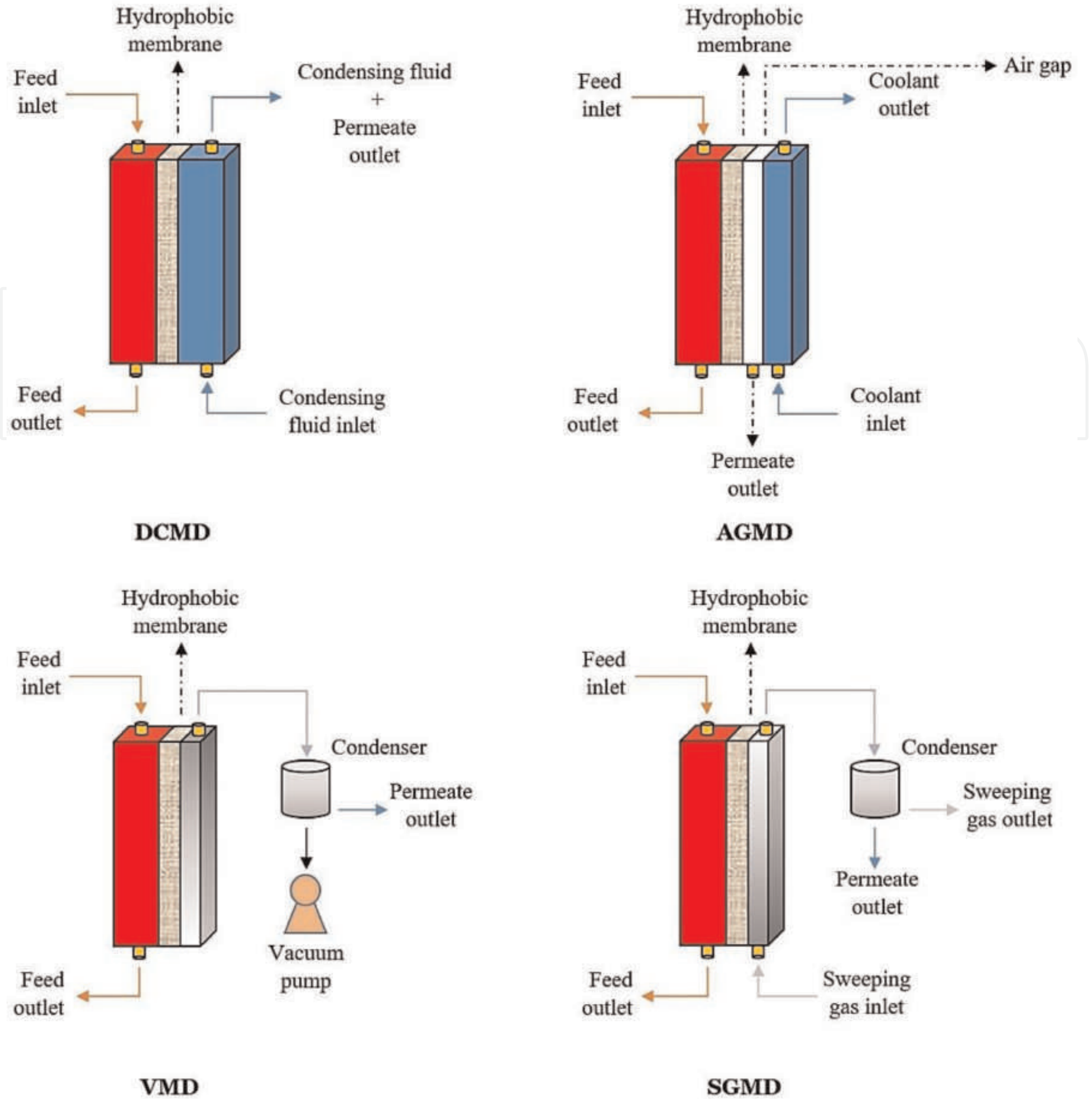

Figure 2.
Schematic of various MD configurations.

feed solution. In this type of MD, condensation occurs outside of the condensing chamber by means of an external condenser. This type of configuration is known as vacuum membrane distillation (VMD) due applied vacuum in the permeate side of the module.

iii. A stagnant air layer is placed between the permeate side of the membrane and condensing wall to reduce heat loss by conduction. In this configuration, vapor molecules pass across both the membrane wall and air layer and eventually condense over a cold surface of condensing wall inside the MD cell. At last, condensed component exits from the condensation chamber by the use of the gravity. This type of configuration is called air gap membrane distillation.

iv. In sweeping gas membrane distillation (SGMD), a cold inert gas is blown into the condensation chamber and sweeps permeated vapor molecules taking them out of the MD cell. In this method, condensation just like VMD takes place outside the module. Due to heat transfer between hot permeated vapor and blown inert gas, the temperature of sweeping gas increases continuously

MD configuration	Application area	Advantages	Disadvantages
Direct contact membrane distillation (DCMD)	• Seawater desalination • Crystallization • Treatment of dye effluents • Arsenic removal from aqueous solution	• High permeate flux • Considered at commercial scale	• High conductive heat loss
Vacuum membrane distillation (VMD)	• Seawater desalination • Treatment of alcoholic solution • Recovery of aroma compounds • Treatment of textile wastewaters	• High permeate flux • Considered at commercial scale	• High risk of membrane pore wetting • Process complexity
Air gap membrane distillation (AGMD)	• Seawater desalination • Concentration of fruit juices • Separation of azeotropic mixtures • VOC removal	• Low conductive heat loss • Process simplicity • Low risk of temperature polarization (TP)	• Lower flux than DCMD and VMD
Sweeping gas membrane distillation (SGMD)	• Brackish water desalination • Separation of azeotropic mixtures • Wastewater treatment • VOC removal	• Reduction of the barrier to the mass transport through forced flow	• High risk of temperature polarization (TP) • Process complexity

Table 1.
Properties of various MD configurations.

along the condensing chamber length. To minimize the effect of heat transfer between hot and cold stream, a cold wall is improvised in the permeate side of the module. This recently introduced method is called thermostatic sweeping gas membrane distillation (TSGMD). **Table 1** presents details of various MD configurations.

2. MD membranes fabrication techniques and design

2.1 Membrane fabrication

As stated earlier, the main characteristics of MD membrane are porosity and hydrophobicity. MD membrane can be supported and unsupported and also might be fabricated in the form of single-layer membrane, composite dual-layer membrane (hydrophobic/hydrophilic), and composite triple-layer membrane (hydrophobic/hydrophilic/hydrophobic). The surface mean pore size of the membrane applied in MD is between 100 Å and 1 μm.

Generally, MD membranes can be fabricated by track etching, sintering, phase inversion, electrospinning, etc. Among these procedures, phase inversion is the most applied method. Also, several types of membranes are fabricated by combining the abovementioned methods. In 2013, Zhu et al. fabricated novel hollow fiber membrane by combining extrusion, sintering, and stretching [15]. Phase inversion method is based on solidification of a homogenous polymeric solution by such several procedure such as non-solvent-induced phase separation (NIPS), evaporation-induced phase separation (EIPS), thermally induced phase separation (TIPS), and vapor-induced phase separation (VIPS) in a controlled way [16]. NIPS and TIPS are the most commonly used techniques to fabricate MD membranes. In NIPS method, the polymer is dissolved in appropriate solvent, and then the polymeric solution is casted on a glass plate or non-woven support. After casting, the polymeric film is immersed into the non-solvent bath. After a while, two phases are formed: a polymer-rich phase and a solvent-rich phase. Solvent/non-solvent exchange continues until the whole polymer component becomes solid. To fabricate membranes by TIPS technique, a solution containing polymer/diluent must be prepared and then is casted via favorable procedure. After precipitation of polymer component by cooling method, diluent extraction causes pore formation [17–20]. In recent years, electrospinning technique has been suggested by many researchers to prepare well-suited MD membranes [21–23]. To prepare electrospun nanofibrous membranes (ENMs), a polymeric solution must be poured into a needle-equipped syringe. Electrospinning apparatus consists of a high-voltage electric source, needle-equipped syringe, syringe pump, and a collector. After overcoming the surface tension, polymeric jet is directed toward a collector (often rotating drum) in the shape of cylindrical nanofibers. To obtain uniform membrane structure, syringe pump has axial movement [13]. The schematic of electrospinning process is shown in **Figure 3**. The properties of commercial membranes used in MD are presented in **Table 2**.

2.2 MD module design

Membrane modules are one of the most important parts of MD process which control the operation parameters. Different types of MD module are manufactured so far especially for each kind of MD configurations. MD module must possess

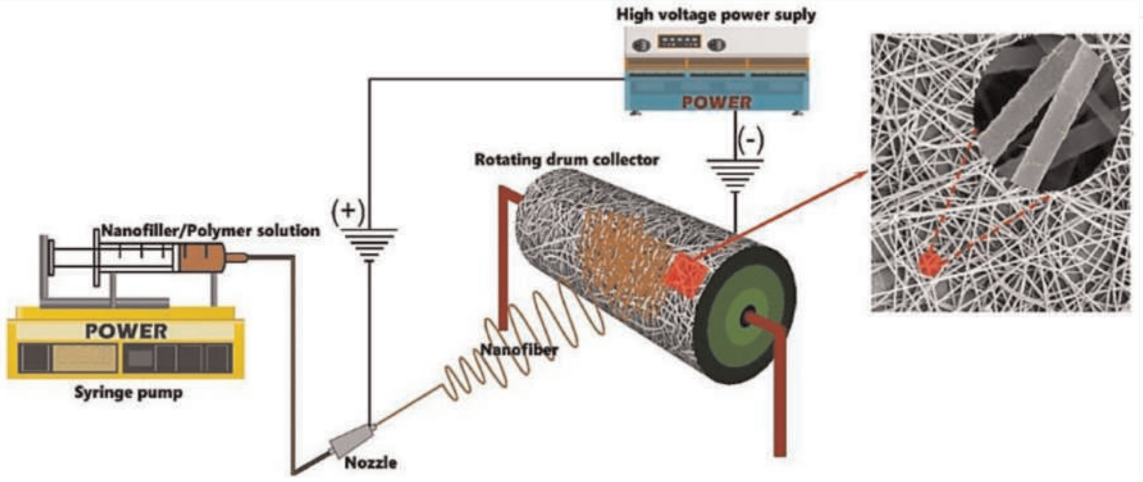

Figure 3.
Schematic of electrospinning process. Source: Reprinted from [24].

Membrane commercial code	Membrane type	Producer	Material	Porosity (%)	Membrane thickness (μm)	Reference
TF200	Flat sheet	Gelman	PTFE/PP	80	178	[25]
GVHP	Flat sheet	Millipore	PVDF	70–75	110	[26]
MD020TP2N	Tubular	Enka Microdyn	PP	75	1550	[27]
Celgard X-20	Tubular	Hoechst Celanese Co.	PP	35	25	[28]
G-4.0-6-7	Flat sheet	Gore-Tex Sep GmbH	PTFE	80	100	[29]
PP 50/200	Hollow fiber	Accurel Membrana	PP	0.5	200	[30]
3 MA	Flat sheet	3 M Corporation	PP	60	91	[31]

Table 2.
Commercial membranes recently used in MD.

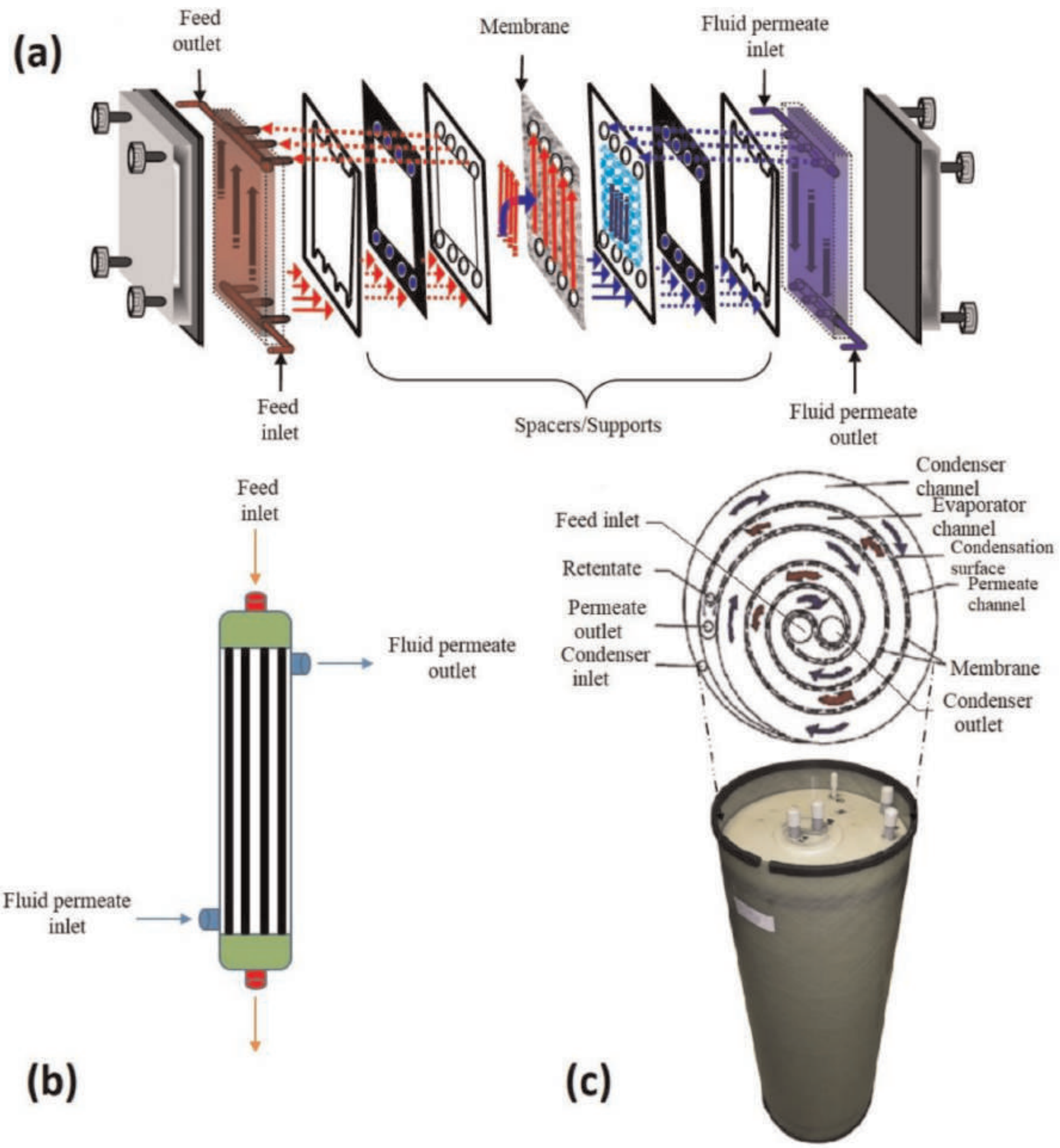

Figure 4.
Different MD modules: (a) plate and frame, (b) capillary, and (c) spiral wound. Source: Reprinted from [32].

Module producer	Effective membrane area (m^2)	Membrane material	Permeate flux (kg/m^2h)	MD configuration	Type of module	Reference
SEP GmbH	4	PTFE	2.5–12.5	DCMD	Spiral	[34]
GE Osmonics SEPA CF	0.014	PTFE	22.3	DCMD	Plate and frame	[35]
Microdyn	0.1	PP	3.6	VMD	Capillary	[36]
Enka-Microdyn	0.036	PP	4	DCMD	Tubular	[37]
Scarab development AB	2.8	PTFE	6.5	AGMD	Plate and frame	[38]
Microdyn	0.1	PP	13	DCMD	Hollow fiber	[37]

Table 3.
Commercial MD modules with different configurations.

required characteristics such as high packing density; high mechanical strength and chemical and thermal stability; low pressure drop; low heat loss; and user-friendly (for cleaning or membrane replacement). As presented in **Figure 4**, MD modules are divided into three major groups including plate and frame, spiral wound, and capillary (**Figure 4**).

i. Plate and frame module is the simplest one among all MD modules. It consists of a series of flat sheet membranes, spacers, and supports which are connected in axial direction. This type of MD module has shown good potential for commercialization due to its tangential flow in which the liquid stream is in direct contact with the membrane surface.

ii. In spiral wound module, supported or unsupported flat sheet membranes are wrapped around a central tube in a spiral formation. Spiral wound module can provide tangential flow and represent high surface to volume ratio which makes it the desirable choice for applying in MD process.

iii. Capillary modules are divided into three main categories: (1) capillary modules, (2) tubular modules, and (3) hollow fiber modules. Capillary, tubular, and hollow fiber membranes are distinguished by their inner and outer diameter which effects on their packing density. The membranes with diameter ranging from 5 to 25 mm are classified as tubular membranes (packing density 300 m^2/m^3). Capillary membranes often have pores with diameter between 1 and 3 mm (packing density 1200 m^2/m^3). The diameters of hollow fiber membranes are usually below 1 mm (packing density 500–9000 m^2/m^3) [33]. These types of membranes are typically assembled and bundled in shell and tube modules. **Table 3** summarizes some MD modules used in desalination process.

3. MD membrane characteristics

MD membranes should have such characteristics to show their best performance in MD process. Before conducting MD tests, the applied membranes must be characterized by different methods to abstain from wetting during experiments. MD membrane characterization techniques are as follows: liquid entry pressure (LEP), porosity, thermal conductivity, water contact angle, and membrane thickness.

3.1 Liquid entry pressure (LEP)

To abstain from membrane wetting, the MD membrane should have three major properties, simultaneously: high water contact angle, high hydrophobicity, and narrow pore size distribution. However, membrane wetting may take place and effect on membrane performance when the feed solution is in direct contact with membrane surface. When the hydraulic transmembrane pressure oversteps LEP, aqueous solution components will prevail over the surface tension and wet membrane pores. Generally, LEP is the maximum pressure value applied onto the feed solution to be treated before the membrane pore wetting happens. Based on Cantor-Laplace equation, the LEP value depends on surface contact angle (θ), surface tension (γ_L), geometric coefficient (β), and maximum pore radius (r_{max}) [39]:

$$LEP = \frac{-2\beta\gamma_L cos\theta}{r_{max}} \tag{1}$$

As can be comprehended from Cantor-Laplace equation, increasing in surface contact angle or decreasing of maximum pore size will enhance LEP value.

3.2 Porosity

Porosity of MD membranes must be as high as possible until the wetting phenomenon does not occur. Porous surface can lead to higher permeate flux. Generally, the ratio of free volume to total volume of the membrane is called porosity. In MD, the ratio between the macrovoid volume and total volume of the membrane is calculated by gravimetric procedure [40]. This technique is based on measuring membrane weights applying a wetting liquid such as 2-propanol, which goes inside the pores, and weighing the membrane before and after wetting:

$$\varepsilon = \frac{(W_W - W_D)/\rho_{wl}}{[(W_W - W_D)/\rho_{Al}] + W_D/\rho_P} \tag{2}$$

where W_W, W_D, ρ_{wl}, and ρ_P are the weights of wet and dry membrane and the density of wetting liquid and hydrophobic polymer.

3.3 Water contact angle

Tendency of membrane surface to be wetted by liquids is often measured by liquid contact angle analysis. In MD, because water is the major component of the feed solution, water contact angle is calculated for determining surface tendency to water droplets. In this technique, the angle between water droplet and membrane surface is calculated. To minimize the errors of calculation, various locations of membrane surface are selected randomly, and the average contact angle is reported as water contact angle. It should be noted that the effect of mean pore size and surface roughness should be considered to specify the exact water contact angle.

3.4 Thermal conductivity

Thermal conductivity of MD membranes must be as low as possible. Heat loss in various MD configurations is attributed to the membrane material and existed gases in the membrane pores. Increasing in thermal conductivity could reduce mass flux which is undesirable for MD process. Since the water vapor thermal conductivity is one order of magnitude lower than polymeric materials to be used in MD, increasing membrane surface porosity could lead to heat loss reduction. So, the presence of macrovoids in the membrane surface will result in reducing thermal conductivity. As stated above, the thermal conductivity of MD membranes is related to both thermal conductivity of polymer (k_p) and gases (k_g):

$$k = \varepsilon k_g + (1 - \varepsilon)k_p \tag{3}$$

It is worth mentioning that most of the polymers used in MD membranes possess similar conductivity value. For example, thermal conductivity of PP, PTFE, and PVDF is about 0.11–0.16 (W/m^2 K), 0.25–0.27 (W/m^2 K), and 0.17–0.19 (W/m^2 K), respectively [41].

3.5 Membrane thickness

The membrane thickness is one of the most effective characteristics on MD membrane performance. The membrane thickness and membrane permeate flux are inversely related to each other. As the membrane becomes thinner, the permeate flux enhances due to the reduction of mass transfer resistance. On the other hand, when the membrane thickness increases, the heat loss decreases. So, there is a trade-off between advantage (lower heat loss) and disadvantage (lower permeate flux) of thicker membrane. It should be noted that the effect of membrane thickness in AGMD on mass transfer can be passed up, because the stagnant air layer controls mass transfer rate.

4. MD process conditions

The effects of various operational parameters on MD performance must be controlled to achieve the best results. Some of these parameters are as follows: (i) feed temperature, (ii) feed concentration, (iii) membrane type, (iv) feed flow rate, and (v) long operation.

4.1 Feed temperature

The feed temperature has a powerful effect on the permeate flux. Based on the Antoine equation, by increasing the temperature, the vapor pressure increases exponentially. So, the permeate flux will increase exponentially by increasing of the temperature [42]. When the temperature difference between the feed and permeate side of the membrane is kept constant, the distillate flux will enhance when the temperature of the feed side increases, which means the vapor pressure is more dependent to the higher temperature. In other words, the increase in vapor pressure gradient when the hot fluid temperature increases is more than the time which the cold fluid temperature decreases. Also, some researchers found out that increasing the temperature difference between the feed and permeate side of the membrane will increase diffusion factor positively [43–45].

4.2 Feed concentration

When the feed concentration increases, the permeate flux will decrease considerably due to the reduction of vapor pressure and increment of temperature polarization. Generally, when NaCl solution concentration was increased from 0 to 2 mol, about 12% decline was observed in permeate flux [45]. In fact, reduction of vapor pressure induced by concentration increment caused distillate flux reduction. Also, researchers demonstrated that there are three reasons for flux decline as a result of increasing feed concentration, reduction of water activity, reduction of mass transfer coefficient caused by concentration polarization, and reduction of heat transfer coefficient caused by decline in membrane surface temperature [46].

4.3 Membrane type

As discussed earlier, MD membranes should have porous surface with high mean pore size. The distillate flux is proportional to the surface pore size and porosity and inversely proportional to the thickness of the membrane and pore tortuosity. Also, membranes must present high LEP value to prevent membrane wetting. Furthermore, unsupported membranes with a certain pore size showed higher flux than supported membranes with the same pore size [47].

4.4 Feed flow rate

The effects of feed flow rate on SGMD are negligible, while it is considerable in DCMD and VMD. In general, increasing of feed flow rate leads to permeate flux increment. This is due to the improved mixing and the reduction of temperature boundary layer thickness on the feed side of the membrane. By increasing feed flow rate, the laminar flow regime turns into a turbulent regime, and the distillate flux reaches asymptotic values [48]. In fact, by increasing of feed flow rate, Reynolds number and heat transfer coefficient increase which lead to the reduction of temperature polarization.

4.5 Longtime operation

MD membranes must show stable performance during experiments for days and months. Actually, membrane stability is the most important challenge in MD commercialization. Several experiments showed after membrane compaction, the permeate flux increased at initial hours of the tests [49–51]. Then, the flux was reduced until reaching a steady state. Partial pore wetting and fouling were conveyed as reasons for the flux reduction during longtime MD experiments [46].

5. Transport mechanisms

5.1 Heat transfer

Measurement of heat transfer in MD is extremely complicated because of simultaneous heat and mass transfer. Based on the principal theory of heat transfer, a thermal boundary layer is formed at a fluid/solid interface with different temperatures. In MD module, a hot fluid is in direct contact with solid surface (membrane, with a thickness of δ) in which the thermal boundary layer will be formed adjacent to the membrane surface. Due to the existence of temperature gradient in MD module, two boundary layers will be formed on the feed side (with a thickness of δ_F)

and the permeate side (with a thickness of δ_P) of the hydrophobic membrane. Inside the thermal boundary layer, the feed temperature reduces from T_{bF} (feed bulk) to T_{mF} (membrane surface). Also, the permeate temperature increases from T_{bP} (permeate bulk) to T_{mP} (membrane surface). Since MD process depends on vaporization of a component, the latent heat should be transitioned from feed bulk to the membrane surface through the thermal boundary layer. Heat transfer coefficient (h_F) plays a key role in heat transfer across the boundary layer. So, the heat flux between the feed bulk and membrane surface is defined as

$$q_F = h_F(T_{bF} - T_{mF}) \tag{4}$$

When vaporization takes place at the membrane surface, the latent heat is transferred to the permeate side of the membrane with vapor stream:

$$q_L = N \times \Delta H_{vap} \tag{5}$$

where N (mol/m^2 K) is the vapor flux through the membrane pores, ΔH_{vap} (J/mol) is the latent heat of vaporization, and q_L (W/m^2) is the heat transferred because of volatile component evaporation. There are some other types of heat transfer in MD process including heat transfer via gas-filled pores (q_m) and heat transfer across the permeate side of the membrane (q_P):

$$q_m = h_m(T_{mF} - T_{mP}) \tag{6}$$

where h_m is the heat transfer coefficient of the membrane which depends on both the heat transfer coefficient of membrane material and the gas which fills the membrane pores. So, the heat transfer mechanism in MD process consists of three different steps: (i) heat transfer through the thermal boundary layer at the feed side, (ii) heat transfer through the membrane, and (iii) heat transfer through the thermal boundary layer at the permeate side.

5.2 Mass transfer

In general, mass transfer mechanism in MD consists of three major categories including Knudsen flow theory, viscous flow theory, and molecular diffusion theory. In MD, surface penetration is ignored because the penetration area of membrane matrix is much lower than the volume of the pores [46]. Moreover, as is stated earlier, MD membrane material has low affinity to water molecules. So, the contribution of transport through the membrane matrix can be ignored. The key parameter to recognize the governing mass transfer mechanism in MD module is Knudsen number (Kn) which is determined as

$$Kn = \frac{\lambda_i}{d_p} \tag{7}$$

where λ_i is the mean free path of the transferred vapor molecules through the pores with a size of d_p. When the Knudsen number is greater than one, the possibility of collisions between vapor molecule and pore wall is more than the collisions between vapor molecule and another one. In this case, the permeability through the membrane pores when a uniform pore size $d_{p,m}$ is assumed can be calculated from the following Equation [29]:

$$\beta_{k,m} = \frac{2}{3}\frac{\varepsilon d_{p,m}}{\tau\delta}\left(\frac{2}{\pi MRT}\right)^{0.5} \tag{8}$$

where ε, τ, and δ are membrane porosity, membrane tortuosity, and membrane thickness, respectively. When the Knudsen number is lower than 0.01, molecular diffusion is the governing mass transfer mechanism, and the membrane permeability is defined as [26]

$$\beta_{M,m} = \frac{\pi}{4RT}\frac{PD}{P_{air}}\left(\frac{{d_{p,m}}^2}{\tau\delta}\right) \tag{9}$$

where P, D, and P_{air} represent the total pressure within a pore, the diffusion coefficient, and air pressure within a pore, respectively. When hydrostatic pressure is used over a membrane owning pores with greater size than mean free path, viscous flow will be the governing mass transfer mechanism. In this situation, the possibility of collisions among vapor molecules is more than the collisions between vapor molecule and pore wall. When a uniform pore size $d_{p,m}$ is assumed for the membrane pores, the permeability can be measured with the following equation [44]:

$$\beta_{V,m} = \frac{\varepsilon}{32RT}\frac{P_m}{\mu}\left(\frac{{d_{p,m}}^2}{\tau\delta}\right) \tag{10}$$

where μ and P_m are the viscosity of transferred vapor molecules and average pressure of the pores.

6. MD applications

MD is going to be an attractive technology for separation processes due to its unique properties. Dealing with water as a key component of chemical and physical processes and high separation factor are the most attractive characteristics of MD technology. Nowadays, MD is used in environmental, food, pharmaceutical, and nanotechnology industries. Also, MD can be used as a single-step process or can be combined with other separation techniques as a last stage [52]. Some applications of MD are the following:

1. Desalination of seawater, brackish water, groundwater, and brines brought from other units.

2. Industrial wastewater treatment including radioactive waste treatment, concentration of nonvolatile acids, volatile acid recovery from industrial effluents, salt recovery by membrane distillation crystallization (MDC), and textile industry effluents.

3. Preparation of distilled water, pure water, and ultrapure water for medical and pharmaceutical purposes.

4. Production of liquid food concentrates such as mandarin juice, sucrose solution, whey, and apple juice.

5. Volatiles removal from fruit juice, alcohols, halogenated VOCs, and benzene by VMD and SGMD.

6. Dealcoholization of fermented beverages and enhanced ethanol production using DCMD.

The most important MD application is desalination of wastewaters including high percentage of salt molecules in order for safe discharge into the environment or to produce drinkable, pure, and ultrapure water. The theoretical 100% rejection of nonvolatile solutes, colloids, and biological matters by MD guarantees the elimination of all unwanted solutes that are often existing in water sources. The treated water by MD shows an electrical conductivity as low as 800 μS/cm with total dissolved solids (TDS) of 0.6 ppm [53].

7. Process challenges

The principal challenges of MD process are temperature polarization, concentration polarization (CP), and fouling of contaminants on the membrane surface. These challenges must be controlled to avoid underperformance in MD process. One of the most undesirable problems in MD is temperature polarization in which the temperature gradient is created between bulk feed and membrane surface at liquid/vapor interface. In fact, by vaporization of a component, liquid bulk temperature decreases, while vapor temperature increases instead. This phenomenon causes a reduction of temperature difference leading to permeate flux decline. Temperature polarization coefficient (TPC) is often defined as the ratio of boundary layer resistance to the total heat transfer resistance:

$$TPC = \frac{T_{mF} - T_{mP}}{T_{bF} - T_{bP}} \tag{11}$$

where superscripts *m* and *b* specify the temperature near the membrane surface and bulk. Based on scientific reports, a reasonable value for TPC to design MD systems lies between 0.4 and 0.7 [54]. Concentration polarization is another problem in MD process. When evaporation occurs, the solute concentration near the membrane surface becomes greater than that of the bulk feed. Similar to the temperature polarization effect, the concentration cannot be measured due to the simultaneous heat and mass transfer. Concentration polarization coefficient (CPC) is often defined as the ratio of the solute concentration near the membrane to the solute concentration in the bulk feed:

$$CPC = \frac{C_{mF}}{C_{bF}} \tag{12}$$

Fouling of contaminants on the membrane surface is also a problem in MD process. Although fouling has lower effect on MD than other pressure-driven membrane processes, it often causes underperformance in membrane process. Fouling and contaminant deposition on membrane surface cause the reduction of effective membrane area and membrane wetting resulting in distillate flux decline and low rejection. So, to reach maximum efficiency in MD process, the effects of these problems should be reduced as much as possible.

8. Recent developments and innovations in hybrid MD systems

MD can be combined with other membrane technologies such as RO, microfiltration (MF), and nanofiltration (NF) as well as common distillation systems (i.e., multistage flash (MSF)) and low-cost energy sources [55]. These hybrid systems will offer high-quality products and lower energy consumption both in the system installation and the discharging concentrated brine. In fact, MD hybrid systems are beneficial if they can rectify other system disadvantages.

Generally, MD hybrid systems can be divided into two major groups: (i) integrated MD systems with membrane processes and (ii) integrated MD systems with other processes. The combination of MD with ultrafiltration (UF) for treatment of oily wastewater was investigated by Gryta et al. [56]. DCMD was applied as final purification technique after UF. The hot UF permeate entered into the DCMD cell linked in parallel form. The MD permeate is collected outside the chamber, and the oil concentrate is returned to the UF modules as feed. The product collected from the UF module commonly contains less than 5 ppm of oil. An additional distillation process over the UF permeate leads to a complete elimination of oil from wastewater with a high removal percentage of 99.9% for total dissolved solids. As an another hybrid system, MD was integrated with RO for desalination by Drioli et al. [57]. MD was suggested to desalinate RO brine (75 g/l) at a temperature of 35°C to improve both efficiency and water recovery. Since MD is less sensitive to brine concentration than RO, more potable water can be obtained by RO/MD hybrid system. The results showed that the recovery factor of hybrid system was about 87% which was higher than that of MD (77%) and RO (40%). There are also some reports about using NF/MD and PV/MF/MD hybrid systems to produce high-quality products [53, 58].

As stated earlier, MD can be integrated with other chemical and physical separation processes. Gryta et al. studied the performance of hybrid bioreactor/MD system to produce ethanol [59]. The fermentation of sugar with *Saccharomyces cerevisiae* (commonly known as baker's yeast) results in the formation of by-products, which can be eliminated by MD. This integration leads to improve the efficiency of sugar conversion to ethanol. The results of the fermentation tests with and without integration with MD process corroborated the advantages of the fermentation carried out with continuous elimination of fermented products by the MD module. One of the interesting characteristics of MD process is its flexibility to use renewable energy source such as nuclear power and solar energy for heating the feed solution [60, 61]. Khayet et al. investigated the possibility of nuclear desalination by DCMD coupled with a nuclear reactor [62]. The results of experiments confirmed the feasibility of water desalination by consuming the heat and electricity generated in nuclear power plant. From the stated examples of MD hybrid systems, it is clear that all of the investigation was in laboratory or pilot scale. So, more investigation must be performed in order to remove the obstacles from commercialization of MD hybrid systems.

9. Economics and energy consumption in MD

As it was stated throughout this chapter, MD process requires an energy source for heating the feed to a specific temperature. The ability of coupling with renewable energy sources such as solar and geothermal energy or industrial waste heat converts MD from expensive laboratory scale process to beneficial industrial one. So, especially in desalination, the water production cost (WPC) will decrease by applying a low-cost energy source. It is worth mentioning that current seawater

Separation process	Production rate	Energy consumption (kWh/m^3)	Reference
RO standard	105,000 m^3/day	4.5	[63]
SPMD	5–27 l/m^2 h	200–300	[64]
AGMD	5.2 l/m^2 h	1	[65]
VMD	0.71 l/m^2 h	3.2	[66]
Brackish water RO (BWRO) with photovoltaic (PV) panels	0.2 m^3/day	1.3	[67]
Solar still	2–6 l/m^2 day	640	[68]

Table 4.
Estimated energy consumption of different separation processes used in desalination.

desalination capacity is about 27 million m^3/day which only meets 3% of freshwater demand. In fact, WPCs for industrial units are less than \$1/m^3, whereas it may vary between \$1/m^3 and 3/m^3 small-scale units. While solar energy-based processes are typically expensive due to the high capital cost, they could slowly become competitive with conventional energy sources in the future. It must be noted that even though the WPCs of solar-powered MD (SPMD) are considerably high, it could be an interesting alternative for water production in remote areas. Generally, lower energy consumption or using low-cost energy sources would reduce the WPC. **Table 4** summarizes energy consumption of different separation processes.

10. Conclusion and future prospects in MD

After several decades of persistent investigation for understanding the concept of MD and its difficulties, there are still many obstacles that must be eliminated for industrialization. Based on recent development, MD process is able to be used in a vast variety of applications such as desalination and wastewater treatment. Although MD process still suffers from some problems which limited its performance such as high-energy consumption, longtime operation, wetting and fouling, and lack of appropriate module, different reports have been presented to enhance permeate flux and solute retention and decrease energy consumption in MD process, including developed membrane modules and hybrid MD systems. So far, the effects of MD operational parameters have been studied over and over, but some areas related to commercialization field are still overlooked or investigated scarcely. Therefore, a vigorous motivation is required for research on the neglected areas such as membrane module design or scale-up variables both in experimental and modeling fields in which the obtained experimental data will be *extremely* beneficial.

Nomenclature

MD	membrane distillation
VLE	vapor-liquid equilibrium
PV	pervaporation
PTFE	polytetrafluoroethylene
PE	polyethylene

PVC	polyvinyl chloride
RO	reverse osmosis
AGMD	air gap membrane distillation
DCMD	direct contact membrane distillation
PP	polypropylene
VOCs	volatile organic compounds
VMD	vacuum membrane distillation
SGMD	sweeping gas membrane distillation
TSGMD	thermostatic sweeping gas membrane distillation
NIPS	non-solvent induced phase separation
EIPS	evaporation induced phase separation
TIPS	thermally induced phase separation
VIPS	vapor induced phase separation
ENMs	electrospun nanofibrous membranes
LEP	liquid entry pressure
Kn	Knudsen number
MDC	membrane distillation crystallization
TDSs	total dissolved solids
TP	temperature polarization
CP	concentration polarization
TPC	temperature polarization coefficient
CPC	concentration polarization coefficient
MF	microfiltration
NF	nanofiltration
MSF	multistage flash
UF	ultrafiltration
WPC	water production cost
SPMD	solar-powered membrane distillation
BWRO	brackish water reverse osmosis
PV	photovoltaic

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Chapter

Ultrasound for Membrane Fouling Control in Wastewater Treatment and Protein Purification Downstream Processing Applications

Amira Abdelrasoul and Huu Doan

Abstract

Membrane fouling is one of the major issues encountered in membrane filtration including microfiltration, ultrafiltration, nanofiltration, and reverse osmosis. Membrane fouling can occur due to the reversible and irreversible deposition of particles, colloids, macromolecules, salts, and other types of elements. As a consequence, fouling causes a significant decrease in the permeate flux due to plugging of membrane pores, and adsorption of fouling material on the membrane's surface and/or in the pore walls. A lot of research efforts have been directed towards fouling remediation techniques or membrane cleaning alternatives. Although most of these methods are relatively functional, they have drawbacks and limitations. Among these methods, the use of ultrasound has been shown to be effective in enhancing mass transfer, cleaning, disinfection, and controlling fouling. In membrane filtration processes, ultrasound can help accelerating the permeate flux towards the membrane and decreasing the concentration of solutes accumulated in the membrane pores and on the membrane surfaces. Ultrasonic fouling control does not require chemical cleaning and can maintain a high permeate flux throughout the filtration process. In addition, wastewater contaminants can be degraded by ultrasound. Therefore, ultrasound creates unique physicochemical conditions, which can be used as an effective tool for membrane fouling control. In this chapter, ultrasound radiation as a unique method to modify physical and chemical properties of a complex fluid with applications in wastewater treatment and protein purification process is highlighted. At first, ultrasonic parameters and how their ability to enhance the delivery of fluid flow to the membrane surface and affect the physical and chemical properties of foulants are discussed. Furthermore, various ultrasonic methods, including continuous and intermittent waves, and its influences on membrane fouling, permeate flux, membrane cleaning and flux recovery are reviewed. The main role of wave streaming as a driving force for fluid acceleration and antifouling control, and the impact of ultrasound-generated bubble cavitation on preventing and removing fouling deposits are described. The challenges of current ultrasonic techniques, which need to be addressed so as to facilitate their widespread and successful implementation, are explored. This chapter examines how the periodic compression/rarefaction cycles of ultrasound can influence mass transfer and membrane fouling. Also, the current knowledge and approaches to advance ultrasonic technology as an effective method for membrane fouling remediation in wastewater treatment and protein purification downstream processing are presented in this chapter.

Keywords: membrane fouling, ultrasound, mass transfer, physicochemical influence, permeate flux, fouling control

1. Overview of membrane fouling mechanisms

Membrane processes are increasingly used in various applications, both upstream and downstream processes, such as microfiltration (MF), ultrafiltration (UF), and emerging processes including membrane chromatography, high performance tangential flow filtration, and electrophoretic membrane contactor. Membrane fouling is an ongoing issue in pressure-driven membrane processes such as UF, MF, nanofiltration (NF), reverse osmosis (RO), and forward osmosis (FO). Membrane fouling is likewise unavoidable in other types of membrane-based processes such as membrane distillation (MD) and membrane bioreactor (MBR). In recent years, the application of UF has expanded as a promising alternative technology to obtain drinking water [1–4]. In addition, UF has become particularly important in concentrating proteinaceous solutions. Examples of commercial membrane processes include filtration of protein solutions in the presence of electrolytes, concentration of whey proteins in the dairy industry, protein recovery from blood plasma, and protein concentration in downstream processing. NF is another promising technology that separates solutes based on solute charge and size. Several research papers on peptide fractionation by NF of model systems of amino acids and peptides, which were based on molecular sieve effect and/or on charge effect depending on the membrane type and the feed phase composition, have been reported [5]. However, one of the major factors, which hinders more wide-spread applications of membrane filtration, is that the permeate flux declines with filtration time [6–9]. This phenomenon is commonly known as membrane fouling, which refers to the blockage of membrane pores by the combination of sieving and adsorption of particulates and compounds onto the membrane surface or within the membrane pores during the filtration process, as summarized in **Figure 1**.

In-depth understanding of fouling phenomenon mechanisms is vital for the advancement of innovative methods for the control of fouling and cleaning of membranes. Membrane fouling is a complex process since it involves chemical and physical interactions between various foulants as well as between the membrane's surface and foulants [10–12]. Membrane fouling reduces the active area of the membrane, blocks the membrane pores, or increases the resistance to the flow though the membrane and hence directly contributes to a declined in the permeate flux and an increased transmembrane pressure, which in turn results in an increase in the power consumption [13, 14]. Membrane fouling presents in the form of pore blockage, particle deposition, adsorption, or gel formation, as shown in **Figure 1**. Adsorption of contaminants on the membrane surface, due to interactions between foulants and the membrane surface, and the membrane's pore walls produces higher hydraulic resistance across the membrane. Alternatively, pore blockage is comprised of the plugging of the membrane's pores that in turn narrows the passage for the permeate through the membrane, resulting in a lower permeate flux [7, 9]. The deposition of foulants by layer-by-layer accumulation on the membrane surface creates additional hydraulic resistance, which is otherwise known as cake resistance [3]. When it comes to fouling caused by the gel formation, the cross-linked three-dimensional networks of deposited particles, including colloidal substances and macromolecules, are created on the surface of the membrane. These formed gel

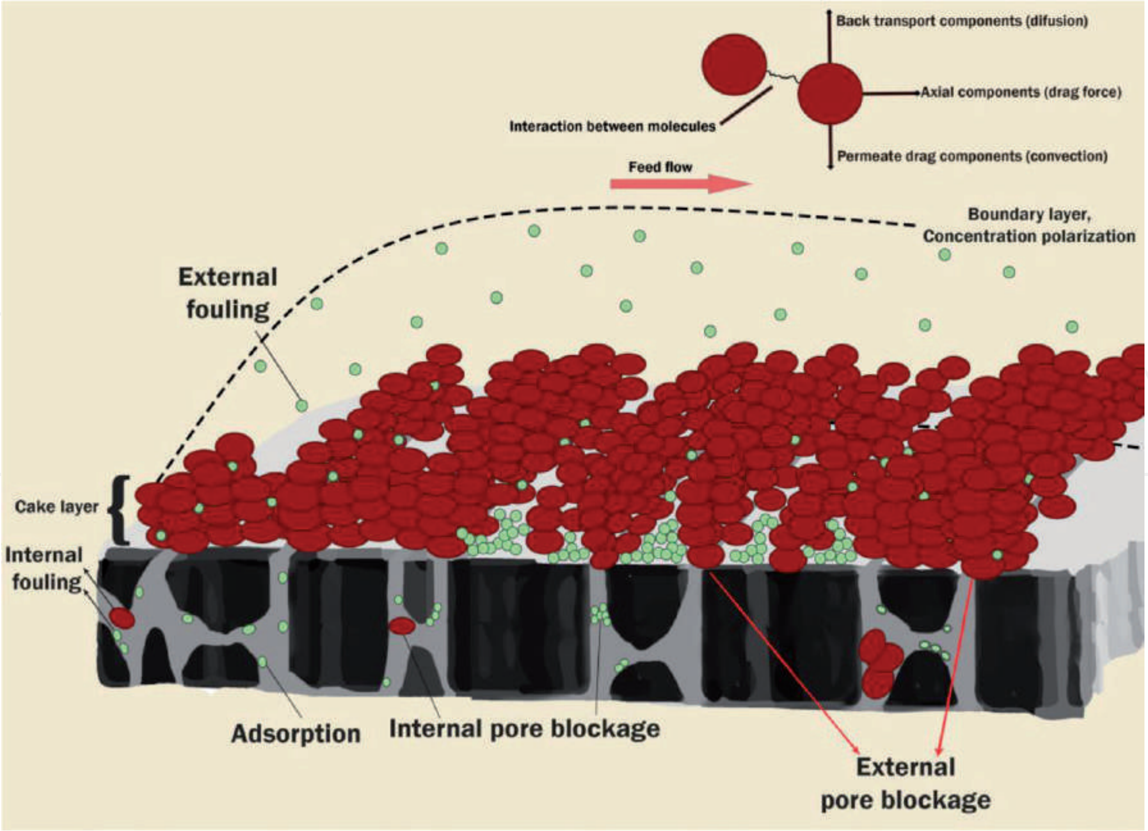

Figure 1.
Membrane fouling mechanisms.

layers lack connectivity between the pores and as a consequence offer greater resistance to mass transport through the membrane. Once the gel layer is formed, any increase in the transmembrane pressure will not result in any improvement in the permeate flux, but it will compress the gel layer [3, 4]. Deposition of foulants on the membrane's surface is generally known as external fouling, whereas fouling within the membrane's pores is defined as internal fouling, as shown in **Figure 1**. In most cases, the process of flux decline transpires in three specific stages due to the fouling mechanisms. During Stage I, there is a rapid flux decrease because of the swift pore blocking happening at the beginning of the process. During Stage II, the flux continues to decrease due to the cake layer formation and consequent growth. In this stage, the flux continues declining, while the cake layer increases and attains greater thickness. During Stage III, the fouling process gets to a relatively steady state, and the cake layer grows to its equilibrium thickness [3, 11, 12, 14]. The change from the initial flux to the steady-state flux may be quite substantial. Diverse foulant types can occur in membrane-based separation processes, dependent on the properties of the feed stream. Membrane fouling can thus be classified based on the foulant types [4, 13]. In this chapter, ultrasound radiation as a unique method to modify physical and chemical properties of a complex fluid with applications in wastewater treatment and protein purification process is highlighted.

1.1 Types of fouling

1.1.1 Organic fouling

The presence of the organic fouling is frequent in the membrane-based separation processes because of the pervasive occurrence of dissolved organic matter (DOM) in wastewater, sewage, and surface water. DOM can be classified into three key categories: (1) natural organic matter (NOM), created through metabolic reactions of organics in various sources of drinking water; (2) synthetic organic compounds (SOC), discharged into wastewater streams and originating from industries and household sources; and (3) soluble microbial products (SMP), produced during biological water treatment processes [15]. When it comes to NOM, the primary constituents in ground or surface waters are humic substances (fulvic acids, humic acids, and humin) created through the decomposition of animal and plant residues. As such, humic substances include aliphatic and aromatic constituents of phenolic and carboxylic functional groups. Furthermore, NOM encompasses nonhumic fractions that are based on amino acids, proteins, transphilic acids, and carbohydrates [16]. There are several mechanisms in which NOM can create organic fouling. NOM may form a gel layer on the membrane surface, be adsorbed or deposited within the membrane pores, or bind to other particles in order to form a NOM/particle fouling layer on the membrane surface. Organic fouling could likewise be produced by transparent exopolymer particles (TEPs) created from polysaccharides and excreted by microalgae [17]. Furthermore, effluent organic matter (EfOM), consisting of SMP and NOM, from biological wastewater treatment may become the source of membrane's organic fouling. EfOM could include compounds including enzymes, nucleic acids, antibiotics, polysaccharides, proteins, and steroids [17]. In general, organic membrane fouling is a complicated phenomenon that is directly influenced by the foulant-membrane surface interactions, foulant-foulant interactions, and feed water's chemistry. For the initial buildup of organic fouling layer, adsorption is a key mechanism, which is responsible for irreversible fouling. It should also be noted that the hydrophilicity or hydrophobicity and molecular size of NOM have a critical role in the formation of the membrane's organic fouling and flux decline [18].

1.1.2 Inorganic fouling

Inorganic membrane fouling is frequently referred to as "mineral scaling." This type of fouling is caused by the elevated concentrations of inorganic compounds in the feed water. Examples of inorganic foulants are calcium carbonate ($CaCO_3$), barium sulfate ($BaSO_4$), calcium sulfate ($CaSO_4$), and silica (SiO_2). The primary cationic species that are responsible for inorganic fouling are Mg^{+2}, Fe^{+3}, Ca^{+2}, and Al^{+3}. Alternatively, the primary inorganic species that can be in equilibrium with cationic scaling components are F^-, CO_3^{-2}, SO_4^{-2}, OH^-, silicic acids, and orthophosphate [19]. The scale formation or inorganic fouling on the membrane surface is controlled by transport and crystallization mechanisms. Crystallization can happen as a consequence of ion precipitation on the membrane surface. This occurs when the overall ion activity in the feed water is above the saturation limit, a dynamic where the feed is essentially supersaturated. Scaling caused by crystallization can occur in two potential ways: surface (heterogeneous) crystallization and bulk (homogeneous) crystallization. During bulk crystallization, the crystal particles deposit on the membrane surface and then create a cake layer, after being formed through homogeneous crystallization in the bulk phase. Supersaturated solutes permit the agglomeration of scale-forming ions because of the random collisions occurring in the bulk phase. The coalescing ion cluster facilitates precipitation once it becomes larger than a critical size. For surface crystallization, the crystals are formed on the membrane surface, while the scale formation occurs through the lateral crystal growth [19]. Inorganic fouling can be influenced by several parameters, including degree of super saturation, shear across the membrane, transmembrane pressure, membrane surface roughness, and the feed solution chemistry [20]. Membranes that have rougher surfaces are more susceptible to inorganic fouling than those featuring smoother surfaces. Greater surface roughness augments free energy on the surface and in turn raises membrane's adhesiveness. Inorganic fouling is more frequent at low-shear rates, higher degrees of super saturation, and higher transmembrane pressure. Furthermore, inorganic fouling can become more aggressive in cases where the wastewater contains smaller particles and greater concentrations.

1.1.3 Colloidal fouling

Common examples of inorganic colloids are colloidal silica, elemental sulfur, precipitated iron, silt, aluminum silicate clays, and corrosion products. Alternatively, organic colloids can be carbohydrates, proteins, fats, oils, and greases. During membrane filtration process, permeate flux is the primary mechanism for the transportation of colloidal particulates from the bulk feed to the membrane surface. Simultaneously, cross flow prompts reverse transport of colloids from the membrane surface to the bulk feed. Reverse transport of colloids is generally controlled by turbulent transport, particle rolling, inertial-lift forces, Brownian diffusion, shear-induced diffusion, and particle-particle interaction forces [11]. For nonporous membranes such as NF or RO, colloidal fouling is triggered by the buildup of particles on the membrane surface that causes the cake layer formation. For porous membranes, including UF and MF, the pore size is large enough so as to facilitate pore blocking; hence, colloidal fouling can be caused by surface accumulation and pore plugging [13]. The surface charge and physiochemical properties of colloids depend on the feed solution chemistry, such as pH, ionic composition, and ionic strength [21]. Furthermore, colloidal fouling depends on other membrane properties. Smoother and more hydrophilic membranes exhibit superior colloidal fouling resistance potential during the initial fouling stage [11, 21]. Colloidal fouling likewise relies on the hydrodynamic conditions, that is, the fouling becomes more problematic at lower cross-flow velocity [21].

1.1.4 Biofouling

Biofouling is caused by the deposition, growth, and metabolism of microbiological cells (bacteria, algae, protozoa, and fungi) or flocs, in conjunction with the production of biofilm on the membrane. Biofouling poses a serious operational problem in membrane-based processes and is a contributing factor to >45% of all membrane fouling [10]. Biofouling begins as an attachment of microbiological cells to the membrane surface, which then causes the formation of biofilm. After the initial attachment, the microbiological cells continue to grow and multiply by using the feed nutrients and/or the organics adsorbed in the membrane surface as its resources. Simultaneously, the extracellular polymeric substances (EPSs) excrete in a manner that anchors the microbiological cells and allows further settlement on the membrane surface. Once their growth is completed, the cells begin to detach and then diffuse to new locations on the membrane surface so as to once again initiate biofilm creation [22]. The biofilm growth can be summarized as a series of steps: (a) formation of a conditioning film through the absorption of organic species (macromolecules, proteins, etc.) on the membrane surface, (b) transportation of microbiological cells from the bulk feed to the conditioning film, (c) attachment of cells to the membrane surface, and (d) creation of biofilm through cell growth [22]. The process of cell attachment is dependent on the membrane properties, including roughness, hydrophobicity, material, and surface charge. The features of microbiological cells and the properties of feed water influence the attachment of cells to the membrane surface [22]. Furthermore, the EPSs play an important role in biofouling. EPS substances tend to be higher molecular weight secretions of the microbiological cells, such as proteins, nucleic acids, polysaccharides, and lipids. EPSs are distinguished as soluble EPS (or SMP) and bound EPS. Bound EPSs are sturdily bound to the microbiological cells, meanwhile the soluble EPSs are loosely bound and appear primarily in the form of dissolved substances in the bulk liquid. EPSs contain hydrophobic and hydrophilic functional groups that allow them to be positioned on hydrophobic and hydrophilic membranes. EPSs offer a way to bind the cells together in three-dimensional matrices. As such, EPS can influence the biofilm's structural stability, adhesion ability, surface parameters, and stability of the microbiological cells [22].

Fouling can be reduced by manipulating particle-to-membrane and particle-to-particle interactions. For this purpose, a wide variety of feed pre-treatment options can be used. However, this can rapidly increase operational cost and complexity [1–3]. Chemical cleaning consists of the use of acid, alkali, or biocide solution to prevent inorganic fouling, organic fouling, and biofouling, respectively. Almost full recovery of permeate flux can be achieved through chemical cleaning; however, it can increase cost and complexity of filtration process due to the use of hazardous chemicals. Furthermore, it produces by-products that are threatening to the environment. Physical cleaning includes periodic rinsing (backwashing and flushing), which consists of passing water through the membrane in the reverse direction of the permeate flux. Backwash with air can also be applied to remove particles through surface shear and increase in mass transferring motion, but it is not compatible to all types of feed solution [7–10]. Another physical technique is the use of pulsed electric or ultrasonic fields during the filtration process to avoid particle deposition [7, 8]. As an alternative to these techniques, the use of ultrasonic field in membrane cleaning and fouling control has been investigated. Ultrasound (US) can create turbulence near the membrane surface and detach particles through the action of cavitation bubbles. The characteristics of the bubbles formed within the system play a major role in the effectiveness of the ultrasound application. The particle detachment can significantly decrease the overall resistance to flow across the membrane, increasing the filtration performance.

2. Theoretical aspects of ultrasound membrane fouling control

The ultrasound influence on membrane fouling control is function of wave parameters, time, the fluid characteristics, pressure, and temperature.

2.1 Ultrasound phenomenon

Ultrasound is a sound (acoustic) wave traveling at a frequency greater than 20 kHz, which is above the normal human hearing range [23]. Unlike the audible sound range, ultrasound has exceptional chemical and physical properties by transmitting high mechanical power through small mechanical movements [24]. As shown in **Figure 2**, ultrasound spreads through a fluid in a series of rarefaction (expansion) and compression waves. Because of this propagation, the molecules within the fluid are exposed to rarefaction and compression cycles in the direction of the wave propagation. This generates an acoustic pressure (P_a) in addition to the fluid's hydrostatic pressure (P_0). The acoustic pressure generated can be calculated using Eq. (1) [24]:

$$P_a = P_A \sin\left(2\pi f t\right) \tag{1}$$

where P_A, f, and t stand for the acoustic pressure amplitude, frequency, and time, respectively.

Three distinctive types of ultrasound are classified based on the sound frequency range, specifically power ultrasound (20–100 kHz), high frequency ultrasound (100 kHz–1 MHz), and diagnostic ultrasound (1–500 MHz) [26].

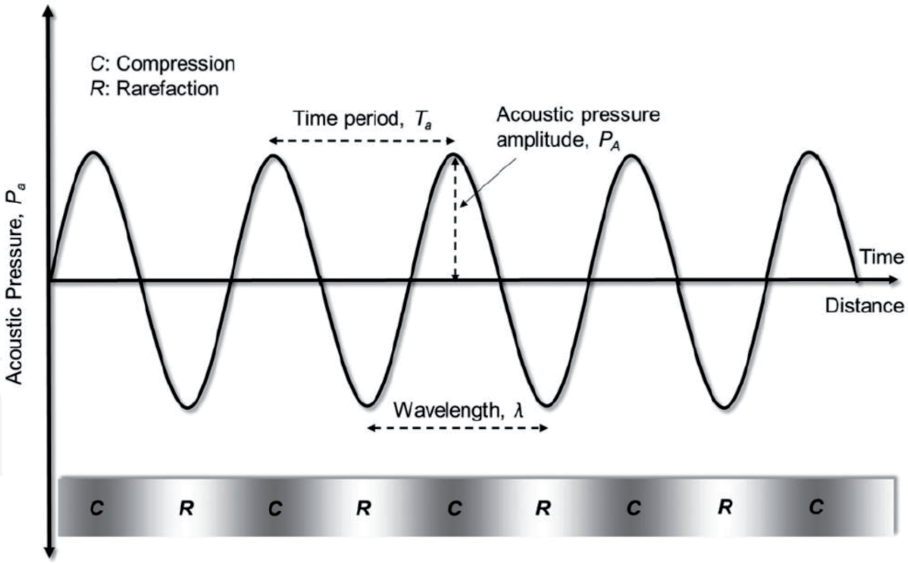

Figure 2.
Schematic diagram of an ultrasonic wave [25].

For processing and industrial cleaning applications, the ultrasound frequency range between 20 and 500 kHz is usually used [26].

2.2 Acoustic cavitation

In the compression cycle, the molecules in the fluid are exposed to a positive acoustic pressure that pushes the molecules closer to one another. Alternatively, in the rarefaction cycle, a negative pressure is applied in order to pull the molecules away from each other. The intermolecular forces are incapable of holding the molecules together, and small vapor-filled voids, or cavitation bubbles, are formed in the liquid whenever the pressure amplitude and the subsequent tensile stress during rarefaction are greater than the tensile strength of the liquid [27]. This phenomenon is known as the acoustic cavitation. The minimum acoustic pressure necessary to transcend the liquid tensile strength and form a cavitation bubble of an initial radius R_0 is termed the Blake threshold (P_b) and is defined by Eq. (2) [27]:

$$P_b = P_o + 2/3\sqrt{\frac{(2\sigma/R_o)^3}{3\left(P_o + \frac{2\sigma}{R_o}\right)}} \tag{2}$$

where P_o is the hydrostatic pressure being applied on the liquid, and σ is the liquid's surface tension. In Eq. (2), the expression $(\frac{2\sigma}{R_o})$ signifies the cavitation bubble's surface tension. It should be noted that Eq. (2) does not properly address inertial and viscous effects and vapor pressure [28]. The creation of cavitation bubbles in a liquid is usually linked to the nucleation phenomenon and the existence of weak spots, including solid impurities, dissolved solids, free-floating gas bubbles, and gas pockets in crevices of solids acting as nuclei [25]. Generally, the ultrasound cannot create cavitation bubbles in pure liquids that naturally have excessively high-tensile strength. However, the existence of impurities drastically lowers the liquid's tensile strength and, as a consequence, the required Blake threshold for the initiation of cavitation. For example, the Blake threshold value for impure liquids is around 1–10% of the Blake threshold for pure liquids [27, 28].

2.3 Cavitation bubble growth

After cavitation bubbles are created, they can disperse in liquid and grow larger. The cavitation bubbles grow because of the rectified diffusion and coalescence.

Coalescence is the process during which smaller cavitation bubbles join together to form larger bubbles. On the other hand, rectified diffusion occurs when the bubble growth undergoes repeated rarefaction and compression cycles produced by the ultrasound. During the compression cycle, the bubbles are compressed, while the contained material, such as gases and vapors, is released into the liquid. The quantity of material leaving or entering a bubble is directly proportional to the bubble surface area. In general, the quantity of the expelled material during the compression cycle is less than the amount gained during the rarefaction cycle because of the lower surface area accessible throughout the compression cycle. As a consequence, the bubbles continue to grow in size, while the ultrasonic field is present. Supplemental to the area effect, shell effect likewise needs to be addressed during rectified diffusion [29]. Shell effect is connected to the liquid shell thickness around the cavitation bubbles. In the compression cycle, the bubbles begin to shrink, while the overall thickness of the liquid shell around them is increasing. As a result, there is a decrease in the gas concentration close to the wall of the bubbles. Thus, a lower concentration gradient exists for the gas movement out of the bubbles across thicker liquid shells. In the rarefaction cycle, the bubbles begin to expand, while the overall thickness of the liquid shell becomes thinner. This change incites an increase in gas concentration close to the wall out of bubbles. A high concentration gradient comes with a thin liquid shell on the bubble under rarefaction. In contrast to the compression cycle, a higher quantity of gas travels into the bubbles during the rarefaction cycle. As a result, the overall outcome is the increase in the bubble size. Generally, the bubbles grow to a maximum size of 2–150 μm [25].

2.4 Cavitational collapse

Once the bubbles have grown to a certain size, degassing can happen where the bubbles leave the liquid due to buoyancy. If the bubbles continue growing to a critical size by rectified diffusion, which is designated as the bubble resonance size (R_r), then they can continue fluctuating around the resonance size, or alternatively growing to a larger size at which they collapse [29]. The bubble resonance size is a function of ultrasound frequency and can be estimated using Eq. (3) [28]:

$$R_r = \sqrt{\frac{3\gamma P_o}{\rho\omega^2}} \tag{3}$$

where ω stands for the ultrasonic angular frequency, γ is the specific heat ratio of gas (Cp/Cv, Cp, and Cv are specific heat of gas at constant pressure and constant volume, respectively) within the bubble, and ρ is the liquid density. For air bubbles in water, Eq. (4) [27] can be used to estimate the resonance radius:

$$R_r \approx \frac{3}{f} \tag{4}$$

where f stands for the ultrasound frequency. The collapse of the bubbles, or cavitational collapse, is controlled by the bubble oscillation frequency (f_b) as expressed in Eq. (5) [28]:

$$f_b = \frac{1}{2\pi R}\sqrt{\frac{3\gamma}{\rho}\left(P_o + \frac{2\sigma}{R}\right)} \tag{5}$$

where R represents the bubble radius.

The bubbles remain intact and continue their growth cycle if the resonant bubble oscillation frequency (the bubble radius is at its resonance value) is smaller than the ultrasound frequency at the end of the compression cycle. This particular dynamic is defined as the noninertial, stable, or steady cavitation, during which the bubbles continue to oscillate over many rarefaction and compression cycles until they grow larger and finally collapse. When the resonant frequency becomes equal to or greater than the ultrasound frequency, the bubbles can grow incredibly fast and then violently collapse into smaller bubbles within a single acoustic cycle [25, 29]. This process is regarded as inertial or transient cavitation and implies that the lifetime of the bubbles is quite short. Transient cavitation happens at high ultrasound intensities, while the stable cavitation usually occurs at low ultrasound intensities. It is relevant to note that stable cavitation may eventually lead to transient cavitation, and transient cavitation may generate smaller bubbles that then experience stable cavitation. **Figure 3** offers a summary of the cavitation bubble growth and the cavitational collapse in an ultrasonic field.

2.5 Dynamics of bubble growth

The radial growth is governed by the Rayleigh-Plesset equation, as presented in Eq. (6) [27]:

$$R\frac{d2R}{dt^2}+\frac{3}{2}\left(\frac{dR}{dt}\right)^2 = \frac{1}{\rho}\left[\left(P_o+\frac{2\sigma}{R_o}\right)\left(\frac{R_o}{R}\right)^{3\gamma} - \frac{2\sigma}{R}-\frac{4\mu}{R}\left(\frac{dR}{dt}\right)-P_\infty\right] \tag{6}$$

where R is the growing bubble's radius, μ is the liquid viscosity, and Po and $P\infty$ are the pressure close to the bubble and pressure at an infinite distance away from the bubble. In the system represented by Eq. (6), liquid is considered incompressible, and the bubble is full of an ideal gas; thus, the system behaves adiabatically. The pressure at an infinite distance from the bubble, P_∞, is dependent on time (t) and can be determined by Eq. (7) [25]:

$$P_\infty = P_o - P_A \sin(\omega t) \tag{7}$$

Equation (8) [29] is applicable for radial growth of a gas-filled transient bubble [30]:

$$R\frac{d2R}{dt^2}+\frac{3}{2}\left(\frac{dR}{dt}\right)^2 = \frac{1}{\rho}\left[P\left(\frac{R_{max}}{R}\right)^{3\gamma}-P_m\right] \tag{8}$$

where $R_{\max}$ stands for the maximum bubble radius before the bubble collapse, P is the pressure (as a sum of the gas pressure, P_g, and the vapor pressure, P_v) inside

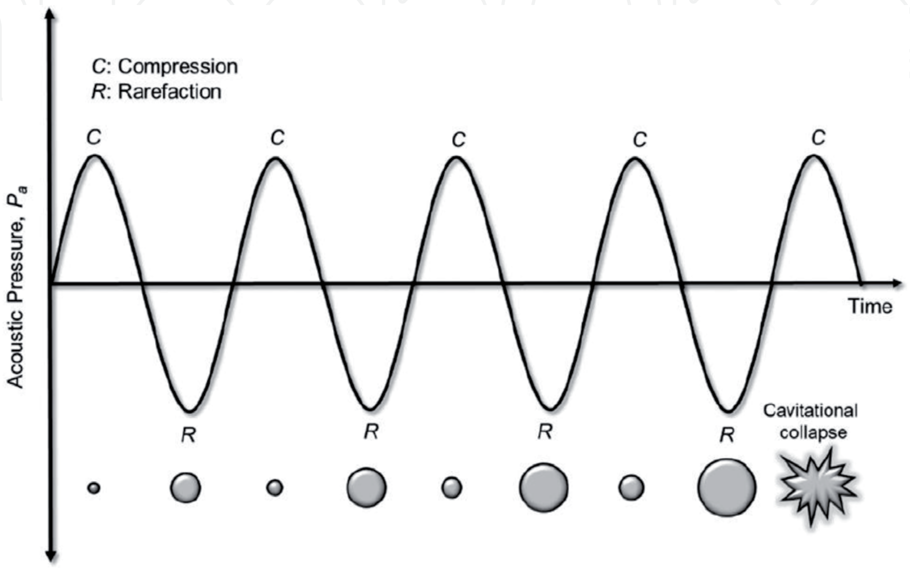

Figure 3.
Schematic diagram of acoustic cavitation, bubble growth, and cavitational collapse [29].

the bubble at the maximum radius value ($P = P_v + P_g$), and P_m is the liquid pressure at the transient collapse moment ($P_m = P_0 + P_A$). The bubble collapse time (τ_m) can be estimated using Eq. (9) [25]:

$$\tau_m = 0.915 R_{max}\left(1 + \frac{P}{P_m}\right)\sqrt{\left(\frac{\rho}{P_m}\right)} \tag{9}$$

2.6 Effects of cavitational collapse

Cavitational collapse generates sonoluminescence, where short light bursts are released [29]. Furthermore, forceful collapse of transient cavitation bubbles may cause significant chemical and mechanical effects in liquid systems due to the concentration of ultrasound energy at the bubble collapse sites. Cavitational collapse creates hotspots with extremely high local pressures and temperatures. Generally, hot spot pressure and temperature can reach up to 1000 atm and 5000 K [31]. The lifetime of a hotspot is rather short, which leads to a very high cooling and heating rate, often surpassing 109 Ks^{-1} [29, 31]. If the gas in a bubble is assumed to be ideal, and the viscosity and surface tension of liquid are ignored, then the maximum pressure (P_{max}) and the maximum temperature (T_{max}) within a collapsing bubble can be calculated using Eqs. (10) and (11) [31]:

$$T_{max} = T_o\left[\frac{P_m}{P}(\gamma - 1)\right] \tag{10}$$

$$P_{max} = P_o\left[\frac{P_m}{P}(\gamma - 1)\right]^{\frac{\gamma}{(\gamma-1)}} \tag{11}$$

where T_o is the ambient temperature.

The local high pressure and temperature conditions at the bubble collapse sites offer locations for high-energy sonochemical reactions that involve free radicals. Such high-energy reactions are usually justified using the "hot spot" model. In this model, there are three specific regions in the presence of sonochemical reactions: (1) a hot gaseous nucleus (thermolytic center), (2) an interfacial region, and (3) the bulk liquid at ambient temperature values [30].

2.7 Factors affecting acoustic cavitation and cavitational collapse in membrane process

There are multiple factors affecting the acoustic cavitation and the subsequent collapse of the cavitation bubbles in an ultrasonic field. Those key factors are examined later.

2.7.1 Ultrasonic frequency and intensity

Lower ultrasound frequency augments the size of the produced cavitation bubbles, thus leading to an intense cavitational collapse. For higher ultrasound frequency values, acoustic cavitation and cavitational collapse are less frequent due to two reasons. First, the negative acoustic pressure during the rarefaction cycle is unable to initiate the cavitation. Second, the compression cycle is much faster and does not provide enough time for the bubbles to collapse [25, 29].

Acoustic cavitation displays an optimal relationship with the ultrasound intensity. The power intensity can be determined calorimetrically or by using the input or output power per unit area of the ultrasound transducer [31]. Ultrasound intensity (I) is directly proportional to the acoustic pressure amplitude (P_A), as expressed in Eq. (12):

$$I = \frac{P_A^2}{2\rho c} \tag{12}$$

where c is the ultrasound speed.

An elevation in the ultrasound intensity raises the acoustic pressure amplitude. This in turn lowers the collapse time (τ_m), as per Eq. (9). In addition, the increase in acoustic pressure amplitude augments the maximum temperature (T_{max}) and the maximum pressure (P_{max}) of bubble collapse, as reflected by Eqs. (10) and (11). Consequently, the bubble collapse becomes significantly more violent and quick at a higher ultrasound intensity. It should be noted that the ultrasound intensity cannot increase past a particular critical value. This critical cutoff point can be explained by the fact that at extremely high acoustic pressure amplitudes, the bubbles are very large, although the time available for the bubble collapse during the compression cycle is insufficient [31]. Furthermore, the larger quantity of bubbles generated at a high intensity can trigger a dampening effect and lower the ultrasound efficacy.

2.7.2 Transmembrane pressure and liquid temperature

Equation (9) indicates that a raised external static pressure (P_0) lowers the collapse time. According to Eqs. (10) and (11), the augmentation of the external pressure increases T_{max} and P_{max} at the point of bubble collapse. As a result, raised external pressure will contribute to a more intense and quick cavitational collapse. High external pressure likewise lowers the liquid vapor pressure. This leads to higher ultrasound intensity that is necessary for the initiation of cavitation [25, 29].

Acoustic cavitation also varies with liquid temperature. A greater temperature causes higher liquid vapor pressure (P_v). As a result, the cavitational collapse is not as intense because of the lower T_{max} and P_{max}, as Eqs. (10) and (11) indicate. For the majority of liquids, higher temperatures imply lower viscosity, which in turn enhances the bubble formation. Since viscous liquids are generally sluggish, they do not let the cavitation bubbles to form easily [28].

2.7.3 Liquid feed and bubble gas characteristics

Cavitation bubbles form reasonably well in liquids with low surface tension, low viscosity, and elevated vapor pressure. Higher vapor pressure, however, also allows for a less aggressive bubble collapse, as outlined in Section 3.7.4. The higher quantity of dissolved gases in liquid augments the number of nuclei available for the subsequent growth of cavitation bubbles. On the other hand, the presence of high concentrations of solid particles reduces the acoustic cavitation because of the weakened and scattered of ultrasonic waves [25, 29].

The overall intensity of cavitational collapse is contingent on the specific heat ratio of the gas located inside the bubble (γ), as shown in Eqs. (10) and (11). Simultaneously, the growth of the gas pressure within the bubble (P_g) causes a less intense cavitational collapse since there is a decrease in T_{max} and P_{max} with P_g, as shown in Eqs. (9) and (10). Thus, gases with lower thermal conductivity generate noticeably higher local heating throughout bubble collapse [28].

3. Influence of ultrasound on membrane fouling remediation

Ultrasound has the capacity to incite critical physical phenomena in heterogeneous solid-liquid systems that can help separate particles from fouled membranes. Ultrasound has been shown to be an effective way in enhancing mass transfer, cleaning, disinfection, and controlling membrane fouling. Some of these relevant physical phenomena include microstreaming, acoustic streaming, microjets, microstreamers, and shock waves, as shown in **Figure 4**. For instance, acoustic streaming is a type of fluid flow that is caused by the absorption of acoustic, or ultrasonic, energy and does not necessitate a cavitational collapse [31]. When the ultrasonic waves propagate, the wave momentum is absorbed by the liquid. As a consequence, unidirectional flow currents are formed within the liquid [29]. Acoustic streaming produces a low flow velocity of about 10 cms^{-1} and happens within a few centimeters of the ultrasonic transducer [29]. The flow velocity becomes greater at higher ultrasound frequencies and increased power intensity. When it is near a solid surface, including the surface

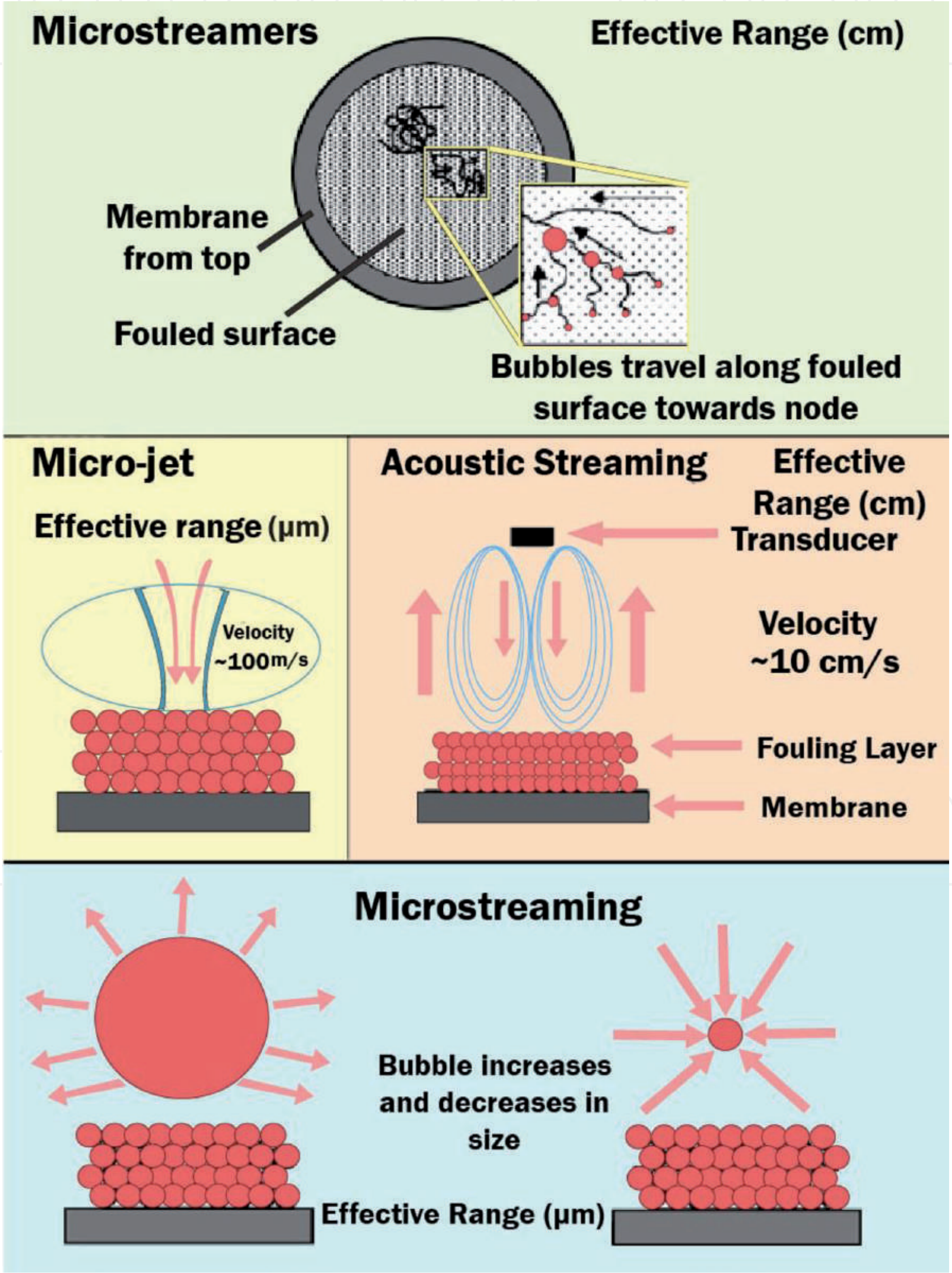

Figure 4.
Influence of ultrasonic on membrane fouling and mechanisms for particle removal/detachment.

of a fouled membrane, the liquid flow generated by acoustic streaming is blocked, causing unidirectional flow parallel to the solid surface that could potentially detach the foulants. Microstreaming is the time-dependent oscillation of liquid molecules located in near the acoustically oscillating cavitation bubbles. Under rarefaction and compression cycles, the oscillation of the cavitation bubbles instigates quick fluctuations in the liquid movement direction and magnitude. Throughout the compression cycle, the cavitation bubbles continue to shrink, while the liquid molecules are moved away from the membrane's surface. Alternatively, in the rarefaction cycle, the cavitation bubbles swell, and the liquid is pushed in the direction of the membrane's surface. The intent is to generate sufficient drag or shear forces that would be able to effectively remove foulants from the membrane's surface. The range of microstreaming effectiveness is relatively limited and generally within the range of 1–100 μm [26, 31]. Microstreamers are produced as a consequence of standing waves created due to the superimposition of the ultrasonic waves redirected from the solid membrane surface and the incoming ultrasonic waves from the ultrasonic transducer. Because of the Bjerknes forces, cavitation bubbles with sizes less than the resonance size are drawn to the standing waves' antinodes. However, cavitation bubbles featuring sizes greater than the resonance size are collected at the nodes. The cavitation bubbles follow a torturous path, forming ribbon-like structures and merging when they come in contact with one another as they move toward the antinodes [26]. In this case, the operational range of microstreamers is several millimeters, and the velocity is around one order of magnitude greater than the average liquid velocity value [30]. It has been shown that microstreamers are involved in detaching foulants from the membrane surface when the antinodes on the membrane surface attract the cavitation bubbles [26, 30]. In a supplement to microstreamers, the appearance of microjets is vital for the release of particles from a fouled membrane. Microjets are created due to the asymmetric cavitation. The liquid movement the vicinity the cavitation bubbles decreases once they are near a solid membrane surface. This in turn produces a differential pressure around the bubbles and a loss of the spherical bubble geometry [30]. Because of the differential pressure, the bubbles tend to discharge strong water jets when they collapse. The microjet's velocity is usually 100–200 ms^{-1}, where the effectual range is in the order of the bubble diameter [31]. Due to the impact of high velocity, microjets can offer a useful capacity for the removal of foulants through erosion and pitting [26]. Lastly, the shock waves produced using ultrasound are critical for the removal of particles from fouled membranes. Throughout rarefaction and compression cycles, shock waves are constantly being generated. Toward the end of compression cycle, the cavitation bubbles abruptly stop once they obtain to their minimum size. At this point, the liquid molecules progressing in the direction of the bubbles are reflected, and this creates high pressure shock waves in the direction of the membrane's surface [25].

3.1 Ultrasound influence on flux improvement and fouling control in wastewater treatment applications

The application of ultrasound for flux improvement in MF and UF processes has been comprehensively investigated. Despite this, research studies linked to ultrasound-assisted flux improvement in NF, MD, FO, RO, and anaerobic membrane bioreactor (AMBR) are currently lacking. Flux improvement related to ultrasound application can be attributed to several key factors. It should be noted that lower-frequency ultrasound reduced the total fouling resistance (R_{tot}) and the reversible fouling resistance (R_{rev}) of polyethersulfone (PES) membrane with dextran feed solution, even with a dead-end UF cell [32]. Lower resistance was linked to a decline in concentration polarization effect because of the cavitation and acoustic streaming generated by ultrasound. As a consequence, when comparing with the flux generated without ultrasound application, the flux at a transmembrane pressure of 0.4 bar was 83 and 33% larger with ultrasound at frequencies of 28 and 45 kHz, respectively. In this study, the irreversible membrane fouling was insignificant. Reductions in reversible and irreversible fouling in cross-flow UF of clay solution, using hollow fiber polysulfone (PS) membrane, were observed at suitable lower ultrasound frequencies [33]. Since there was a reduction in the fouling resistance, at a transmembrane pressure of 175 kPa, a flux improvement of 33% was attained with the aid of ultrasound at 40 kHz. Furthermore, ultrasound has the potential to lower the filtration resistance in AMBR processes [34, 35]. A number of studies have ascribed flux improvement to acoustic streaming and higher turbulence potential [36–38]. For instance, with dextran feed solution, the flux improvement in the UF process was suggested to be due to the acoustic streaming generated by low-frequency ultrasound.

On the other hand, other study indicated that the application of ultrasound did not offer substantial reduction of internal fouling or pore blockage. Furthermore, it was also noted that the use of ultrasound had little to no influence on pore blocking and adsorption of foulant onto hollow fiber in PS UF membranes. In most instances, whenever the membrane was close to the acoustic cavitation zone, the flux was improved by the collaborative elements of acoustic streaming, microjets, microstreaming, and shock waves. It should be noted that external to the acoustic cavitation zone, increased turbulence and acoustic streaming are the primary influencing factors on the flux improvement [37]. In addition, the implementation of ultrasound in ultrafiltration of water containing 1 mM KCl, and 10 mg/L sulfate latex particles acting as foulants, the ratio of final flux (after the duration of 4 hours) to the initial flux was 0.85 and 0.92, respectively, for applied powers of 0.8 W and 3.3 W [39]. This indicates that the negative influences of fouling were practically eliminated. In a study of inorganic fouling of commercial polyamide-based RO membranes using a $CaSO_4$ solution, the effects of microstreaming in the membrane pores and on the membrane surface were believed to be the primary reason behind membrane cleaning and the flux enhancement obtained [40]. In general, for an experimental duration of 3 h, the permeate flux increased by about 50.8% for the 500 mg/L $CaSO_4$ solution and 69.7% for the 1000 mg/L $CaSO_4$ solution with the application of the 20 kHz ultrasound, as compared with the runs without ultrasound. The ultrasound irradiation could likewise improve the flux through the agglomeration of small particles, thus lowering the chances of pore blockage. In ultrafiltration of wastewater using PS hollow fiber membrane, an agglomeration of small suspended particles was detected because of the vibration and microstreamers. The agglomeration that occurs when the ultrasound was used resulted in a greater turbidity removal, compared to the turbidity removal when ultrasound was not employed.

Choi et al. also used 72 kHz ultrasound to lower silica colloidal fouling and calcium sulfate scaling in a commercial cellulose acetate FO membrane [41]. Ultrasound appeared to disassemble silica colloids and calcium sulfate crystals in the feed solution. In terms of flux improvement, the ultrasound-assisted FO (UAFO) process was much more successful than FO. In comparison to FO processes, the initial flux with UAFO was about 25% higher, and 166% higher with calcium sulfate scaling. For silica colloidal type fouling, permeate flux decrease was only 21% for FO, compared to 50% flux drop with FO without ultrasound. The ultrasound-assisted flux improvement during FO filtration of tannin using a thin-film composite (TFC) membrane was also examined. The flux improvement was caused by the lessening of concentration polarization in the membrane's porous support layer [42]. In addition, the reverse salt flux was greater whenever ultrasound was applied. Also, ultrasound was found relevant for the mitigation of silica colloid and calcium sulfate fouling during the membrane distillation (MD) process. In a research study on the effects of ultrasound on the performance of MD, the specific ratio of fouled-membrane flux to the initial flux was upheld at 93 and 97% with calcium sulfate and silica fouling, respectively, because of the microstreaming and shock waves generated by the ultrasound [43].

3.2 Ultrasound influence on fouling control in protein separation/purification downstream processing

The concentration polarization occurs when a concentration gradient of the protein is formed on or near the membrane surface. Similarly, this phenomenon is predominantly a function of membrane hydrodynamics. Conversely, fouling is the result of accumulation of proteins drawn toward filtering surface by convective flow of filtrate through the membrane. Membrane cleaning is significantly enhanced by cavitation and acoustic streaming induced by ultrasonic waves. Ultrasound generates acoustic streaming and cavitation bubbles in a liquid medium. Cavitation bubbles cause microstreaming, microstreamers, microjets, and shock waves, as described in **Figure 4**. Acoustic streaming and shear forces imposed by cavitation bubbles reduce protein fouling on the membrane surface. This leads to an increase in permeate flux. Several mechanisms of protein release from a protein-fouled surface by the effects of ultrasound were proposed, as presented in **Figure 4** for the removal/detachment mechanisms. Acoustic streaming does not require the collapse of cavitation bubbles, and it was defined as the absorption of acoustic energy resulting in fluid flow [44]. This protein removal mechanism is expected to be important near surfaces with loosely attached particles or with readily dissolvable surfaces. Higher frequency ultrasound tends to have higher energy absorption by liquid and thus greater acoustic streaming flow rates than lower frequencies at the same power intensity [45]. In addition, higher power intensities lead to greater acoustic streaming flow rates due to higher energy gradients in liquid between acoustically and nonacoustically stimulated areas. Acoustic streaming causes bulk water movement toward and away from the membrane cake layer, with velocity gradients near the protein cake layer that may scour proteins from the surface. The effect of ultrasound on the flux and solute rejection in cross-flow UF of BSA-lysozyme binary protein mixture, using PES membrane (30 kDa MWCO), was investigated and reported [44, 45]. The authors observed that ultrasonic wave not only enhanced the UF flux but also increased the lysozyme rejection. Particularly, at ultrasound wave of 25 kHz and 240 W, increases in UF flux of 135 and 120% were obtained with PES membrane at pH of 11 in the upward and downward modes, respectively, in contrast to the case without ultrasound [44, 45]. Enhanced flux in continuous UF processes was achieved with an interrupted ultrasound, and more hydrophilic ultrafilter membranes in the upward operating mode were achieved [46]. It was noticed that the effectiveness of ultrasound in membrane protein purification depends on many factors, such as orientation and position of ultrasonic field, ultrasonic frequency and power, ultrasonic radiation angle, position of ultrasonic vibration plate in the membrane module, membrane material, membrane housing, operating pressure, and the fouling material. It was widely believed that ultrasonic cavitation, acoustic streaming, ultrasonic-induced vibration of membrane, and ultrasonic heating were the main causes for the enhanced separation performance and permeate flux [44]. Electric and ultrasonic fields can reduce membrane fouling and in turn of enhanced flux, when both the fields were applied simultaneously [47]. Both electric and ultrasonic fields reduced the fouling when applied individually, but the extent of improvement by the ultrasonic field could be minimal. The improvement by the electric field is invariably considerably greater than that due to the ultrasonic field, particularly when the proteins are well dispersed (high zeta potential).

In another case study examined the filtration of whey solution, using a PS membrane and a cross-flow UF apparatus, the flux improvement was primarily caused by the mechanical vibrations and acoustic streaming instead of the acoustic cavitation. For shorter filtration times, the decline of the permeate flux was caused by the pore blockage. On the other hand, the decline in flux was controlled by the growth of cake layer with longer filtration times. Ultrasound lowered the resistance of the initial deposit layer and the growing cake layer [26]. The specific ratio of the steady flux with ultrasound in comparison to the steady flux without ultrasound was determined at about 1.2 and 1.7 throughout the complete experimental range.

3.3 Fouled membrane cleaning and flux restoration

Ultrasound can be effectively used for cleaning fouled membranes. A number of researchers have explored the use of ultrasound as a potential membrane cleaning method. Ultrasound-assisted cleaning of membranes may be conducted in different ways. For instance, the membrane can be cleaned in an ultrasonic cleaning bath or, alternatively, washed online in a filter using cleaning chemicals or washed with water while applying ultrasound irradiation. In a reported study, Anodisc™ γ-Al_2O_3 ceramic membrane was exposed to ultrasound inside a closed washing vessel containing water [39]. The membranes were specifically fouled with sulfate polystyrene latex particles. Once the external cleaning was performed, a complete retrieval of clean water flux was detected for all frequencies, with the exception of 1062 kHz, since the ultrasonic treatment time and power intensity were higher than 30 s and 1.05 W cm^{-2}. In addition, an exterior ultrasonic cleaning vessel using a 1 mM KCl solution was used to wash the Anodisc™ γ-Al_2O_3 ceramic and polyvinylidene difluoride (PVDF) membranes [39]. It was reported that the membranes were almost completely washed, while the water flux after washing was near the original level of clean water flux in new membranes. In a different study, cellulose MF and PS UF membranes were washed inside a filtration cell using a combination of ultrasound and water washing [48].The cellulose and PS membranes were initially fouled using milk solution and peptone solution. Complete and partial washing for the PS and the cellulose membrane was obtained at 28 kHz, respectively. Similar membrane washing procedures have also been used in other research studies [49, 50]. Different ways of cleaning nylon MF membrane that were fouled using Kraft paper mill effluent were comparatively examined. The experimental results obtained suggest that the washing efficacy was best (97.8%) when ultrasound was implemented in conjunction with forward flushing. Several studies combining EDTA chelating agent and ultrasound were carried out to clean fouled spiral wound PES membranes in ultrafiltration of skimmed milk solution. A synergistic effect was detected when EDTA and ultrasound were simultaneously applied. The best cleaning was noted when 3 mM EDTA and ultrasound mixed waveform were applied simultaneously. Furthermore, it was stated that a 5-minute period of forward flushing with ultrasound and sequestering agent EDTA was sufficient for membrane cleaning without supplementary washing. Comparable experimental results were obtained, where synergistic outcome was perceived in cases where the ultrasound was applied together with EDTA during cleaning of PVDF MF membranes fouled with a 1% milk solution [51].

4. Challenges in industrial applications of ultrasound

Although research has shown the efficacy of ultrasound as a method to improve membrane cleaning and flux, hands-on ultrasound applications in membrane-dependent separation processes still have a number of critical challenges. One such issue is associated with membrane damage. When exposed to ultrasound, the membranes can become vulnerable to damage due to the intense cavitational collapse contingent on the power density, frequency, and the irradiation time of ultrasound.

A number of research studies have offered examples of membrane integrity loss and membrane damage due to ultrasound exposure [45, 52, 53]. The ultrasound power intensity needs to be carefully coordinated so as to minimize energy consumption and potential membrane damage. An in-depth study on the influences of 47 kHz ultrasound on polymeric membranes was conducted. During this experiment, three polymeric membrane were used: PES (MWCO: 3, 10, 30, and 100 kDa), PVDF (MWCO: 40 kDa), and polyacrylonitrile (PAN; MWCO: 40 and 50 kDa). Once a 2-hour ultrasonic treatment was completed, PES membranes were affected over the entire surface area, while PVDF (40 kDa) and PAN (50 kDa) were influenced on the edge areas. Except for PAN (40 kDa), other membranes showcased significant differences in their water permeability, with membrane degradation occurring primarily within the first 5 min of exposure to ultrasound. A research study examined the effect of 40 kHz ultrasound on polymeric MF membranes [53]. The membranes used included mixed ester of cellulose nitrate and cellulose acetate (CN-CA), PES, nylon 6 (N6), and PVDF. Except for PVDF membranes, at a power intensity of 2.13 W/cm^2, all membranes used showed partial damage that caused an increase in water flux after 60 min of ultrasound session. PVDF membrane had some damage only at a power intensity of 3.7 W/cm^2 after a 90-min exposure. Another study likewise confirmed some impairment to ceramic Anodisc™ γ-Al_2O_3 membranes after a sonication of 20 kHz for 5 min [39]. Membrane damage took the form of pitting on the membrane surface, which was caused by microjets and shock waves. Alternatively, it was found that PVDF hollow fiber UF membranes were damaged by ultrasound at 8.68 kW/m^2 within 6 min of exposure [54]. The number of research studies focused exclusively on ultrasound-induced membrane damage is relatively low. There is a lack of research on membrane materials that can offer a range of resistance potential against damage incurred by ultrasonic treatment. Consequently, further research is necessary for the proper assessment of the effects of ultrasound on the integrity of membranes consisted of diversified materials. Another key challenge that needs to be addressed is related to the industrialization of ultrasound-assisted membrane process. The vast majority of all research studies on the application of ultrasound to membrane cleaning and flux improvement have been done with laboratory-scale cross-flow units. Although there are a high number of such ultrasound studies, effective commercial application of ultrasound technology requires further in-depth case studies with large-scale membrane process; these, however, are currently not available. New research investigations must be conducted on the relevance of ultrasound in cleaning of full-scale membrane modules. There is a common agreement in scientific research community that ultrasound is a highly encouraging method for membrane cleaning and flux improvement; however, the economic value and industrial application feasibility are still challenges that must be addressed. Contingent on the real-life operating conditions, the power requirements of ultrasound could be so high as to constraint its applicability on an industrial scale. Currently, there has been no study on the specific economics behind membrane-based, ultrasound-assisted, or membrane cleaning process types. Thus, the economic viability of ultrasound-assisted membrane cleaning and flux improvement demands urgent response. The exact source of ultrasound likewise poses another issue when it comes to the effective applications of ultrasound in large-scale membrane processes. In general, research studies have been dependent on the usage of probes, horns, or ultrasonic baths. Due to their limitations, all of these ultrasound sources will most likely to be ineffectual in large-scale applications. As a result, research into ultrasound transducer technologies is becoming essential. Additional experimental work is necessary for the examination of the success of ultrasound in flux improvement and washing processes for diverse membrane module types. The majority of research studies have concentrated on flat sheet membranes, and only a small number of studies on spiral wound or hollow fiber membranes, for which the ultrasound applications are much more strenuous due to membrane configuration. Another research gap is in the understanding of the effects of ultrasound on cleaning and flux improvement in membrane processes other than UF and MF. The absence of these critical research studies is a difficult challenge for future implementation of ultrasound-assisted membrane processes on a larger industrial scale.

5. Conclusion

This review paper recapitulates some of the critical research efforts currently being made toward effective ultrasound-assisted membrane cleaning and flux improvement. As the experimental outcomes reviewed in this chapter suggest, ultrasound, including continuous and intermittent waves, is an efficient method of flux improvement, membrane fouling minimization, and membrane cleaning because it has a distinctive capability to produce unique physical and chemical effects that can successfully remove foulants from the membrane surface. Despite these advantages, ultrasound application cannot significantly deter pore blockages and is limited to external fouling. Although it is an effective method for membrane cleaning and flux improvement in wastewater treatment and protein purification downstream processing, ultrasound-assisted membrane technology is still in its developmental stages due to a number of key limitations. The primary issues preventing a more effective use of ultrasound-assisted membrane technology include concerns about installation in large-scale systems, absence of suitable transducers, and scarcity of relevant data on its economic feasibility. In addition, mathematical concepts and model descriptions are needed to understand membrane fouling and permeate flux as a function of ultrasonic parameters. Substantial research enquiries are necessary for further analysis and remediation of membrane damage by ultrasound, the efficacy of ultrasound applications for membranes other than those of the flat-sheet type, and the economics of the ultrasound-assisted membrane process.

Nomenclature

λ (m)	wavelength of one pressure oscillation
f (Hz)	frequency of the ultrasound wave, which is the number of pressure oscillations per unit time, and the inverse of the time period of one oscillation
f_b(Hz)	bubble oscillation frequency
c (m/s)	ultrasound speed, which is the distance of wave propagation per unit time [ultrasound speed = frequency × wavelength, ($c = f\lambda$)]
P (W)	power of ultrasound wave, which is the time rate of the energy of ultrasound passing through a surface perpendicular to the direction of the wave propagation
I (W/m^2)	intensity of ultrasound wave, which is the ultrasonic energy passing a unit surface perpendicular to the direction of wave propagation per unit time
P_a (Pa)	acoustic pressure, which is the pressure created as a result of compression or rarefaction zones relative to the fluid hydrostatic pressure
P_A (Pa)	acoustic pressure amplitude, which is the maximum height of the ultrasonic wave

P (Pa)	pressure inside the bubble at the maximum radius value [$P = P_v$ (vapor pressure) + P_g (gas pressure)]
P_m (Pa)	liquid pressure at the transient collapse moment [$P_m = P_0 + P_A$]
$P\infty$ (Pa)	pressure value at an infinite distance away from the bubble
Po (Pa)	hydrostatic pressure being applied on the liquid or pressure value close to the bubble
P_{max} (Pa)	maximum pressure
Pb (pa)	Blake threshold pressure
ω (Hz)	ultrasound's angular frequency
γ (unitless)	specific gas heat ratio within the bubble
ρ (Kg/m^3)	liquid density
μ (cP)	liquid viscosity
σ (N/m)	liquid's surface tension
R_0 (m)	cavitation bubble of initial radius
R_{max} (m)	maximum bubble radius before the collapse
R (m)	bubble radius
R_r (m)	bubble's resonance size, which is a function of ultrasound frequency
T_a (s)	time period of one oscillation
t (s)	time
τ_m (s)	bubble collapse time
T_{max} (K)	maximum temperature of the feed

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