



Enzyme-based control of membrane biofouling for water and wastewater purification: A comprehensive review

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ABSTRACT

The current work provides an insight into biofouling and enzyme-based mitigating techniques during the application of membrane-based separation for water and wastewater purification. The study emphasizes underlying mechanisms of biofouling formation. The roles of extracellular polymeric substances (EPS) in the interaction with the membrane surface as well as in biofilm stability and diversity that govern biofouling severity are thoroughly discussed herewith. In addition to EPS, the quorum sensing (QS) process that regulates the bacterial communication process for biofilm formation and subsequent biofouling is also comprehensively reviewed. The relationship among EPS, QS, and biofouling is systematically described for the first time in this study. Derived from the appreciation of the EPS-QS-microbe nexus, an overall picture of the to date enzyme-based techniques and their underlying mechanisms to control and remove biofoulants is critically analysed and drawn for the first time. In this study, the limitations of the current biofouling control techniques are indicated before future research directions were proposed for further treatment improvement.

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1. Introduction

Over the last few decades, membrane filtration has evolved to become an essential process for water and wastewater treatment. Some of the techniques in membrane filtration can offer excellent effluent quality and be easily integrated with other treatment processes (e.g. biological processes) (Bilal Asif and Zhang, 2021; Cong Nguyen et al., 2020; Vu et al., 2020). However, membrane fouling remains a major hurdle to cost effective water and wastewater treatment (Faria et al., 2017; Herzberg et al., 2009). In a study conducted to evaluate the cost of fouling in full-scale reverse osmosis and nanofiltration installations in the Netherlands, Jafari et al. (2021) found out that the average cost of fouling accounted for around 11% and 24% of operating expenditure in nanofiltration and reverse osmosis plants, respectively. Of several types of fouling, biofouling caused by the deposition and growth of bacteria on the membrane surface can be considered as one of the most demanding obstacles to further application and improvement of membrane technology due to the fast replication of microbes over time.

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A range of physicochemical techniques have been developed and adopted to control and remove biofouling (Al-Amoudi and Lovitt, 2007; Al-Juboori and Yusuf, 2012). Nevertheless, most of these strategies are only to address the fouled membrane after the occurrence of biofouling. These methods can even cause damage to the membrane and threaten the microbial community, especially in membrane-based biological hybrid systems, e.g., aerobic membrane bioreactors (MBRs), anaerobic membrane bioreactors (AnMBRs), and membrane microalgal reactors. Thus, exploring an effective alternative to prevent the biofouling formation at the initiation stage would be of significant interest in order to allow a sustainable operation of membrane-based processes for water and wastewater treatment.

The use of different enzymes has proven to be effective to control and remove biofouling as well as friendly to the membrane and environment (Arguello et al., 2003; Bao et al., 2019; Duan et al., 2015). This strategy is derived from the understanding of the nature of biofouling. In detail, quorum sensing (QS) biomolecules for microbial communication that regulate biofilm formation, and the extracellular polymeric substances (EPS) matrix that stabilizes and provides nutrients for microbial growth can be degraded by various enzymes. In other words, the primary purpose in using enzymes is to hydrolyse these biopolymers (i.e. QS molecules and EPS), thereby controlling biofouling. However, most of the review papers in the literature have only paid attention to using enzymes to quench QS molecules, but overlooked their ability to control biofouling via the degradation of EPS. In addition, to date studies have yet to critically and comprehensively demonstrate the underlying mechanisms of using enzymes as well as their applications for biofouling control during membrane filtration.

In previously published articles, the methods of removing biofoulants were discussed, but most of the publications focused on the presentation of mechanical methods using rotating and vibrating membranes, as well as ultrasound and chemical reagents, among which oxidants and surfactants played a major role (Alkhatib et al., 2021; Bhoj et al., 2021; Kumar et al., 2021; Li et al., 2020). Hence, this study is an attempt to systematically and comprehensively review enzyme-based technologies used to prevent and clean the bio-fouled membrane. Also, mechanisms by which enzymes mitigate membrane biofouling based on EPS and QS are thoroughly discussed. The interplay between QS and EPS in biofouling is also demonstrated. It is expected that this review can be a stepping-stone for further advancement and application of enzymes to effectively control biofouling in the membrane-based water and wastewater purification system.

2. Occurrence of biofouling during membrane filtration

2.1. Fundamentals of membrane biofouling

2.1.1. Definition

Biofouling refers to the attachment of microorganisms followed by the development of biofilm layers on the membrane surface during its applications in water and wastewater purification. The adoption of membrane-based processes (i.e. microfiltration, ultrafiltration, nanofiltration, reverse osmosis, membrane distillation, forward osmosis, etc.) to treat or purify non-sterile water and wastewater has always potentially faced the biofouling problem (Cong Nguyen et al., 2020; Liu et al., 2020a; Vu et al., 2021, 2019). Biofouling occurs in the applications of above single membrane processes and even more terribly in those of the hybrid processes integrating biological treatment and membrane filtration, such as MBRs, osmotic membrane bioreactors (OMBRs), and AnMBRs (Anjum et al., 2021).

A variety of bacterial species in the environment, such as *Pseudomonas*, *Aeromonas*, *Corynebacterium*, and *Fluviicola* could be involved in biofouling (Zhang et al., 2014). It is acknowledged that among different kinds of membrane fouling, biofouling is the most complicated and challenging issue hindering the maturity of membrane-based processes due to the fast replication and the robust resilience of microorganisms in the surrounding environment. It is estimated that in reverse osmosis filtration, biofouling can contribute to 45% of all membrane fouling (Nguyen et al., 2012).

2.1.2. Microorganism attachment and biofilm development

The occurrence of membrane biofouling consists of four stages (Fig. 1) (Gule et al., 2016; Nguyen et al., 2012). At first, the dissolved organic and inorganic materials in aqueous solution are adsorbed onto the wetted membrane surface to form a preconditioned film. This process occurs within minutes of placing the membrane in the aqueous solution. In the second stage, biofouling initiates with the transportation of bacteria towards the conditioning film followed by the attachment process and the development of a primary film. Subsequently, the formation and development of biofilm due to the fast reproduction of bacteria are dominant. At the final stage, the detachment process of part of the biofilm takes place to disperse biofoulants in the bulk solution.

Bacteria are transported towards membrane surface via the fluid dynamic forces and Brownian motion, and then attached to the surface via adhesive proteins and electrostatic interactions (Nandakumar and Yano, 2003; Redman et al., 2004). Proteins are the robust adhesives that can firmly attach onto wetted membrane surfaces (Nandakumar and Yano, 2003). At the early stages, bacteria with small rods and long motile flagella are the first living organisms to colonize the membrane surface (Nandakumar and Yano, 2003).

In the next stage, the colonized bacteria grow and secrete EPS which play a role as the matrix of bacterial film. This bacterial film develops and becomes thicker. This film is now referred to as biofilm. In other words, biofilm is a mixed consortium of diverse bacterial species (e.g. bacteria, microalgae and protozoa) and their extracellular by-products (i.e. EPS). In most biofilms, bacteria account for 5%–25%, and the matrix of extracellular materials makes up 75%–95%

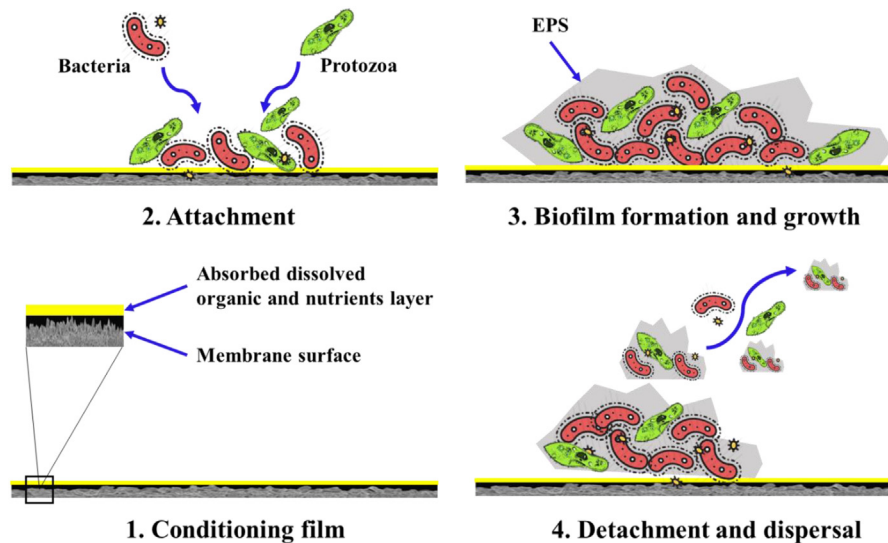


Fig. 1. The formation and development of biofouling (1→4) in a membrane-based process for water and wastewater purification.

Table 1

Typical factors affecting the formation and severity of membrane biofouling.

Microbial community in the bulk medium	Chemistry of the bulk mediums	Membrane properties	Operational conditions
Microbial diversity	pH	Roughness	Applied pressure
Population density	Temperature	Porosity	Flux
Growth phase	Viscosity	Surface charge	Velocity
Nutrient status	Salinity	Hydrophobicity	Water recovery rate
Hydrophobicity	Organic carbon	Concentration polarization	Membrane orientation in FO filtration
Charge	Nutrients	Chemical composition	Operation mode (e.g. on-off mode in MBR systems)
Physiological response	Suspended matter	Water and solute permeability	Membrane configurations

(Nandakumar and Yano, 2003; Nguyen et al., 2012). The diversity and distribution of microbial community within biofilms is governed by the intercellular signalling and gene exchange among bacterial species (Nandakumar and Yano, 2003).

Biofilms can facilitate the attachment of propagules of large fouling organism. The exposure of bacteria upon dissolved oxygen in water at different levels leads to a vertical distribution of species on the membrane surface. The aerobic forms occupy the top layer, whereas the deeper layer is abundant of the anaerobic species. It was reported that the growth of biofilm is mostly due to the division of the initially attached cells rather than the continuous fresh colonization of microbes from the bulk medium (Nandakumar and Yano, 2003). The release of microorganisms from the biofilm to the bulk medium is as a mechanism of dispersion of these organisms (Nandakumar and Yano, 2003).

The formation and severity of membrane biofouling are dependent on several factors including the properties of membrane, the chemistry and bacterial characteristics of the feed solution and draw solution in case of forward osmosis (FO) filtration and the operational conditions of the membrane-based system (Table 1) (Cong Nguyen et al., 2020; Liu et al., 2020a; Maddah and Chogle, 2017; Nguyen et al., 2012; Vu et al., 2019; Zhang et al., 2014). The initial bacterial community of the bulk mediums can regulate the bacterial structure of the biofouling layer. The compositional properties of the bulk mediums are responsible for the provision of food and nutrients for the development of microbes. The membrane materials, morphology, charge and hydrophobicity can govern the attachment of microbe to the membrane surface. The severity of biofouling can be significantly influenced by the operational parameters. In a membrane-based system for water treatment, the synergistic effects caused by the interaction among these factors can result in the exacerbation of biofouling.

2.1.3. Role of extracellular polymer substances in biofouling

Extracellular polymeric substances comprise a variety of high molecular weight biopolymers secreted by microorganisms (Nguyen et al., 2012). These substances consists of polysaccharides, proteins (i.e. enzymes), nucleic acids (i.e. DNA

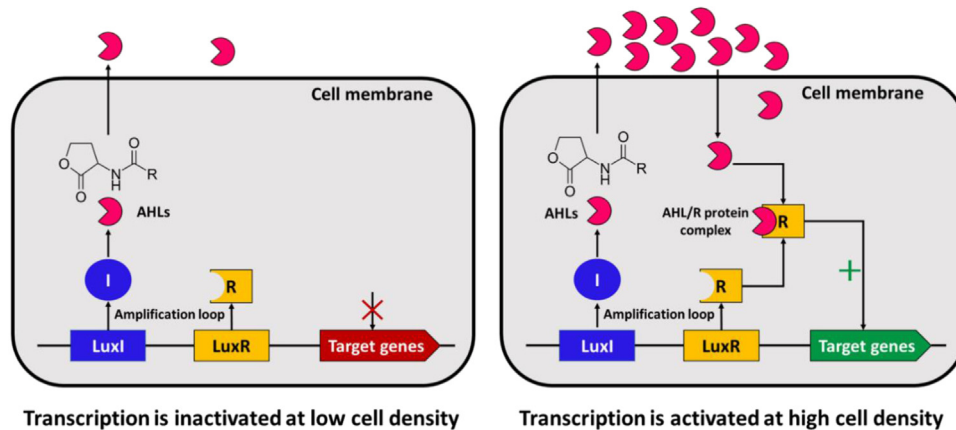


Fig. 2. The LuxI/LuxR-type quorum sensing in Gram-negative bacteria. The LuxI protein is a signalling molecular synthase that can induce the formation of AHLs. The AHLs can be transported through the cell membrane via diffusion when the population density is high. The LuxR receptor that is a transcriptional activator of the Lux operon can bind to the diffusing AHL in order to make an AHL/LuxR complex, thus activating the transcription of its target genes.

and RNA) and water (Nazir et al., 2019). These components significantly affect the physicochemical properties of the biofouling layer. It is reported that this matrix consists of 95%–99% water in volume (Gule et al., 2016; Nguyen et al., 2012). The EPS properties vary in the depth of the biofilm layer. The acidic exopolysaccharides predominantly contribute to the dry weight of outer layer EPS, whereas lipopolysaccharides are dominant in the biofilm matrix closer to the bacteria cells (Nandakumar and Yano, 2003).

EPS are crucial for the formation and development of biofilm. It is a three-dimensional matrix to bind the microorganisms together as well as a nutritious substratum to promote their growth (Sheng et al., 2010). EPS matrix regulates the structural and functional integrity as well as the organization of biofilm community (Limoli et al., 2015). Also, this matrix enables biofilm cells to withstand severe environmental conditions, such as UV radiation, abrupt pH changes and toxins (Nandakumar and Yano, 2003; Nazir et al., 2019). EPS can be divided into two different fractions including bound EPS and soluble EPS. The bound EPS are close to the cells and normally composed of sheaths, capsular polymers, condensed gels and attached organic materials. The soluble EPS known as soluble microbial products indicates the type of EPS weakly bound to cells or dissolved in the surrounding solution. The soluble EPS have better binding capacity for organics than the bound EPS.

The interaction between EPS and membrane surface is biofouling controlling factor in the membrane-based system (Liu et al., 2012; Sudmalis et al., 2020; Tsuneda et al., 2003). The EPS contain charged groups (e.g., carboxyl, hydroxyl, sulfhydryl and phenolic) and polar groups (e.g. aromatics and aliphatics in proteins, and hydrophobic regions in carbohydrates) (Limoli et al., 2015; Liu et al., 2012; Sheng et al., 2010). These characteristics make EPS both hydrophilic and hydrophobic, enabling them to attach to both hydrophilic and hydrophobic surfaces. In particular, in the presence of divalent metal ions (e.g. calcium), the cross-linking of EPS and membrane surface can be established via the bridging effects via these ions (Wang and Waite, 2009). It is reported that the adhesive capacity of microbial cells to membrane surface is weakened due to the electrostatic repulsion at low EPS content, but becomes greater by polymeric interaction at high EPS content (Nguyen et al., 2012). Also, polysaccharides of EPS were reported to have stronger adsorbing affinity to reverse osmosis and nanofiltration membranes, compared to their proteins component (Herzberg et al., 2009).

2.2. Biofilm colonization and propagation

2.2.1. Quorum sensing process in microbial community

QS is defined as the cell-to-cell communication process through the synthesis, secretion and uptake of signalling molecules called as auto-inducers in the surrounding environment. This process is a key mechanism for assessing the microbial population densities and controlling gene expression at the population level (Chen et al., 2019; Lade et al., 2014). During QS process, a specific autoinducer interacts with a specific transcriptional regulator directly or via the activation of a sensor kinase to regulate the target gene for a specific phenotype (e.g. bioluminescence, virulence, motility, competence, extracellular production and biofilm formation) (Fig. 2 and Table 2) (Chen et al., 2019; Lade et al., 2014; Li and Tian, 2012; Siddiqui et al., 2015). In general, QS process is to coordinate the population behaviour to promote nutrient availability, defend against another hostile species as well as withstand negative environmental conditions (Lade et al., 2014).

There are a variety of classes of signalling molecules (i.e. autoinducers), which are classified based on the utilization of bacteria. Among them, three major classes of QS signalling molecules include N-acyl homoserine lactones (AHLs), autoinducing peptides (AIPs) and autoinducer-2 (AI-2) (Lade et al., 2014). In addition to these three main autoinducers,

Table 2

Quorum sensing autoinducers and QS-regulated phenotypes in Gram-negative and Gram-positive bacteria.

Autoinducers	Bacteria	Regulated phenotypes	References
3-oxo-C6-HSL	<i>Vibrio fischeri</i>	Light production	Engebrecht et al. (1983), Neelson et al. (1970)
3-oxo-C10-HSL	<i>Vibrio anguillarum</i>	Virulence	Defoirdt et al. (2004)
AI-2	<i>Vibrio harveyi</i> <i>Vibrio cholerae</i> <i>E. coli</i> <i>Y. pestis</i>	Bioluminescence, symbiosis Virulence Biofilm formation, motility Virulence	Chen et al. (2002), Miller and Bassler (2001) Miller et al. (2002) Sperandio et al. (2001), Wood (2009) Gelhaus et al. (2009)
3-oxo-C12-HSL C4-HSL	<i>Pseudomonas aeruginosa</i>	Virulence factors Biofilm maturation and adhesion	Pearson et al. (1994) Kuramitsu et al. (2007)
C4-HSL	<i>Aeromonas hydrophyla</i> <i>Serratia marcescens</i>	Biofilm formation Swarming	Swift et al. (1997, 1999) Miller and Bassler (2001)
C6-HSL	<i>C. violaceum</i> <i>A. salmonicida</i>	Violacein, antibiotics and enzyme production Enzyme production	Cha et al. (1998), McClean et al. (1997) Swift et al. (1999)
AIP-I, AIP-II, AIP-III, AIP-IV	<i>Staphylococcus aureus</i>	Cross-signalling between strains and species, biofilm formation, virulence factors	George and Muir (2007), Lyon et al. (2000), Malone et al. (2007), Wood (2009), Yarwood et al. (2004)
Diffusible signalling factors	<i>X. campestris</i>	Endoglucanase production	Wang et al. (2004)

diffusible signalling factors and *p*-coumaroyl homoserine lactones are also used for microbial communication as reported elsewhere (Decho, 2015; Lade et al., 2014; Schaefer et al., 2008). Each type of autoinducer is detected and responded by a precise sensing apparatus and regulatory network (Table 2) (Li and Tian, 2012; Miller and Bassler, 2001).

Among the autoinducers, AHLs are the most extensively studied bacterial signals (Decho, 2015). AHLs are derived from L-homoserine lactone and a fatty acid (Lade et al., 2014). These compounds vary in chain-length of the acyl side chain, degree of saturation and the presence or absence of an oxygen atom at C-3. AHLs are produced by Gram-negative bacteria (e.g. *Aeromonas hydrophyla*, *A. salmonicida*, *Vibrio fischeri*, and *Nitrobacter winogradskyi*) (Neelson et al., 1970; Sun et al., 2018; Swift et al., 1999). In other words, most of Gram-negative bacteria utilize AHLs for the regulation of QS mediated behaviours.

AIPs comprise 5–34 amino acids residues and normally are generated by Gram-positive bacteria (e.g. *Staphylococcus aureus*, *Staphylococcus sp.*, *B. subtilis* and *Ent. faecalis*) (Hamoen et al., 2003; Kleerebezem and Quadri, 2001; Lade et al., 2014). AI-2 is a group of inter-convertible furanones derived from 4,5-dihydroxy-2,3-pentanedione (Lade et al., 2014). The AI-2 substances are secreted by both Gram-positive and Gram-negative bacteria (e.g. *V. harveyi*, *E. coli*, and *Y. pestis*) for interspecies communication (Lade et al., 2014; Li and Tian, 2012; Miller and Bassler, 2001).

2.2.2. The relationship among quorum sensing, extracellular polymeric substances and membrane biofouling

Quorum sensing governs membrane fouling via its impacts on biofilm formation. In other words, the close interconnection between QS and biofilm growth can be able to determine the severity of membrane fouling. The impacts of QS on membrane fouling can be indirectly monitored through observing the fate of autoinducers against operational parameters of the membrane system (e.g. transmembrane pressure (TMP) and water flux). Yeon et al. (2009a,b) observed an increase in TMP coincided with the increased AHLs level of the biofilm in a lab-scale continuous MBR. Oh et al. (2012) reported that the decrease of AHLs in MBR resulted in the significant delay in TMP increase (i.e. membrane biofouling) during the filtration process. It is also reported that a decrease in biofilm formation during reverse osmosis filtration is a result of the reduced production of AHLs.

The interaction between QS and EPS production plays a crucial role in biofilm formation and stabilization. The QS signal molecules (e.g. AHLs, AI-2 and AIP) are reported to promote the production of extracellular protein and other EPS, which of composition and quantity are closely related to biofouling (Ouyang et al., 2020; Song et al., 2014). On the other hand, EPS matrix that is complex in composition can affect the movement, diffusion and efficiency of signalling within a biofilm (Decho, 2015).

In the biological wastewater treatment systems, Gram-negative bacteria are dominant, and thus the impacts of AHLs-mediated QS on bacterial EPS are of importance (Ouyang et al., 2020; Song et al., 2014). In details, AHLs-mediated QS can control the production and composition of EPS, especially protein of tight EPS, thus microbial aggregate formation (Liu et al., 2018; Lv et al., 2014; Ma et al., 2018; Sun et al., 2018). The presence of AHLs molecules can regulate the synthesis of adenosine triphosphate (ATP) that is utilized to provide energy for bacterial metabolism (e.g. EPS synthesis), thus influencing the stability of biofilm (Chen et al., 2019; Zhang et al., 2019). Zhang et al. (2019) demonstrated that a sharp decrease in EPS contents in initially unstable granules could be due to the reduction of AHLs level caused by lower ATP synthesis in microbes.

Although the autoinducers are capable of regulating the EPS production, the presence of EPS matrix in biofilms can influence the mobility of these signalling molecules. It is demonstrated that the QS process is only efficient at short distances (i.e. $< 10 \mu\text{m}$), and enclosed within the EPS matrix (Decho, 2015). In other words, the autoinducers (e.g. AHLs) are present and mobile within the EPS. The EPS matrix is highly hydrated and full of saccharide components which can be used to protect and preserve cells, extracellular enzymes, and signalling molecules during desiccation (Decho, 2015). In addition, the lipid vesicles that are abundant in the EPS matrix can protect AHLs from degradation during transit from one cell to another as well as allow these autoinducers to diffuse and assist the cell communication (Decho, 2015; Mashburn-Warren et al., 2008).

2.3. Impetus for biofouling control during membrane filtration

2.3.1. Flux decline

Membrane water flux decline is a prominent consequence caused by the EPS layer of biofilm. The presence of this layer leads to the formation of a low permeability biofilm, and increase in the hydraulic resistance and concentration polarization (CP) to permeate flow (Cheng et al., 2018; Faria et al., 2017; Herzberg et al., 2009; Lan et al., 2021; Ren et al., 2021). Fonseca et al. (2007) showed that nanofiltration permeate flux decline during biofouling correlated to the membrane-associated EPS content. According to a study conducted by Chong et al. (2008) on reverse osmosis filtration, the exacerbated CP followed by decrease in permeate flux was ascribed to the reduction of turbulent flow in close proximity to the membrane surface due to the EPS layer. A significant water flux decline of 60% due to biofouling have been observed by Lan et al. (2021) as they performed an ultrafiltration treatment of wastewater for 20 h.

2.3.2. Membrane biodegradation

In addition to the decline of water flux, the development of microbes in biofilms can lead to the biodegradation of membrane. The presence of several microbes and their acidic by-products can degrade membranes. It is reported that extracellular enzymes secreted by the bacteria strain *Pseudomonas sp.* present in the activated sludge could be able to degrade amide bonds that are abundant in polyamide membranes (Yamano et al., 2008). When operating a long-term bioreactors integrated with FO membranes, Luo et al. (2016) observed a bio-damage to both polyamide and cellulose triacetate membranes upon their exposure to activated sludge.

2.3.3. Increase in salt passage and deterioration of permeate quality

The deterioration of salt rejection followed by the impaired permeate quality is a repercussion of the enhanced CP and membrane biodegradation caused by biofouling. In the presence of biofouling, the hindered back-diffusion in thick layer of dead cells, and the cake enhanced CP phenomenon can result in the increase of salt fouling at the membrane surface vicinity, thus increasing the gradient for solute penetration (Herzberg et al., 2009). In addition, the enhanced solute passage through the membrane can be attributed to the larger membrane pore radii after biodegradation (Luo et al., 2016; Maddah and Chogle, 2017).

2.3.4. Increase in treatment cost

The negative impacts of biofouling on the performance of membrane system (i.e. flux decline, increased hydraulic resistance, enhanced CP, membrane biodegradation and reduced salt rejection) can increase the treatment costs significantly. Higher energy consumption is required to compensate for the loss of effective pressure due to biofilm resistance and enhanced CP, thus higher costs (Fujioka et al., 2020). Also, the increase of treatment cost can result from higher intensity of aeration in the membrane bioreactors to improve air scouring effect for fouling control. Due to membrane biodegradation, the frequency of cleaning membrane maintenance and replacement is greater, which increases the cost. In addition, the downgraded quality of permeate caused by biofouling requires extra treatment steps, thus increasing overall treatment costs. It is reported that biofouling accounts for 50% increase in total costs in desalination treatment (Maddah and Chogle, 2017).

3. Enzymatic treatment to control biofouling

3.1. Underlying mechanisms

The development of effective methods of removing pollutants or preventing their formation involves a thorough analysis of the operating conditions of the equipment, the properties of the membrane and the characteristics of substances contained in water or wastewater. Additionally, attention should be paid to the biological and chemical properties of pollutants, the place of their deposition on the membrane and the rapidity of biofilm formation (Bagheri and Mirbagheri, 2018). For many years, scientists have been studying thousands of substances that can help stop the formation of biofilm by preventing the bacteria from production of adhesive agent. For this purpose, changes in the surface charge, hydrophobic properties or surface roughness, as well as the use of low-energy surface acoustic waves and ozonation were applied (Rabin et al., 2015; Chen et al., 2013a). Furthermore, as inhibitors of the biofilm formation, compounds with the ability to inhibit gene expression i.e. aryl rhodanines (Opperman et al., 2009), cis-2-decenoic acid (Davies and

Table 3
Advantages and disadvantages of enzymatic preventing techniques.

Enzymatic preventing techniques	
Advantages	Disadvantages
Low or even nontoxicity	Low stability and resistance
High antibiofouling efficiency	Lower mass transfer through the vessel
Low risk of bacterial resistance development	High cost of enzymes
Possibility of using separable materials with easy recovery	The difficulty of feasibility for the pilot- and real-scale installations

Marques, 2009), D-amino acids (Kolodkin-Gal et al., 2010), N-acetylcysteine (Perez-Giraldo et al., 1997), compounds with bactericidal and bacteriostatic properties, i.e. silver (Roe et al., 2008) or furanones (Baveja et al., 2004), and anti-adhesive compounds such as silica colloids/silane xerogel (Privett et al., 2011) were used. Nevertheless, the diverse composition of the biofilm significantly complicates attempts to prevent the above-mentioned process.

Increasingly better knowledge of the structure of biofilm allows the development of innovative biological methods that will focus on disrupting the interactions within the biofilm. Enzymes can penetrate the biofilm and destroy the integrity of EPS, which protects bacterial cells from antimicrobial agents (Sadekuzzaman et al., 2015). Table 3 summarizes advantages and disadvantages of using enzymatic preventing techniques (Ergon-Can et al., 2019; Kose-Mutlu et al., 2019; Xiong and Liu, 2010).

Derived from the understanding of biofouling and its controlling factors, four key mechanisms to control membrane biofouling using the enzymatic treatment were presented in the literature (Fig. 3). The first mechanism is to use enzymes to degrade organic matter which is the precursor of biofouling present in wastewater prior to filtration commencement. The second mechanism implies the use of enzymes to destroy the integrity of EPS and its components, thus breaking the stability of microbial community and subsequent biofouling mitigation. Another principle is to employ enzymes to degrade signalling molecules (i.e. autoinducers) in order to interrupt the microbial communication for biofilm formation. The last principle also resulted from interruption of autoinducers is the indirect reduction of EPS secretion, thereby leading to the decreased biofouling (Bagheri and Mirbagheri, 2018). The action of enzymes may result in the degradation of carbohydrates, lipids, proteins and other EPS components. Two groups of enzymes are most often used in the process of polysaccharide degradation: lyases (EC 4) and hydrolases (EC 3). Polysaccharide lyases are characterized by the ability to break some glycosidic bonds in the acid polysaccharide through the β -elimination mechanism. In contrast, hydrolases can degrade polysaccharides by catalyzing the hydrolysis of glycosidic bonds in their chain (Richards and Cloete, 2010). On the other hand, proteins are broken down with the use of proteolytic enzymes (EC 3.4), mainly exopeptidases and endopeptidases. Exopeptidases detach single amino acids from the end of the peptide chain, while endopeptidases cleave peptide bonds within the chain (Al-Juboori and Yusuf, 2012). Additionally, among the enzymes that effectively degrade EPS, Malaeb et al. distinguished also proteinase K, trypsin, subtilisin, dispersin B, mutanase, dextranase, antimycotic protein lysozyme and DNases (Malaeb et al., 2013). Nevertheless, we strongly believe that increasing the mechanical stability and enhancing the catalytic activity of the enzyme system would be possible through the use of immobilized enzymes (Jankowska et al., 2021).

3.2. Enzymatic preventing techniques

3.2.1. Enzymatic quorum quenching

In the quorum quenching process, to prevent the development of quorum sensing on the membrane material, signalling compounds are deactivated by introducing molecules that mimic their action and block their receptors or by the modification and degradation of signalling molecules (Chen et al., 2013b). Even though the general mechanism of quorum sensing is fairly well understood, only a limited number of enzymes are known to date that can interact with bacterial particles or deactivate autoinducers. *N*-acylhomoserine lactones as the most widely used autoinducers have become an important part of research into the effectiveness of the quorum quenching process in wastewater treatment. Chen et al. (2013b) proposed three sites in the structure of the AHL molecule that are probably most susceptible to the action of enzymes (Fig. 4). Examples of enzymes used in quorum quenching along with their source of origin are presented in Table 4.

Lactonases are enzymes responsible for the hydrolysis of the homoserine lactone ring, but during catalysis, they do not break down the bond between the lactone and the side substituent. Lee et al. (2020) developed a system with lactonase from *Rhodococcus* sp., which was entrapped in the mesoporous silica medium, to inhibit the formation of biofouling on the membrane during the treatment process of restaurant wastewater. This solution allowed for the removal of quorum sensing signalling molecules through adsorption (due to mesoporous and hydrophobic silica structure) as well as enzymatic degradation. The relatively small size of the quorum quenching (QQ) medium allowed to avoid blockage of the membrane module and did not affect the quality of the treated water. Lactonase was also successfully used in the degradation of the signal molecules of *Pseudomonas aeruginosa* (C6-HSL and C12-HSL), which prevented secondary contamination of drinking water with this bacteria. The enzymatic ability to degrade AHLs allowed to inhibit early

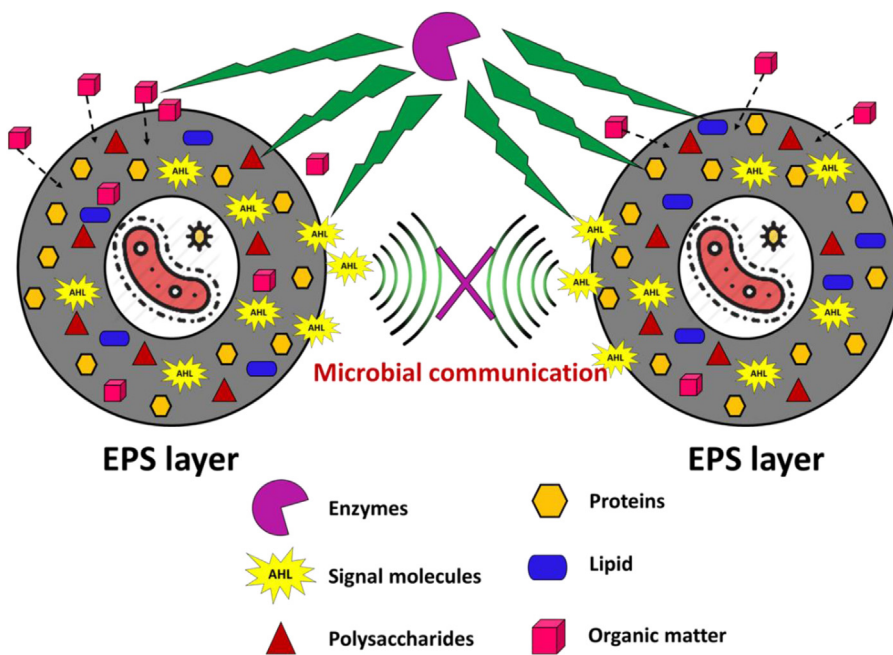


Fig. 3. Key enzyme-based mechanisms to control biofouling.

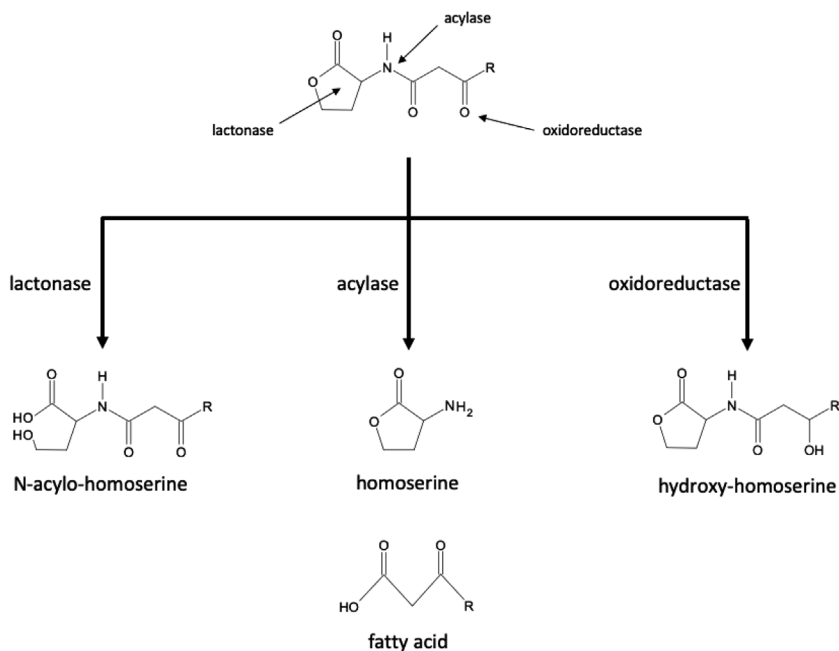


Fig. 4. Possible degradation mechanisms of quenching enzymes towards AHLs molecules.

proliferation and biofilm formation, significantly reduce a number of toxic products (i.e. pyocyanin and rhamnolipid), and decrease the bacterial deposition on the membrane (Liu et al., 2020b). Therefore the application of lactonase is effective not only in wastewater purification but also as a strategy for drinking water treatment.

The second important group is AHL acylase, which are enzymes that catalyze the hydrolysis of the amide bonds between the homoserine lactone and the acyl side chain in the AHL molecule, whereas the chemical structure of the homoserine lactone is not degraded. Shah and Choo (2020) examined acylase, which is capable of degrading C8-HSL, one of the most common signal molecules present in MBRs used for wastewater treatment. The tests were carried out in

Table 4
Quorum quenching enzymes involved in the degradation of AHLs molecule.

Enzyme	Source of enzyme	Type of degraded AHL	References
AHL-acylase AiiD	<i>Ralstonia</i> sp. XJ12B	3-oxo-C8-HSL, 3-oxo-C10-HSL, 3-oxo-C12-HSL	Lin et al. (2003)
Oxidoreductase CYP102A1	<i>Bacillus megaterium</i>	C12-HSL, 3-oxo-C12-HSL, C14-HSL, 3-oxo-C14-HSL, C16-HSL, C18-HSL, C20-HSL	Chowdhary et al. (2007)
AHL-acylase AiiC	<i>Anabaena</i> sp. PCC7120	C4-HSL C14-HSL	Romero et al. (2008)
AHL-acylase Aac	<i>R. solanacearum</i> GMI1000	C7-HSL, C8-HSL, 3-oxo-C8-HSL, C10-HSL	Chen et al. (2009)
AHL-lactonase AidH	<i>Ochrobactrum</i> sp. T63	C4-HSL, C6-HSL, 3-oxo-C6-HSL, 3-oxo-C8-HSL, C10-HSL	Mei et al. (2010)
AHL-lactonase AiiM	<i>M. testaceum</i> StLB037	3-oxo-C6-HSL, C6-HSL, 3-oxo-C8-HSL, C8-HSL, 3-oxo-C10-HSL, C10-HSL	Wang et al. (2010)
AHL-lactonase QsdR1	<i>Rhizobium</i> sp. NGR234	3OC8-HSL	Krysciak et al. (2011)
AHL-lactonase AidC	<i>Chryseobacterium</i> sp. StRB126	C6-HSL, C8- HSL, C10- HSL, C12-HSL, 3OC6- HSL, 3OC8- HSL, 3OC10- HSL, 3OC12-HSL	Wang et al. (2012)
AHL-lactonase PON1 + PON3	Mammalian liver, serum	C7- HSL, C12- HSL, C14-HSL, 3OC12-HSL	Bar-Rogovsky et al. (2013)
AHL-lactonase PON2	All mammalian tissues	C7- HSL, C12- HSL, C14-HSL, 3OC6- HSL, 3OC10- HSL, 3OC12-HSL	Hagmann et al. (2014)
AHL-lactonase QsdH	<i>Pseudoalteromonas</i> <i>byunsanensis</i> 1A01261	C4- HSL, C6- HSL, C8- HSL, C10- HSL, C12- HSL, C14-HSL, 3OC6- HSL, 3OC8-HSL	Huang et al. (2012)
AHL-acylase AibP	<i>Brucella melitensis</i> 16M (ATCC 23456)	C12-HSL 3OC12-HSL	Terwagne et al. (2013)
AHL-acylase HacB (PA0305)	<i>P. aeruginosa</i> PAO1	C6- HSL, C7- HSL, C8- HSL, C10- HSL, C12- HSL, C14-HSL, 3OC10- HSL, 3OC12- HSL, 3OC14-HSL	Wahjudi et al. (2011)
AHL-acylase QsdB	Soil metagenome	C6HSL, 3OC8-HSL	Tannieres et al. (2013)
Oxidoreductase BpiB09	Soil metagenome	3OC12-HSL	Bijtenhoorn et al. (2011)

anaerobic conditions, and the QQ enzyme allowed the reduction of biofilm formation using both the model solution of *Pseudomonas aeruginosa* and real sludge.

Autoinducers can also be deactivated by oxidoreductases in the process of oxidation or reduction of the long-chain AHL. Ruan et al. (2020) investigated the effect of the presence of nitrate reductase and nitrite reductase in the reaction system during nitrate rich wastewater treatment in sequential batch reactors on membrane fouling caused by *Pseudomonas aeruginosa* bacteria. The implementation of oxidoreductases into the system not only increased the efficiency of nitrate removal from wastewater but also made it possible to inhibit the quorum sensing.

A very important application of QQ enzymes, from the economic and environmental point of view, is in the prevention of biofouling in membrane bioreactors. However, so far research in this area has mainly been performed on a laboratory scale, essentially due to the fact that the quorum quenching method began to be discussed in public in 2009. Since then, the potential of the method has been growing steadily and one of the first reports of attempts to use the process on a pilot scale (10 m³/day) with real municipal wastewater appeared (Lee et al., 2016). It should be noted that the use of quorum quenching allowed to reduce energy costs by at least 30% (Aslam et al., 2018). Promising results allow assuming that someday the proposed enzymatic methods might be an effective commercial large scale strategy for the use of real solutions.

To further increase the effectiveness of enzymatic quorum quenching, enzyme immobilization can be used. Yeon et al. immobilized acylase onto magnetic particles. The use of the biocatalytic system allowed to maintain the initial catalytic activity in a continuous process for up to 29 days. In addition, the proposed method allowed the reduction of biofouling formation, but also did not negatively affect the activity of enzymes. The use of magnetic particles facilitates relatively easy separation of the biocatalyst from the reaction system by means of an external magnetic field (Yeon et al., 2009a,b).

3.2.2. Immobilized enzyme to mitigate biofouling

Enzymes that are attached to the membrane can provide in-situ biofouling control strategy through the degradation of EPS and its components (i.e. polysaccharides, proteins, etc.) or QS molecules as well as the destruction of bacterial cells. The first of the mentioned groups of enzymes include polysaccharide-degrading enzymes, which can degrade polysaccharides, one of the main disruptors in water purification processes using membrane techniques. Therefore, Meshram et al. (2016) immobilized alginate lyase on cellulose acetate ultrafiltration membrane. In tests with the use of model wastewater solutions, immobilized alginate lyase retained 80% of its initial catalytic activity after 21 days of use. By comparison, the free form of this enzyme maintained 20% of its activity. On the other hand, when a real solution of tap water was used, in which the alginate concentration was 50 mg/L, the immobilized alginate lyase remained active even after 10 reaction cycles.

Among the enzymes responsible for the degradation of QS molecules or disruption of their functioning, acylase is the most commonly used. Kim et al. (2011) used a submerged membrane bioreactor with a microfiltration membrane for wastewater treatment. In their research, acylase was immobilized on the membrane and placed in the flow cell. Wastewater containing EPS was subjected to enzymatic degradation. The immobilized acylase retained more than 90% of the initial catalytic activity over the 20 reaction cycles. After 38 h of the continuous process at 2 bar with the immobilized enzyme, there was no significant decrease in water flux. However, the value of the flux in the process with membrane without biocatalyst decreased to 60%, which suggests the formation of a biofouling layer. On the other hand, Grover et al. (2016) performed multipoint covalent immobilization of acylase from *Aspergillus melleus* on medical grade polyurethane films. Immobilized enzymes were used to inhibit biofilm formation by two strains of *Pseudomonas aeruginosa* (ATCC 10145 and PAO1). Acylase-containing polyurethane coatings reduced biofilm formation by approximately 60%. Additionally, it is worth noting that the immobilization of acylase increased the stability of the system, which could be stored at 37 °C for 7 days with 90% of the initial activity. Lee et al. (2014) adsorbed acylase into spherical mesoporous silica with magnetic nanoparticles and then the obtained system was used in advanced water treatment. The application of this QQ enzyme slowed down the formation of *Pseudomonas aeruginosa* biofouling on the membrane surface, resulting in increased filtration efficiency. In addition, the magnetic properties of the support facilitate easy separation of the biocatalyst from the membrane reactor.

The immobilization of enzymes can effectively prevent biofilm formation also via their damaging impacts on microbial cells. Porcine kidney acylase immobilized on a hydrophilic polymer membrane can drastically reduce the bacterial viability and the rate of biofilm formation (Bao et al., 2019). The combination of the hydrophobicity of the material and the enzymatic degradation of bacteria allowed for the creation of an effective system. In addition, lysozyme is capable of breaking down the cells of *Agrobacterium tumefaciens* bacteria. The results confirmed that the enzyme caused a significant distortion of the bacterial cells, reducing their viability and changing the morphology of their surface (Bao et al., 2020). It should be mentioned that Saeki et al. (2013) prepared a biocatalytic system with lysozyme covalently immobilized on a polyamide reverse osmosis membrane by the use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and *N*-hydroxysuccinimide. The enzyme system demonstrated antibacterial activity against Gram-positive bacteria *Micrococcus lysodeikticus* and *Bacillus subtilis* for 5 months after storage at 5 °C. Moreover, Duan et al. (2015) used graphene oxide and chemically reduced graphene oxide as a support in the immobilization of lysozyme. After immobilization of the enzymes on the carbon material, deposition of the biocatalyst was performed on the ultrafiltration membrane by the phase inversion method. The prepared biocatalytic system showed effective antibacterial activity against the Gram-negative bacteria *Escherichia coli*. Moreover, the products of lysozyme action were confirmed to be safe and non-toxic. In the above-presented studies, the permeation properties of membranes were determined with pure water. Saeki et al. (2013) noticed that the water flux in process with an enzyme-modified membrane was only 50% of the value of flux when a conventional membrane was used. However, in the studies by Duan et al. (2015) the result was quite opposite. The pure water flux was twice as high when using an enzyme-immobilized membrane. We think these differences may be due to three various factors. The first is the membrane morphology, i.e. the pore size or the thickness of the membrane layers. Another reason may be the hydrophilicity of the membrane or the additives on it and finally, too dense deposition or overload of enzymes on the membrane.

An interesting solution to improve the reduction biofouling of the membrane might be the use of enzyme co-immobilization. Mehrabi et al. (2020) decided to degrade *Staphylococcus aureus* and *Staphylococcus epidermidis* - the main human pathogens that are resistant to antibiotic treatment. α -Amylase and lysozyme were covalently co-immobilized on a polydopamine/cyanuric chloride functionalized polyethersulfone membrane. The action of two antibacterial enzymes removed more than 87% of the biofilm.

3.3. Enzymatic cleaning methods

The presence of various impurities on the membrane surface has a huge impact on the decrease in the efficiency of subsequent membrane processes or in the permeability of the membrane material. The solution to the above problem is cleaning of the membrane, which can be done once a day or even once a year, depending on the occurrence of biofouling. There is no universal and ideal method for cleaning membranes. Nevertheless, the most effective agents are those allowing the removal of many impurities, achieve the maximum efficiency of the process, but are also gentle on the membrane material and do not adversely affect its structure and properties (Al-Amoudi and Lovitt, 2007).

Table 5
Examples of enzymatic cleaning agents.

Enzymatic cleaning agent	Feed water	Membrane	Flux recovery	References
Terg-A-Zyme	Bovine serum albumin, whey protein	PSF	89.1% 91.0%	Munoz-Aguado et al. (1996)
Lipase A + TritonX100 + ProteaseA Alkazyme + Zymex	Abattoir effluent	PSF	100% 100%	Maartens et al. (1996)
Maxatase [®] XL (Endopeptidase) P3Ultrasil [®] 62 (proteases + anionic tensioactive agents)	Whey protein	IM	–	Arguello et al. (2003) Arguello et al. (2005)
Proteinase M	Bovine serum albumin or bovine serum albumin + beta-lactoglobulin	PES	–	Petrus et al. (2008)
Amylase + TritonX100	Humic acid	PSF	94%	Yu et al. (2010)
Mixtures of proteases, lipases and amylases	Dry dog food with synthetic raw sewage	HVLP	–	Teo and Wong (2014)
Mixture of protease, lipase, and sodium dodecyl sulphate	Coal chemical wastewater	Thin film composite polyamide	77%	Lee et al. (2020)

Biological cleaning (enzymatic cleaning or energy uncoupling) is gentle and does not damage the membrane and deteriorate its properties. Enzymatic agents are characterized by high specificity in choosing the foulant and effectively remove it in the layer of the sediment. Examples of various enzymatic cleaning agents are summarized in Table 5. Optimization of enzymatic membrane cleaning processes is based on understanding the interactions between the foulant and the enzyme as well as the foulant and the membrane. Moreover, the economic aspect is very important, as well as the impact of the cleaning agent used on the lifetime and efficiency of the membrane (Wang et al., 2014).

Munoz-Aguado et al. (1996) were the first scientists to use enzymes to clean ultrafiltration membranes that had become contaminated with proteins and lipids. They noticed that the enzymes were more effective as compared to detergents and pointed out that the enzymes work efficiently at their optimal concentration. This is a significant difference compared to detergents, the concentration of which is most often increased until the cleaning agent destroys the membrane material. Proteins and lipids are one of the main membrane foulants, especially in wastewater treatment, and their removal is difficult due to their hydrophobicity. In order to clean the membranes from this type of contamination, lipases and proteases are used. Allie et al. (2003) used the lipases from *Candida cylindracea*, *Pseudomonas mendocina* and *Aspergillus oryzae* and the proteases from *Bacillus licheniformis*, *Aspergillus oryzae* and Protease A to remove these contaminants from flat-sheet polysulphone membranes. They showed that lipases themselves remove lipids and proteins very effectively. However, the combination of lipases and proteases results in an even more effective cleaning process.

Presented studies facilitate further development of enzymatic membrane cleaning methods. Researchers began optimization and transfer of the enzymatic processes, from a laboratory scale and batch bioreactors to a pilot scale and continuous bioreactors (te Poele and van der Graaf, 2005). It has been observed that the efficiency of enzymatic cleaning processes is dependent on enzymatic agent concentration, pH of cleaning solution, recycling or non-recycling of permeate, and cleaning time. However, the most important factors are the processing time and the concentration of the enzymes used, as during the cleaning the enzyme may deposit on the membrane surface, which can negatively affect the foulant removal. Additionally, it is necessary to know the composition of the foulant and adapt the cleaning method to the type of impurity due to the speed of removing various impurities from the fouling layer (Petrus et al., 2008).

Therefore it can be seen that enzymatic cleaning methods are very often used as an agent to mitigate biofouling on the membrane. Nevertheless, the importance of enzyme agents in wastewater treatment and industry is gradually increasing. In addition, the great advantage of using enzymes are the mild process conditions, limited formation of by-products, and no influence on the properties of the membrane and its ageing processes.

4. Future outlooks and challenges

Investigation of enzyme-based control of membrane biofouling has confirmed that its application can provide an excellent prospect for water and wastewater purification. Nevertheless, there are several obstacles that need to be addressed in the near future to allow the process to be transferred from the laboratory to a larger scale, including an industrial scale. Although the enzyme-based approach has been demonstrated to be environmentally-friendly and effective in controlling biofouling, the economic feasibility of this method, especially in full-scale applications is still questionable due to the cost and instability of the enzyme (Kose-Mutlu et al., 2019). Nevertheless, despite the high cost of enzymes, further steps are taken, among which immobilization plays an extremely important role, aimed at

selecting the appropriate amount of the enzyme and, consequently, increasing their activity in the processes of biofouling removal. While the economic feasibility of enzymatic processes is questionable, it should be emphasized that it is a green technology that does not require the use of toxic reagents and due to that fact overcome the economical drawbacks of this approach. The most important issues that limit the practical application of enzyme systems in biofouling control and require novel solutions are:

- Optimization of enzyme production and development of new technologies is of necessity in order to reduce their production costs.
- Development of enzyme immobilization methods and the application of innovative supports, including membranes, which will enable the improvement of the stability of biocatalytic systems under harsh process conditions.
- Extensive analysis of the complex mechanism of interaction between enzyme-support, enzyme-biofouling, and enzyme-membrane. Evaluation of the impact of the application of immobilized biocatalysts on the properties of the membrane.
- Detailed characterization of bacteria involved in biofilm formation as well as mixtures of different bacterial cultures. Optimization of the biodegradation process of a wider range of autoinducers.
- Application of enzymatic membrane reactors with immobilized biocatalysts for continuous processes of biofoulants degradation in water and wastewater purification. Characterization of the effect of process conditions on removal efficiency.
- Development of solutions facilitating the transfer of a laboratory scale solution into a larger scale to facilitate real wastewater treatment.

5. Conclusions

This review is an attempt to comprehensively provide the underlying mechanisms of membrane biofouling formation followed by an overview of enzyme-based controlling techniques during the application of membrane-based separation for water and wastewater purification. In this study, the roles and interaction of EPS and quorum sensing in biofouling formation were thoroughly discussed. The enzyme-based mechanisms to control membrane biofouling and biofoulants removal were systematically outlined. Further the to date preventing and cleaning strategies were summarized herewith and it was indicating which approach should be considered as the most promising. The discussions revealed that enzymatic cleaning and quorum quenching approaches were effective in preventing and eliminating biofilm and its formation on the membrane surface. The efficacy of these methods could be increased by using immobilized enzymes.

CRedit authorship contribution statement

Karolina Bachosz: Conceptualization, Literature review, Writing – original draft. **Minh T. Vu:** Conceptualization, Literature review, Writing – original draft. **Long D. Nghiem:** Project administration, Supervision, Writing – review & editing. **Jakub Zdarta:** Supervision, Writing – review & editing. **Luong N. Nguyen:** Supervision, Writing – review & editing. **Teofil Jesionowski:** Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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