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Transforming Infection Management with Organic Bioelectronic Materials and Devices

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ABSTRACT

Synergies between the emerging field of organic bioelectronics and microbiology are paving the way for significant advances in biomedical research and medical technology. While in vitro models of infections form the foundation of our current understanding, they cannot replicate the complexity of biological systems. Organic bioelectronics, utilizing conjugated conducting polymers, bridge the gap between abiotic and biotic environments using ions and electrons as charge carriers. Polymer formulations can be easily tuned so that desirable electrochemical properties can be achieved and deposited for use as surface coatings, hydrogels, or 3D composites to monitor or control in vitro as well as in vivo systems. In this review, we explore the role of organic bioelectronics in infection management, highlighting their potential for modeling, detection, prevention, and treatment. These technologies offer new strategies to control microbial colonization, improve infection diagnostics, and enhance therapeutic approaches while addressing challenges such as antibiotic resistance.

1 | Introduction

Bacterial infections and the emergence of multiresistant bacterial strains pose major global threats to public health [1, 2]. Pathogenic bacteria are responsible for a range of severe conditions, such as sepsis and urinary tract infections (UTI), and are dominant in unique disease microenvironments that complicate disease modeling, detection, and treatment [3–5]. The complexity underlying bacterial behavior is becoming increasingly evident as both planktonic and biofilm lifestyles play important roles for infection and colonization. Recent advances in bacterial electrophysiology reveal a role of electrical signaling in mediating long-range communication and coordination within biofilms, raising important questions about the role of bioelectricity in bacterial lifestyle and pathology [6–11]. While classical treatments target the planktonic form of bacteria using chemical agents that disrupt cell wall integrity, cell division, and other key processes, modern strategies must take a multifaceted approach to minimize the risk of development of treatment resistance [12, 13]. Similarly, fast and sensitive detection systems which recognize bacterial pathogens in their different lifestyles are required to complement existing culture-based and PCR based methods [14]. Recognizing that bioelectricity, which lies at the core of numerous fundamental biological processes, plays a role also in bacterial pathogenicity opens new possibilities for infection modeling, prevention, detection and intervention [15].

Organic bioelectronics can harness the sensitivity, biocompatibility, and versatility of conducting polymers to address key challenges in detection and management of bacterial infections. Reflecting the interplay between cellular behavior and native electrochemistry found in biological systems, organic conducting polymers can bridge the gap between abiotic and biotic environments [16]. This is achieved by translating electrical signals into ion fluxes that induce biological responses and vice versa, effectively connecting the cellular world and the bioelectronic world.

Owing to the organic nature of conducting polymers, they exhibit high biocompatibility and mechanical flexibility [17]. The basic building block of all conducting polymers is a conjugated backbone wherein distinct types of backbones lend specific properties to the polymer. An organic conjugated polymer is transformed into electrically conducting polymer by a process called doping, where the polymer backbone is oxidated or reduced and counterions are incorporated [18]. This dynamic system exhibits a unique combination of ionic and electrical conductivity, where counterions associate or dissociate based on the redox state of the polymer [19]. Ion movement for charge equilibration drives ionic conductivity. Redox switching modifies polymer backbone charges, with p-doped polymer reduction leading to dedoping. Monomeric counter-anions diffuse out, while the polymeric ones remain. Conducting polymers that have been proven to perform well in biological applications are based on the polythiophene backbone. A more planar backbone achieved via addition of an ethylenedioxy group to the thiophene ring enhances polymer transparency and conductivity in the resulting conjugated polymer poly(3,4-ethylenedioxythiophene) (PEDOT) [18]. PEDOT has been used extensively in biological applications with a range of negatively charged counter ions. Ionic conductivity exemplified with tosylate (Tos) and polystyrenesulfonate (PSS) facilitates biomimetic devices by regulating local ion homeostasis and enhances specialized drug delivery applications (Figure 1). The choice of the negatively charged counterion and the reversible redox reactions taking place on the surface will affect the electrochemistry, surface topography, charge, and energy of PEDOT [20]. By adjusting these parameters, researchers can better replicate dynamic biological systems, particularly during infection modeling.

The documented ability of conducting polymers to interface with biological systems through electrochemical interactions highlights the expanding role of bioelectricity in living organisms. In recent years, bioelectricity has been recognized as a key regulator of cellular processes, extending beyond classical neuronal electrophysiology to influence a wide range of biological functions, including bacterial behavior and host–pathogen interactions. Gaining insight into how electrical signals regulate cellular activity is essential for understanding of bacterial physiology and pathogenesis. This growing interest has led to studies of bacterial bioelectric properties, revealing notable similarities with eukaryotic electrophysiology. Within this review, we explore the role of bioelectricity in biological systems, with an emphasis on bacterial electrophysiology and its relevance to infection dynamics and biomedical applications.

2 | Biocompatibility of Conducting Polymers

Biocompatibility, in the context of organic bioelectronics, denotes the ability of a conducting polymer device to perform its intended electrical function at the tissue or fluid interface, without unacceptable local or systemic responses over the intended period of use. To avoid over generalizing, "high biocompatibility" claims should be supported by contextual assays specific to the intended tissue, due to the variability of the body's environments and possible interactions between devices and cells [21]. Such risk-based biocompatibility assessments should be aligned with the International Organization of Standardisation guidelines (ISO 10 993-1; Biological evaluation of medical devices), with considerations for the type of body contact (surface, external, or implant) and the length of contact time [22]. For nearly all medical devices, three primary categories of biocompatibility assessments are performed: cytotoxicity, irritation, and sensitization [23]. Additional tests for systemic toxicity, genotoxicity, carcinogenicity, hemocompatibility, and implantation studies [22, 23] are coupled to the tests for their performance under electrical use. These evaluations include checking for changes in electrical properties over time, such as shifts in impedance, as well as determining the safe limits for injecting electrical charge. The tests also examine how well the device materials remain attached when exposed to repeated movement or stress and whether any harmful substances might leak out from the device.

Biocompatibility of conducting polymers therefore depends not only on their biological response but also on the material formulation and operational context. The following subsections summarize what is known from experimental evidence, the influence of polymer chemistry, major challenges, and comparative aspects across polymer classes.

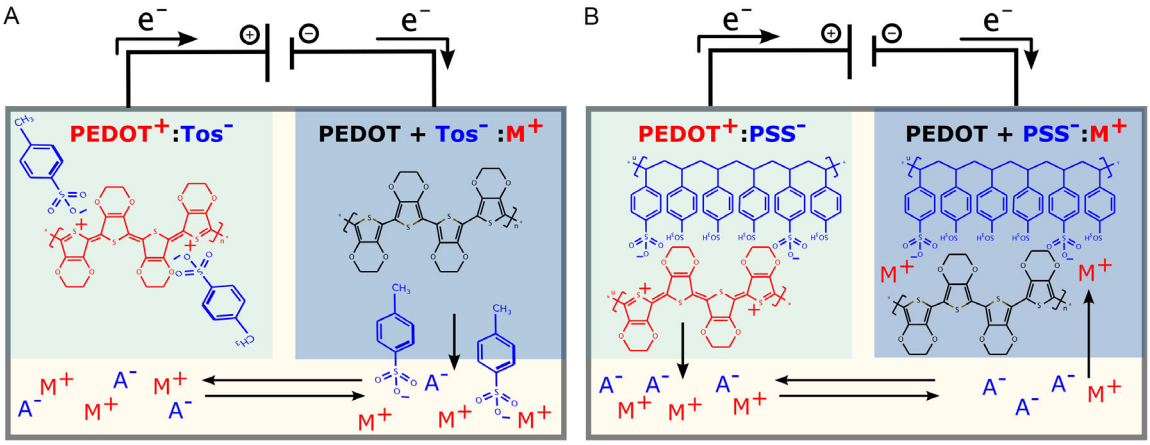

FIGURE 1 | Exchange of ions between oxidized/reduced conducting polymer and the electrolyte. (A) The small monomeric counter ion Tos^- exits the polymer, enabling charge equilibration. (B) The larger polymeric counter ion PSS^- remains within the polymer matrix, and charge balance is maintained primarily by the influx of cations. Adapted from [19] under the terms of the CC-BY-NC license. Copyright 2015, The Authors, published by RSC.

2.1 | Evidence from In Vitro and In Vivo Studies

Across neural and skin interfaces, conducting polymer films, coatings, and hydrogels generally support cell viability and proliferation in vitro [21, 24]. Short-to-mid-term in vivo tissue responses have also shown promising performance as long as PEDOT-based materials are properly processed. Their success mainly depends on the type of dopant, residuals, and how the material has been sterilized [21, 25]. Recently, an efficient one-step strategy for the fabrication of PEDOT: PSS-ionic liquid colloidal (PILC) ink formulation showed favorable biocompatibility in fibroblasts, and in mouse models without postprocessing [26]. Studies in rodents with flexible PEDOT: PSS microelectrodes have shown that these electrodes can record stable signals over time, while also causing less inflammation and tissue damage compared to bare metal electrodes [27]. However, long-term and large-animal evidence of compatibility, remains limited and application-specific [28]. While available data are encouraging, biological responses are strongly influenced by polymer backbone chemistry and counterions, which determine surface and interfacial properties.

2.2 | Influence of Backbone Chemistry and Counterions

Backbone identity (e.g., PEDOT, polypyrrole, polyaniline) and counterion choice (small anions such as Tos or polymeric sulfonates such as PSS) affect mixed ionic–electronic transport, swelling, surface charge, leachable, and protein adsorption, which are key determinants of cytocompatibility and inflammation [29, 30]. While additives (e.g., crosslinkers, surfactants, ionic liquids) and postprocessing treatments (e.g., thermal, acid rinses) can reduce leachable and improve stability, they may alter conductivity. These tradeoffs should be reported together with extraction conditions and electrical biases used during biocompatibility assays [21, 22]. Techniques for tailoring the properties of PEDOT: PSS to enhance biocompatibility have also been extensively reviewed [30]. Among these, postfabrication biofunctionalization of PEDOT: PSS surfaces or bulk through bonding biocompatible molecules, segments, or side chains can further improve cell–material interactions [31]. Despite this chemical tunability through various functionalization approaches, several challenges remain related to the long-term biological response and material stability during extended in vivo implantation, as discussed below.

2.3 | Known Challenges

Foreign body responses and inflammatory signaling are the main risks for implants and can lead to device encapsulation within fibrous tissues and disruption of the material interface [21]. These are driven by modulus mismatch and micromotion, which are avoided by the use of soft, hydrated organic conducting polymer-hydrogels that possess tissue-like mechanics, and robust adhesion strategies [32, 33]. Exposure to biological fluids like interstitial fluid and blood is a key consideration for biosensors, since the introduction of shear flow could trigger unwanted electrochemical reactions that alter sensitivity and specificity. Long-term electrical biasing in electrolytes can cause dopant loss, delamination, and interfacial chemistry changes as well as the release of toxic residuals [21]. Recent reviews outline the effect of dopant choice, crosslinking, and additives on cytocompatibility and long-term stability in neural and skin interfaces [25]. Additionally, sterilization methods may shift oxidation state, swelling, and conductivity of the polymer [34]. In the context of transient organics, the same double and triple bonds that enable conductivity, limit the biodegradability of conjugated polymers due to their strong bond dissociation energies, delaying translation into the clinic [17]. While biodegradable PEDOT: PSS composites are under development, additional in vivo verifications are still required [30, 35, 36]. For bioresorbable devices that degrade and are completely eliminated from the body, compatibility depends on both degradation kinetics and byproducts, in addition to initial tissue tolerance [37, 38]. These limitations highlight the importance of systematically comparing different conducting polymer classes to achieve a balance between conductivity, stability, and biological responses.

2.4 | Comparison across Polymer Classes

While most conducting polymer classes have been able to support cell adhesion and growth in a variety of tissues, as well as in vivo studies in rats, comparative reviews consistently find PEDOT: PSS to offer a favorable balance of conductivity, processability and cytocompatibility. This contrasts with polypyrrole and polyaniline which rely on careful formulation to avoid oxidation-state dependent cytotoxicity and narrow stability windows [39]. Hydrated PEDOT-based hydrogels and glycolated polythiophenes show promise for soft interfaces, particularly in the context of brain tissue, forming the "next-generation neural biointerfacing technology" [40].

Overall, the biocompatibility of conducting polymers results from their chemical composition, processing history, and operational environment. No single material can be universally described as "highly biocompatible" without considering these specific conditions. Defensible biocompatibility claims for conducting polymer-based devices should therefore include ISO-aligned safety assessments, relevant electrical characterization, transparent material formulation, and precise in vivo validations to ensure that both biological compatibility and desired functionality are achieved during the intended lifetime of the device.

3 | Electricity in Biological Systems

Bioelectricity influences processes from the molecular level to that of whole-organism physiology [41]. Movement of ions and interactions between charged and polar molecules are governed by electrostatics and electrical forces, fundamental to processes like protein folding and binding [42]. The distribution of electrostatic potential on molecules gives rise to dipole moments that make them responsive to external electric fields [43]. Changes in electrostatics can affect molecular orientations and interactions which in turn may influence enzymatic reactions and signalling pathways. Cellular compartmentalization allows for the separation and control of these changes, as well as the establishment of electrochemical gradients across membranes which are maintained by ion channels and pumps [44]. These gradients can generate electric fields, typically around $50\,\mathrm{mV\,mm^{-1}}$ at the tissue level (with transepithelial currents of $10–100\,\mathrm{mA\,cm^{-2}}$) and have large consequences on growth,

development, and regeneration [45]. Several similarities between biological and electrical systems can be drawn, including in the analogy between cell membranes and capacitors. Biological membranes function like an insulating dielectric material that separates and stores charges on either side to create a potential difference. However, unlike capacitors optimized for electrical storage, biological membranes are restricted by the need for fluidity and temperature stability, making them more adaptable to biological functions. Biological membranes and their associated proteins are constantly exposed to strong electrochemical potentials. In resting cells, transmembrane potentials of ~50–100 mV occur across lipid bilayers only ~5 nm thick, generating local electric fields on the order of 10^7 V m^{-1} [46–48]. These strong potentials create opportunities to harness inherent energy of membranes for the modulation and control of biological processes. Studies specific to mitochondrial membranes have revealed complex dynamics in membrane potentials linked to mitochondrial morphology, localization, and metabolic state [49–51]. Given the evolutionary relationship between mitochondria and bacteria, these observations raise questions about bacterial membrane potential dynamics [52]. The specific pattern of electrical energy discharge from the membrane serves a variety of functions, including in signalling. This understanding has led to the development of electroceuticals, which use electrical stimulation to modulate biological functions with improved specificity and precision compared to traditional pharmaceuticals [18]. Electrophysiology and the generation of action potentials have traditionally been associated with neuronal activity but also play key roles in other areas of biology including bacteriology. Intracellular electron transfer reactions have long been known as fundamental for bacterial metabolism, whereas the acknowledgement of extracellular electron transfer has led to the development of biotechnological processes including microbial fuel cells, microbial electrosynthesis, and microbial bioremediation [53]. Thus, it is evident that the principle of bioelectricity forms the basis of a wide range of biological systems beyond eukaryotic systems, particularly in microbiology where it plays a crucial role in bacterial physiology. Recent discoveries reveal that bacteria like neurons, use ion channels and membrane potential fluctuations for communication and adaptation. Understanding these bacterial electrophysiological mechanisms have contributed to emerging research in microbiology, with significant implications for infection biology and bioelectronics. The following section explores how bioelectricity shapes bacterial behavior and its potential for biomedical innovations.

4 | Importance of Electronics in Bacteriology

The concept of electrochemical signalling via membrane potential has traditionally been considered a unique characteristic of eukaryotic systems. However, the recent discovery of bacterial bioelectric signal transduction has caused a paradigm shift, highlighting the dynamic nature of bacterial membrane potentials (with the resting values of −140 ~ −75 mV [54]) and their roles in various physiological functions, including cell-to-cell signalling, inflammation, and gene expression. Similarly to neuronal cells, bacteria possess many classes of ion channels including sodium, chloride, calcium-gated potassium channels, and ionotropic glutamate receptors. The observation of pulsing membrane potentials in growing *Bacillus subtilis* (*B. subtilis*) colonies suggested that bacterial glutamate-regulated YugO potassium (K^+) ion channels can modulate membrane potential as a method of cell–cell signaling [55]. These oscillations, driven by periodic release of intracellular K^+ maintained at ~300 mM (about 40 times higher than the external concentration), transmitted across biofilms over distances of ~1.5 mm without noticeable loss of amplitude. Spatially propagating waves of potassium mediate long-range electrical signals that depolarize neighboring cells, demonstrating that bacteria engage in communication beyond quorum sensing. This understanding was extended as membrane potential oscillations were found to be coupled to metabolic oscillations, allowing distant biofilm communities separated by ~2 mm to synchronize their metabolisms over periods of about 10 h, with a phase difference of 0.06 π. Under standard 30 mM glutamate, biofilms oscillated in-phase, whereas a 25% reduction in glutamate concentration induced antiphase oscillations that enabled time-sharing of nutrients under limiting conditions (Figure 2A) [10]. Similarly, biofilms have been demonstrated to influence distant bacterial populations through long-range electrical signaling. Potassium ion channel-mediated signals from a *B. subtilis* biofilm alter the membrane potential of remote cells, directing their motility (Figure 2B) [56]. Deletion of the TrkA gating domain in biofilm cells reduced electrical signal amplitude by ~75% and decreased attraction of motile cells by ~70%, whereas deletion of the potassium uptake gene KtrA in motile cells, which made their membrane potential ~57% more negative, enhanced attraction by more than twofold. *Pseudomonas aeruginosa* (*P. aeruginosa*) also responds to these signals, highlighting the role of bioelectricity in cross-species bacterial communication. Bacterially induced ionic oscillations also play a role in inflammation. This type of signaling was first shown for the toxin α-hemolysin, which when secreted by uropathogenic *Escherichia coli* (UPEC) induces low frequency [Ca^{2+}] oscillations in infected primary rat renal epithelial cells [57]. These oscillations occurred with a dominant frequency of ~1.4 mHz, increasing intracellular calcium from a basal level of ~0.1 μM to 0.5–1.5 μM, and were maintained for up to 2.5 h. The toxin activates both Ca^{2+} influx via voltage-operated L-type calcium channels, and Ca^{2+} release via activation of inositol triphosphate receptors, resulting in an oscillatory second messenger response that stimulates expression of proinflammatory cytokines IL-6 and IL-8. The same bacterial toxin, α -hemolysin, was recently shown to mediate organ communication within the infected host [58]. By triggering splenic nerves to upregulate interferon (IFNγ) expression in the spleen, the inflammatory responses in renal epithelial cells were modulated.

The ability of nerves to sense bacterial infection and regulate expression of immune system genes also applies in reverse: There is now evidence that bacteria can sense external electrical stimuli from electrodes to regulate their own gene expression [8]. *Shewanella oneidensis* MR-1 (*S. oneidensis* MR-1) is capable of sensing the potentials of biased extracellular electrodes via the Arc regulatory system, and accordingly regulate expression of catabolic genes, particularly those for NADH-dependent pyruvate catabolism [59]. When exposed to electrodes poised between −0.1 and +0.5 V (vs. SHE), MR-1 showed potential dependent regulation of over 300 genes, with an increase in NADH dehydrogenase expression, demonstrating quantitative control of metabolism by external redox potential. More recently, electrical stimuli were demonstrated to activate the master

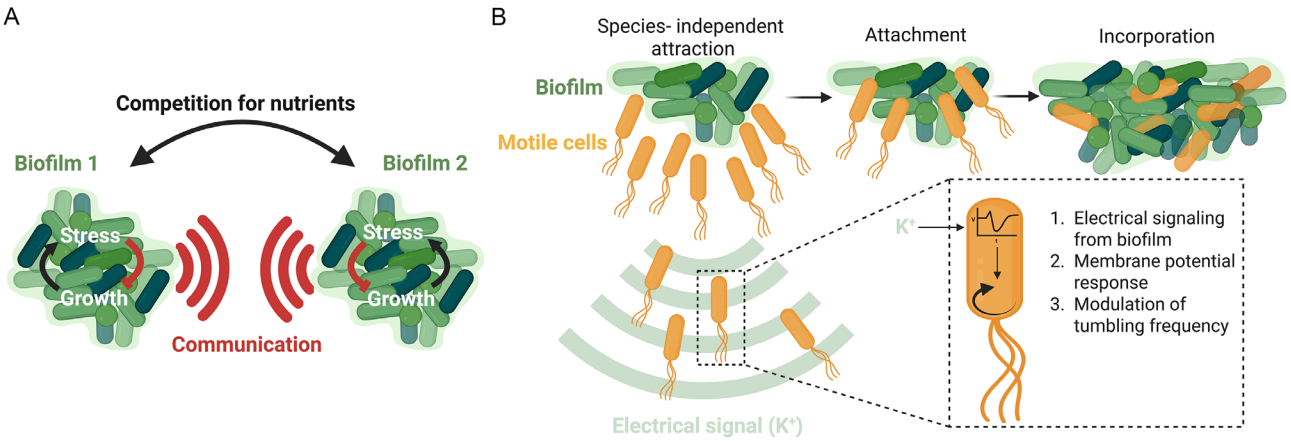

FIGURE 2 | Electrochemical communication in biofilm and planktonic forms of bacteria. (A) Individual biofilms experience periodic growth pauses due to metabolic oscillations. These oscillations are supported by electrical communication, which can connect distant biofilms (indicated by red signals). Additionally, two biofilms can also be linked through competition for nutrients (shown by black arrows). Adapted with permission from [10]. Copyright 2017, AAAS. (B) Electrical signaling mediated by ion channels in *B. subtilis* biofilms attracts distant motile cells, resulting in the incorporation of various species into an existing biofilm community. Adapted with permission from [56]. Copyright 2017, Elsevier.

modulator of biofilm formation, CsgD, in *Salmonella* serovar *Enteritidis* (*S.* Enteritidis) [60]. Using high-resolution, large area fluorescence-based image analysis of *S. Enteritidis* biofilms formed on electroactive surfaces, it was shown that electrical biasing at +0.5 V (vs. Ag/AgCl) increased the extracellular matrix (ECM) to cell fluorescence ratio by ~2- to 2.5-fold, while the total number of bacterial cells remained unchanged. In all, this comprehensive understanding of communication between bacterial cells in interaction with the host's nervous and immune systems and electrochemical induction of bacterial gene expression, have opened new pathways for bioelectronic applications to control bacterial lifestyle. These findings support the development of tools based on conducting polymers, to effectively model various infection microenvironments. These polymers not only allow researchers to simulate complex biological conditions but also enable the rapid and sensitive detection of bacterial pathogens, which is essential for timely intervention. Additionally, the unique properties of conducting polymers offer promising solutions for addressing challenges related to biofilm formation, thus improving both prevention and treatment approaches. In the following sections, we explore the potential of these materials to transform infection modeling, detection, prevention, and intervention strategies in microbial infections.

5 | Conducting Polymers in Infection Modeling

UTIs, catheter-associated infections, respiratory infections, wound infections, gastrointestinal infections, and bloodstream infections are each governed by a unique set of variables that affect the infection microenvironment and dynamic formation of biofilms. Traditional in vitro assays such as microtiter plate biofilm formation assay, time to kill attached bacteria assay (tK100) and serial plate transfer test reduce the complexity of the 3D environments down to cell cultures and cell culture media placed in suspension or on rigid plates [61]. These simplified models do not take the diverse anatomical features, immune responses, and the range of physiological conditions into consideration, meaning that solutions tested on in vitro models may not be sufficiently reliable to be implemented in vivo. The limitations of traditional in vitro assays in capturing the complexity of infection microenvironments have driven the development of more physiologically relevant models. To better replicate the urinary tract environment, a biomimetic proximal tubule-on-chip (PToC) platform was designed to model the hydrodynamic conditions that UPEC must overcome to adhere and establish infections [62]. In this PToC model mimicking kidney flow, the majority of UPEC inoculum (0.5 mL $\approx 2 \times 10^8$ CFU over 1 min) moved directly through the system and a minority produced heterogeneous adhesion: ~50% of bacteria bound for 1–2 min, ~43% for 2.5–30 min, and ~7% for >30 min. The generation time of adherent cells was ~20 min, enabling microcolony formation under flow. This approach provides a more accurate representation of fluid shear stresses, enhancing our understanding of biofilm formation and bacterial pathogenesis in UTIs. Building on this concept, organic conducting polymers are now being used to advance the next generation of infection modeling systems, where in vivo conditions are not just replicated in in vitro systems but are also regulated. In addition to fluid flow, other UTI-specific variables such as exfoliation of human uroepithelial bladder cells, can be controlled by electrically inducing cellular detachment. A notable example of this is the growth of human epithelial cells on films of self-doped, water-soluble PEDOT-S:H polymers [63]. When an electrical potential of +1 V was applied to the polymer, the expulsion of H^+ and related structural changes caused the PEDOT-S:H polymer to disintegrate and caused the epithelial cells to detach from the underlying PEDOT: PSS electrode surface (Figure 3A). Notably, induced cellular detachment using PEDOT-S:H, improves preservation of cell surface antigens compared to traditional enzymatic detachment methods like trypsinization. In addition to cellular detachment, specific cellular growth patterns can be regulated on PEDOT-based organic electrochemical transistors (OECTs). *Salmonella enterica* serovar *Typhimurium* (*S. Typhimurium*) biofilms have been allowed to form in transistor channels, where the resultant biofilm growth gradients matched the previously established electrochemical gradients, specifically with decreased growth on more reduced areas [66]. These results are promising for the possibility of creating

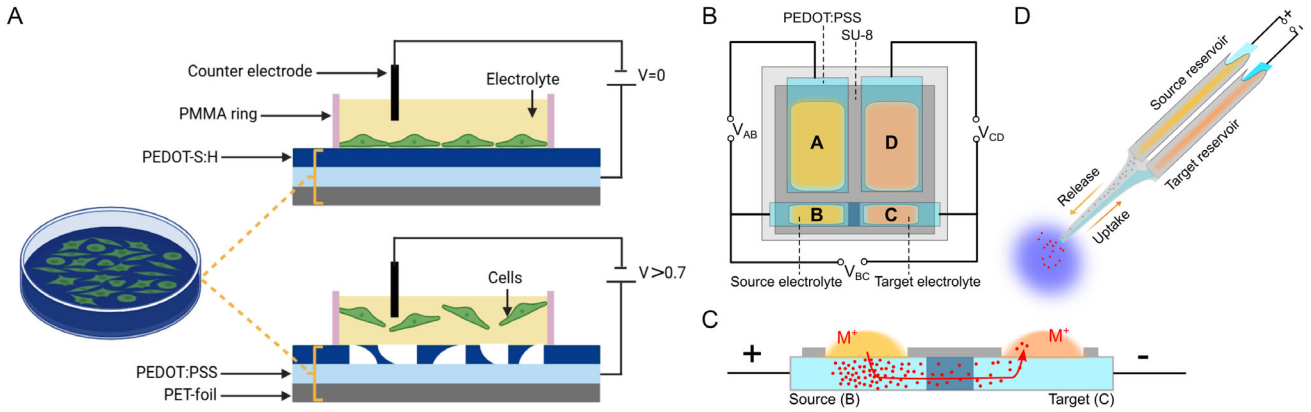

FIGURE 3 | Conducting polymer-based devices for infection modeling. (A) Schematic showing adherent cells cultured on PEDOT-S:H within a custom-designed cell culture dish. When an electrical potential is applied, both the PEDOT-S:H and the attached cells begin to detach. Once the polymer is fully detached, the free cells are released. Adapted with permission from [63]. Copyright 2011, Wiley-VCH. (B) The schematic top view of ion pump device. The four PEDOT: PSS electrodes are labeled as A to D. The region of PEDOT: PSS that is overoxidized (dark blue) between electrodes B and C conducts ions but not electrons. Voltage V_{BC} drives ion transport, while V_{AB} and V_{CD} are used to regenerate electrodes B and C. (C) Schematic cross-section of the B and C electrodes. The cation M^+ with high concentration in the AB electrolyte (left) associates to PSS in the polymer film. When voltage V_{BC} is applied, PEDOT in the B electrode oxidizes, neutralizing its positive charge with PSS and releasing M^+. At the same time, the C electrode receives an electron, reducing its PEDOT: PSS. This creates a net flow of M^+ from left to right, with each transported ion corresponding to one charge measured between electrodes B and C. Adapted with permission from [64]. Copyright 2007, Springer Nature. (D) A miniaturized ion pump utilizing conducting polymers for precise delivery of positively charged acetylcholine. The applied voltage can accurately control the delivery rate, facilitating dynamic stimulation of individual neuronal cells. Adapted with permission from [65]. Copyright 2009, Springer Nature.

biomimetic model systems where biofilm growth patterns are modulated using redox properties.

One of the challenges associated with modeling dynamic host–pathogen interactions is avoiding unwanted interference. Controlled stimulation of multicellular models can cause undesired convection in the growth media and disturbance of chemical gradients involved in cell–cell signaling. Miniaturized organic electronic ion pumps (OEIPs) based on PEDOT allow for convection-free, spatiotemporally resolved delivery of ions. OEIPs were used for Ca^{2+} delivery, where applying short pulses of potential to OEIPs induces local oscillations of small ions (e.g., Ca^{2+} and K^+) at specific frequencies (Figure 3B,C) [64]. The original PEDOT: PSS-based OEIP achieved ion delivery with an on/off ratio >300 and was miniaturized to 50 µm-wide channels for single-cell stimulation. This capability makes them useful for studying bacterial oscillatory cell–cell signaling and inflammatory responses. OEIPs were also utilized for H^+ delivery, with the applied potential regulating the formation of pH gradients [64]. Given that pH plays a crucial role in infection modeling, particularly in gastric mucosa infections like *Helicobacter pylori* (*H. pylori*) invasion, this precise control is essential. The range of OEIP-delivered cations has been expanded to include positively charged biomolecules, such as acetylcholine, for convection-free stimulation of individual neuronal cells (Figure 3D) [65, 67]. The device delivered acetylcholine through 10 µm channels with delivery rates of ~0.26 pmol s^{-1} and ~0.55 pmol s^{-1} for 20 and 40 V, respectively. This advancement is particularly valuable for infection modeling as it enables precise control of neuronal signaling, which can influence immune responses during infections. By examining how acetylcholine affects immune cells in the presence of pathogens, researchers can better understand host–pathogen interactions and the ways pathogens may exploit neuronal pathways. This approach enhances the usefulness of infection models by enabling precise control over biologically relevant microenvironments.

As demonstrated in the examples above, conducting polymers offer a versatile platform for modeling infection dynamics. Their ability to regulate biofilm formation, influence host–cells interactions, and enable noninvasive monitoring contributes to the development of more physiologically relevant in vitro models. These advancements not only improve our understanding of pathogen behavior but also create opportunities for novel diagnostic approaches. In the next section, we explore how these material properties (i.e., responsiveness to biochemical changes and electrical signaling) are being applied in early detection of bacterial infections, helping to bridge the gap between experimental research and clinical applications.

6 | Conducting Polymers in Infection Detection Systems

Early and accurate detection of bacterial pathogens is essential for effective prevention and intervention strategies. However, standard clinical techniques for infection detection rely on microbiological and molecular assays, which, although routinely performed, are time-consuming and require patients to attend the clinic. Clinical microbiology laboratories still primarily use traditional culture-based methods, where samples are plated on agar, and bacterial colonies are counted. These methods present several limitations: bacterial colony formation is slow, often requiring more than 24 h; they are low-throughput and primarily optimized for planktonic bacteria rather than biofilms; and they are labor-intensive, demanding trained personnel and strict aseptic techniques. Imaging assays provide the most reliable method for verifying biofilm formation, but their dependence on specialized instruments, expensive equipment, and skilled operators makes them impractical for routine clinical use [68–70]. These limitations have increased interest in developing tools for rapid, sensitive, and real-time infection detection, operating in clinical

and point-of-care settings [71, 72]. Conducting polymers and oligomers with conjugated backbones have emerged as promising materials in this field, enabling the development of biosensing platforms that integrate electrical and optical detection strategies. Several biosensing approaches have been explored, including electrochemical sensors (e.g., amperometric, potentiometric, impedimetric sensors) and optical biosensing techniques, such as optotracing which is a nonconventional imaging-based method. These approaches utilize the unique properties of conjugated polymers and oligomers, including their mixed ionic–electronic conductivity and biocompatibility to enhance sensitivity and enable real-time monitoring of bacterial activity. In the next sections, we discuss these different detection strategies and their applications in infection diagnostics.

6.1 | Amperometric/Voltammetric Conducting Polymer-Based Sensors

Amperometric/voltammetric conducting polymer-based sensors represent a reliable approach for detecting infections by utilizing the electrochemical activity of bacteria for real-time monitoring. By applying a potential to the sensors, they measure the current produced by redox reactions involving bacterial metabolites, allowing for sensitive detection of bacterial presence and activity. A notable example is the whole-cell setup used to study *S. Enteritidis* biofilm formation on charged PEDOT: PSS surfaces [60]. This setup utilized two vertically positioned PEDOT: PSS slides as both anode and cathode, with a constant bias potential of −0.5 V applied during bacterial incubation (Figure 4A,B). The observed current changes, particularly the gradual increase after 45 min, indicated bacterial growth and metabolic activity altering the redox state of the conducting polymer (Figure 4C). To ensure sterility and prevent contamination, a custom-designed biofilm reactor setup was used based on a Coplin jar for secure placement of microscope slide sized surfaces as well as a 3D printed lid for placement of electrical contacts. This setup demonstrates how conducting polymer-based amperometric sensors can effectively differentiate between sterile conditions and bacterial presence, making them highly relevant for real-time infection detection applications. Expanding on this work, a voltammetric conducting polymer-based sensor was developed for detecting *P. aeruginosa* through its secreted redox-active molecules [73]. The study demonstrated that structuring PEDOT: PSS electrodes significantly improved sensitivity and selectivity. Using cyclic voltammetry (CV) and square wave voltammetry (SWV), the sensor effectively

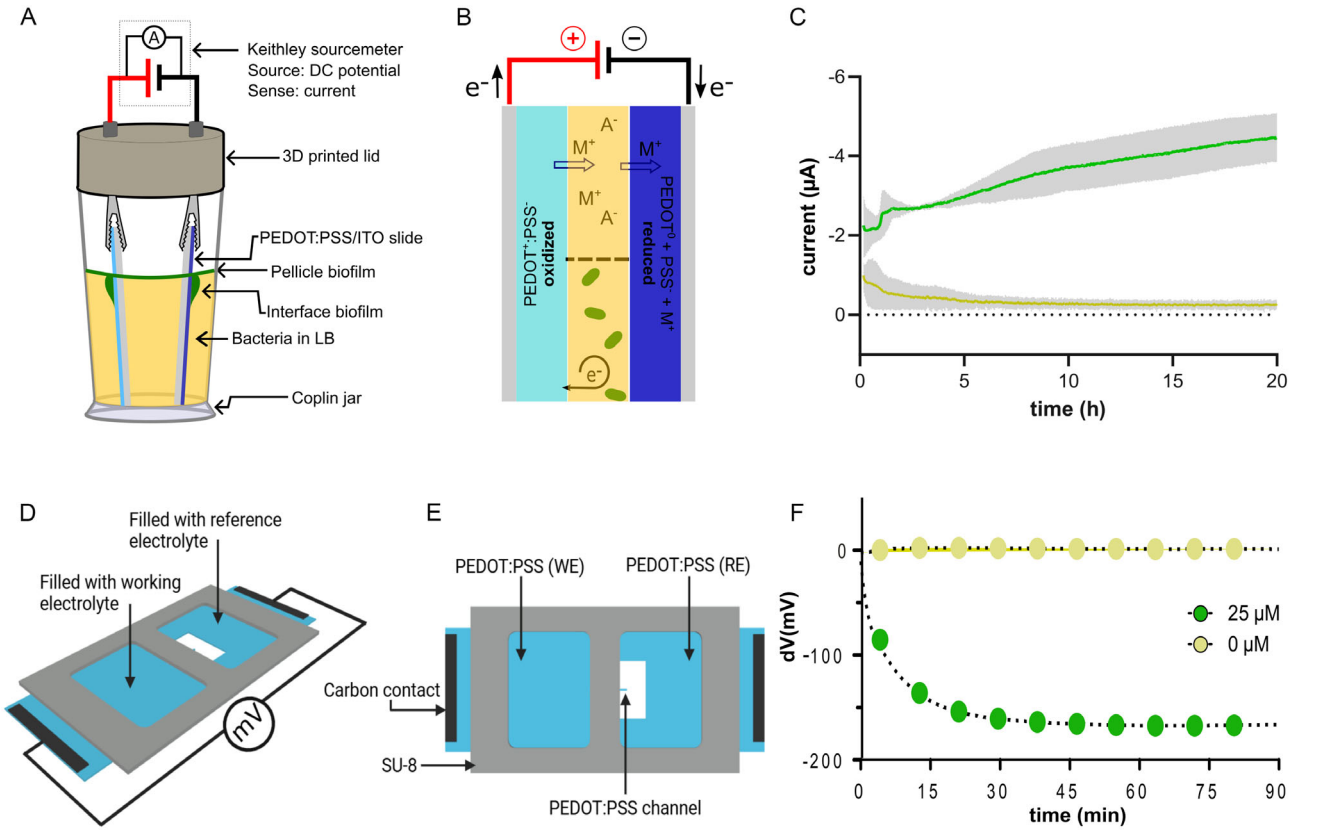

FIGURE 4 | Amperometric and potentiometric conducting polymer-based sensors for infection detection. (A) Schematic of the biofilm reactor in whole-cell mode, featuring two vertically oriented PEDOT: PSS/ITO slides functioning as anode and cathode during a 24 h incubation of *S. Enteritidis* in LB medium at 37°C. (B) Illustration of electrochemical reactions in the whole-cell setup using sterile LB medium (top) and a culture of *S. Enteritidis* (bottom). (C) Current flow through the circuit in sterile LB medium (yellow lines) compared to *S. Enteritidis* cultures (green lines) at −0.5 V. Adapted from [60] under the terms of the CC-BY license. Copyright 2024, The Authors, published by Wiley-VCH. (D) Schematic illustration of the sensor design, featuring two PEDOT: PSS electrodes and a channel, with electrolyte reservoirs patterned on top using SU-8 hydrophobic photoresist. The analyte is placed on the working electrode, while the reference electrolyte is positioned on the reference electrode. (E) Schematic top view of the same device. (F) Recording of the potential difference over time for the bacterial redox-active compounds applied to the electrochemical sensor at concentrations of 0 µM (yellow line) and 25 µM (green line). Adapted with permission from [53]. Copyright 2019, Elsevier.

detected key *P. aeruginosa* metabolites, including pyocyanin (detected in the 1–55 μM range), *Pseudomonas* quinolone signal (detected in the 5–55 μM range), and 2′-aminoacetophenone (tested in the 1–2 mM range), by amplifying their electrochemical signals. This work demonstrates the potential of PEDOT: PSS-based voltamperometric sensors for infection monitoring, further establishing them in biomedical diagnostics. An electrochemical sensor for bacterial metabolism was also developed to detect nicotinamide adenine dinucleotide (NADH) using polythiophene nanoparticles [74]. Here, composite films of isotactic polypropylene and polythiophene nanoparticles were created for carbon screen-printed electrodes, enabling the monitoring of NADH oxidation, released during bacterial respiration, over a linear concentration range of 200 μM to 5 mM with a detection limit of about 200 μM. The anodic current density increased from 20.7 μA cm^{-2} at 200 μM NADH to 46.4 μA cm^{-2} at 500 μM NADH, demonstrating the sensor quantitative sensitivity. This approach successfully identified both Gram-positive and Gram-negative bacteria, while showing no response to eukaryotic cells, as NADH remains primarily within mitochondria.

6.2 | Potentiometric/Chronopotentiometric Conducting Polymer-Based Sensors

Potentiometric conducting polymer-based sensors offer a promising approach for detecting bacterial infections by monitoring changes in electrical potential associated with bacterial activity. These sensors utilize conducting polymers to form a sensitive interface that responds to the binding of bacterial metabolites or other biomolecules. When an analyte interacts with the biorecognition element on the biosensor, it induces a change in potential between the working electrode and a reference electrode. This change can be precisely measured, enabling the sensitive detection of bacterial presence and activity. In this regard, a potentiometric conducting polymer-based sensor was designed for rapid, label-free detection of bacteria by monitoring secreted redox-active compounds [53]. Here, a two-electrode system utilizing PEDOT: PSS was employed to identify low-molecular-weight redox-active metabolites released by bacteria (Figure 4D,E). The sensor effectively detected and quantified these compounds at micromolar concentrations, 1–50 μM for ascorbic acid, 25–250 μM for glutathione, and 5–100 μM for cysteine, achieving response times as quick as 13 min. The PEDOT can be reduced by electrons transferred from bacterially secreted redox biomarkers, such as ascorbic acid, glutathione, and cysteine, enabling the detection of contamination in samples that do not contain bacterial cells. When applied to detect *S. Enteritidis*, the sensor exhibited a reduction of the PEDOT: PSS electrode and a shift in potential to negative values due to the action of secreted redox-active compounds (Figure 4F). Furthermore, the sensor successfully identified uropathogenic strains of *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Enterococcus faecalis* (*E. faecalis*), *P. aeruginosa*, *Proteus mirabilis* (*P. mirabilis*), and *Klebsiella pneumoniae* (*K. pneumoniae*) in complex media and processed urine. A novel chronopotentiometric sensor was also developed using reduced graphene oxide (rGO) combined with PEDOT: PSS for the detection of *S. aureus* at concentrations as low as 10 CFU/mL, with a linear range up to 10^5 CFU/mL, representing a significant improvement in potentiometric conducting polymer-based sensors [75]. This approach integrated a positively charged antimicrobial peptide to facilitate bacterial binding, which can be modified to enhance specificity for detecting other strains. By measuring potential responses over time under a constant current (4 μA, 0.5 s pulse), the sensors enabled real-time monitoring of bacterial interactions. When exposed to *S. aureus*, the sensors exhibited notable changes in potential, directly correlating with the presence and activity of the bacteria. This approach not only enabled rapid detection but also demonstrated the effectiveness of combining conducting polymers with antimicrobial peptides as recognition elements in biosensing applications.

6.3 | Impedimetric Conducting Polymer-Based Sensors

Impedimetric conducting polymer-based sensors present an advanced solution for detecting bacterial infections by measuring changes in impedance resulting from bacterial interactions. These sensors utilize the unique electrical properties of conducting polymers, which create a responsive platform that reacts when bacteria adhere to the sensor surface. The binding of bacterial cells induces variations in impedance, specifically affecting charge transfer resistance and double layer capacitance, which can be accurately monitored. A featured example is the developed impedimetric conducting-polymer-based sensors for rapid, sensitive, and label-free detection of pathogenic bacteria [76]. Here, the electrodes were coated with a bacteria-imprinted conducting poly (3-thiopheneacetic acid) (BICP) film specifically to detect *S. aureus*. Under optimized conditions, the sensor achieved a linear range from 10 to 10^8 CFU/mL, with a response time of 10 min. This method enhances detection specificity by providing a tailored surface for bacterial binding. When *S. aureus* interacts with the imprinted film, the binding of bacteria blocks charge transfer between the redox probe and the electrode surface, leading to an increase in impedance that correlates with bacterial concentration. These measurable changes in impedance, particularly in charge transfer resistance and capacitance, indicate the presence of bacteria and can be quantified to determine pathogen levels. A composite film of polystyrene sulfonate-coated poly(3,4-ethylenedioxythiophene) (PNaSS@PEDOT) microspheres was also developed for detecting *E. coli* using electrochemical impedance spectroscopy [77]. When *E. coli* at the level of 10^6 CFU/mL interacts with the PNaSS@PEDOT microspheres, measurable changes in impedance occur due to alterations in charge transfer processes at the electrode interface, allowing for correlation with bacterial concentration. Additionally, the composite material could disrupt the bacterial cell wall when an oxidation potential of +0.6 V (vs. Ag/AgCl) was applied, serving as an antifouling coating that can be regenerated through a constant potential application. This dual functionality demonstrates the potential of smart surfaces and conducting polymers in impedimetric sensors for the rapid and effective detection of bacterial infections, making them valuable tools for diagnostics and environmental monitoring.

6.4 | Organic Electrochemical Transistors (OECTs) in Infection Detection

OECTs are composed of source, drain, and gate electrodes immersed in an electrolyte solution [78]. When a voltage is

applied to the gate electrode, the OECT injects ions from the electrolyte into an organic conducting polymer channel, typically using PEDOT: PSS, which is connected to the source and drain electrodes. This ion injection modifies the doping level of the polymer, resulting in changes to its conductivity that can be measured as a variation in current [79]. The inherent mechanical flexibility of OECTs makes them particularly well-suited for integration into point-of-care and portable diagnostic devices [80]. Additionally, OECTs can be functionalized with specific biorecognition elements, such as antibodies or peptides, that selectively target bacterial cells, enhancing their utility in infection detection [78]. A notable examples is a designed sensor platform that integrates OECTs with specific biorecognition elements aimed at targeting bacterial cells [81]. When *E. coli* is captured on the PEDOT: PSS surface with specific antibodies, the transfer characteristics of the OECT shift to higher gate voltages (up to 55 mV shift with a Pt-gate electrode) due to electrostatic interactions between the negatively charged bacteria and the conducting polymer. The device exhibited a detection limit of 10^3 CFU/mL within the range tested up to 10^8 CFU/mL, with optimal sensitivity achieved in KCl electrolyte. By applying a gate voltage, the OECT adjusts the conductivity of the organic polymer channel, enabling sensitive detection of bacterial binding events. An OECT was recently developed to detect *S. Enteritidis* growth through changes in source-gate current [82]. The sensor utilized PEDOT: PSS as the active layer integrated with a Pt gate electrode and an electrolyte solution containing the bacteria. Importantly, the signal could also be measured in filtrates of bacterial cultures free of bacterial cells, indicating that charged metabolic products, rather than bacterial cell multiplication, were responsible for changing the device transfer characteristics. The study demonstrated that the OECT could detect *S. Enteritidis* at low concentrations within just a few hours. By recording real-time changes in source-drain current at a gate voltage of +0.5 V, the OECT effectively monitored bacterial growth in both transparent and opaque media, providing an alternative to optical methods.

6.5 | Optical Probes in Infection Detection

π-conjugated oligo- and polymers have been widely investigated as chromophoric probes for microbial and cellular detection, taking advantage of their delocalized π-electron backbones that provide tunable optical responses [83]. These materials undergo distinct fluorescence or color changes upon interacting with biomolecules, enabling label-free optical discrimination of bacterial species and infection states. Building on advances in chromophoric probes, optotracing-based on conjugated oligomers introduces a paradigm shift in infection detection. Optotracers are oligothiophenes with conjugated backbones whose fluorescent properties depend on binding to biomacromolecules like amyloid fibrils or certain polysaccharides. An ON-switch of fluorescence is observed upon binding and a shift in excitation maximum depends on the specific structure of the binding target. By enabling real-time, noninvasive imaging of pathogen behavior and host responses, optotracers play a crucial role in pathogen detection. Unlike traditional imaging techniques that require external staining or fixation, optotracers are nondestructive, preserving the integrity of biological structures. Their conformation-dependent optical properties allow selective binding to biomolecules, including cellulose and amyloid curli fibers which are key components in bacterial biofilms [84, 85]. EbbaBiolight 680, was recently used to track the appearance of spatiotemporally controlled curli fibril patterns during UPEC and *S. Enteritidis* biofilm formation in real time (Figure 5A) [84, 86]. Such real-time monitoring is particularly valuable in infection detection, as biofilm development plays a critical role in bacterial persistence and antibiotic resistance. Furthermore, optotracers enable the separate observation of bacterial cell proliferation and ECM production during growth on conducting polymers [60]. It was demonstrated that only ECM production increased upon electrical stimulation of the polymer surface, highlighting the potential of optotracers for investigating infection dynamics at the biofilm-material interface (Figure 5B).

Building on these capabilities, a novel diagnostic assay was developed to detect biofilm-related UTIs by identifying cellulose in urine [5]. This assay employs optotracers to detect cellulose, a component of the UPEC biofilm, providing a direct, rapid method for diagnosing biofilm-related UTIs. The assay's ability to detect cellulose in under 45 min and distinguish biofilm from planktonic bacteria offers new insights into UPEC biofilm formation in the urinary tract and may significantly impact antibiotic treatment strategies.

Overall, these studies demonstrate the optotracing capability in Gram-negative bacteria such as UPEC and *S. Enteritidis*, where fluorescence signal arises from optotracer binding to ECM components like cellulose and curli amyloid fibrils. Extending beyond Gram-negative systems, recent research has shown that optotracing is equally effective for visualizing both planktonic and biofilms of Gram-positive pathogens like *S. aureus*. In their planktonic cells, optotracers bind to cell wall components (e.g., peptidoglycan, lipoteichoic acid) providing rapid and selective method for easy bacterial visualization and quantification [87]. Additionally, it has recently been shown that optotracers bind to fibrillated phenol soluble modulins (fPSMs), which are functional amyloid peptides that form the structural scaffold of the *S. aureus* biofilm matrix [88]. This diversity in binding mechanisms demonstrate the ability of optotracing for infection detection in both Gram-negative and Gram-positive species, enabling the mapping of specific structures and their evolution under physiological conditions.

In addition to optotracing based on conjugated oligomers, several conjugated polymers have also been reported as chromophoric probes for bacterial detection. Cationic poly(3-hexylthiophene) (P3HT) nanoparticles have been identified as dual fluorescent and electrochemical probes, where fluorescence quenching upon binding to *E. coli* enabled highly sensitive bacterial detection down to 5 CFU/mL, while simultaneously exhibiting antimicrobial activity with a minimum inhibitory concentration (MIC) of 2.5 μg mL^{-1} [89]. This demonstrates the dual diagnostic and therapeutic potential of conducting polymers acting as chromophores. Unlike most purely optical sensors, this system also integrates an electrochemical transduction mode with a limit of detection of 250 CFU/mL, highlighting its multifunctional nature as both a fluorescent and electrochemical bacterial sensor. Similarly, the conjugated polymer MEH-PPV (Poly[2-methoxy-5-(2′-ethylhexyloxy)−1,4-phenylenevinylene]) has been employed as a fluorescent reporter whose emission is modulated by interaction with bacterial cell surfaces, enabling direct pathogen detection within the range of 10^4–10^5 CFU/mL in complex biological media [90]. The study emphasized the advantages of

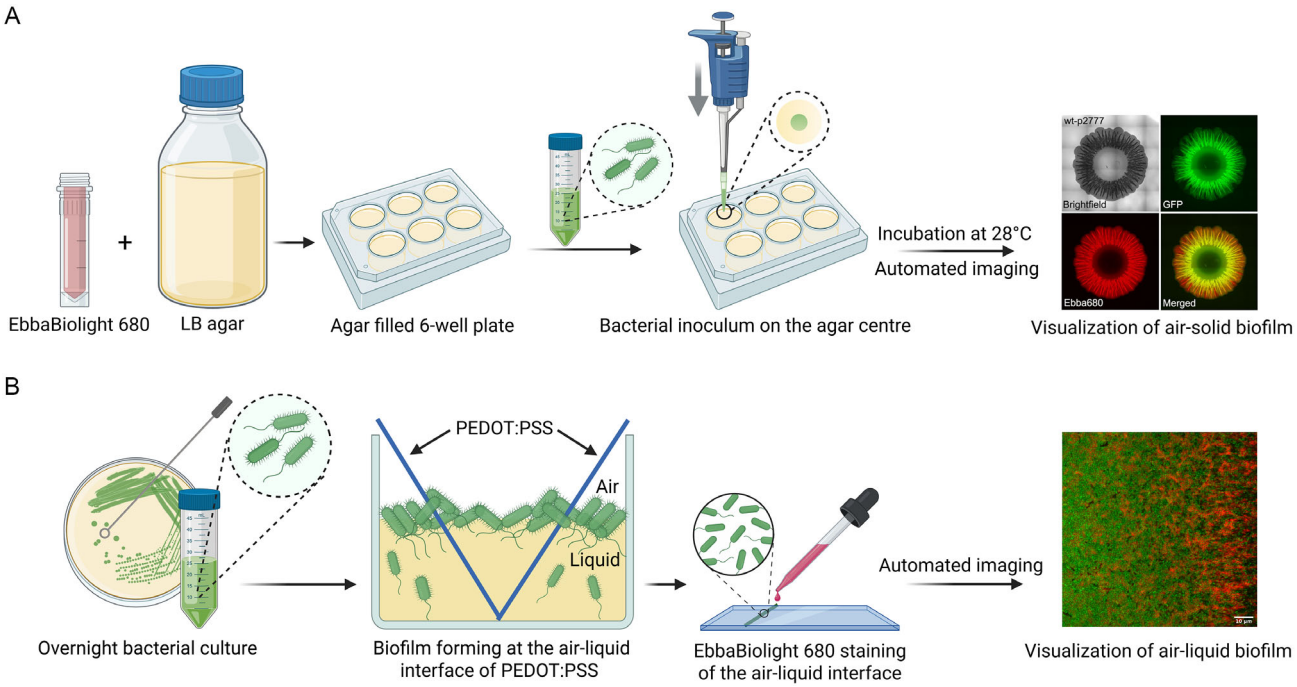

FIGURE 5 | Optotracing for visualization of biofilm dynamics and distinguishing bacterial proliferation from ECM production. (A) A 6-well plate filled with LB agar supplemented with an optotracer. A 10 μL bacterial inoculum is applied to the agar, followed by incubation and visualization at the air–solid interface, which results in bright field, GFP-expressing planktonic cells (green), biofilm curli (red), and merged images. Adapted from [84] under the terms of the CC-BY license. Copyright 2021, The Authors, published by Elsevier. (B) Biofilm formation at the air–liquid interface of the conducting polymer PEDOT: PSS, followed by ECM labeling using an optotracer, visualizing bacterial cells (green) and the increasing ECM production (red) at the periphery. Adapted from [60] under the terms of the CC-BY license. Copyright 2024, The Authors, published by Wiley-VCH.

MEH-PPV for rapid fluorescence-based diagnosis owing to its high fluorescence efficiency, good photostability, and low cytotoxicity. A vancomycin-conjugated polythiophene (PTPVan) displayed visible color and fluorescence changes upon binding to Gram-positive bacteria, allowing selective imaging through confocal microscopy [91]. Here, selectivity is achieved through the incorporation of the antibiotic vancomycin, which provides molecular recognition toward Gram-positive bacterial cell walls, introducing a targeted sensing element absent in nonfunctionalized polymers. In another example bridging electrochromism and biology, a water-soluble naturally oxidized electrochromic polymer ox-PPE (poly(3,4-propylenedioxythiophen-alt-3,4-ethylenedioxythiophene)) went through a visible color change upon metabolic reduction by live bacteria, enabling Gram-type discrimination and antibiotic susceptibility testing within 2.5 h [92]. The study showed that ox-PPE responds to reducing species released by metabolically active bacteria, allowing rapid colorimetric detection within 30 min at bacterial concentrations as low as 10^4 CFU/mL using 25 μg mL^{-1} ox-PPE. This reduction was driven primarily by metabolic thiols such as cysteine (detectable below 4.9 μM) and glutathione, both present extracellularly in the low micromolar range.

As shown in the examples above, advances in conjugated oligo- and polymer-based biosensing methods have significantly improved the detection of bacterial pathogens. These systems enable rapid and sensitive identification, supporting timely clinical interventions that may improve patient outcomes. Beyond early diagnosis, they also provide valuable insights into biofilm dynamics and bacterial behavior, forming a solid foundation for more effective infection management strategies. The potential applications of conjugated conducting polymers extend beyond detection; they can also be used to develop antimicrobial surfaces that help prevent biofilm formation at an early stage. Considering such capability, the next section explores the role of conducting polymers in infection prevention, highlighting how they can complement detection tools as part of a comprehensive infection control strategy.

7 | Conducting Polymers in Infection Prevention

Preventing biofilm formation from the outset is a more effective and cost-efficient strategy compared to treatment options; thus, antimicrobial surfaces have long been utilized to coat medical devices for this purpose. Recent advancements in electroenhanced antimicrobial coatings present substantial improvements over conventional antibacterial systems that rely on silver nanoparticles (AgNPs). For instance, the electrically conducting conjugated polymer, PEDOT-MeOH: PSS, can be covalently bonded to silver nanoparticles, enabling the controlled release of Ag^+ ions upon oxidation (Figure 6A) [93]. This approach was demonstrated by applying an electrical stimulus (5 Hz, 4 $V_{peak\text{-}to\text{-}peak}$ square wave between −2 and +2 V) to the conducting polymer when in contact with *S. aureus*, effectively inducing the release of Ag^+ ions (~12.8 nM, below the MIC = 100 nM), which successfully prevented biofilm formation on the surface (close to 90% reduction). Notably, the findings revealed that the bactericidal effects of this hybrid system surpassed the individual impacts of electricity and AgNPs alone in preventing biofilm establishment. In parallel with release-based strategies, intrinsic

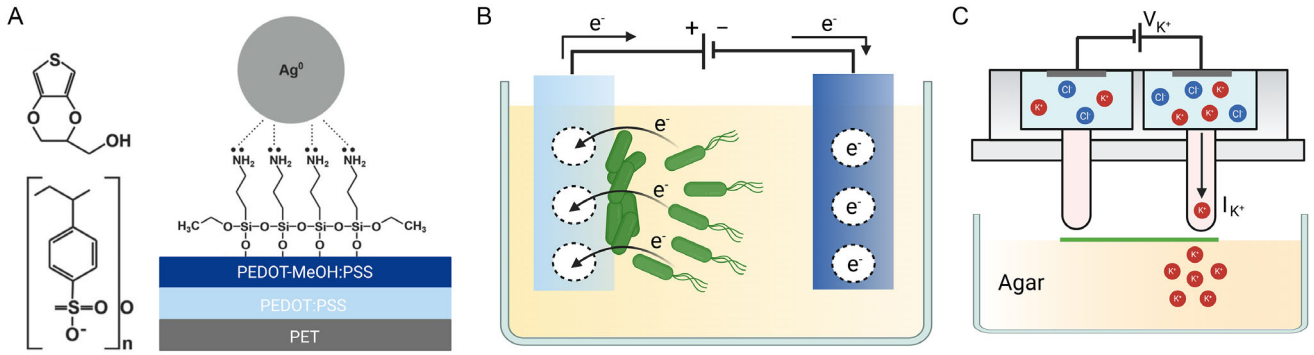

FIGURE 6 | Conducting polymer materials and devices for infection prevention. (A) Chemical structures of EDOT-MeOH and PSS used in the formation of the composite, which includes a PEDOT-MeOH: PSS film electropolymerized on Orgacon (PEDOT: PSS-coated PET), an intermediate (3-aminopropyl) triethoxysilane (APTES) layer, and AgNPs bound via coordinate bonds to the amine groups. Adapted with permission from [93]. Copyright 2017, Wiley-VCH. (B) Illustration of electrochemical modulation of biofilm formation. The setup features an anode and a cathode, each influencing bacterial growth differently. The anode (left electrode) is maintained in an oxidized state, serving as a renewable electron acceptor that enhances bacterial electron transfer (black arrows), thereby promoting biofilm formation. Conversely, the cathode (right electrode) remains in a reduced state, creating an electron-rich surface that disrupts bacterial electron transfer and inhibits biofilm development. Adapted from [66] under the terms of the CC-BY license. Copyright 2017, The Authors, published by Springer Nature. (C) Schematic illustration of the ion pump mechanism, depicting the direction of potassium ions (K^+) movement during the actuation process. The diagram highlights how K^+ ions are delivered to the bacterial biofilm (green layer formed on agar) through hydrogel filled glass capillaries, enabling localized control of membrane potential and influencing biofilm growth dynamics. Adapted from [94] under the terms of the CC-BY license. Copyright 2024, The Authors, published by Springer Nature.

antifouling/antimicrobial chemistries can be engineered directly into conducting polymers via their side chains, independent of external additives. Zwitterionic moieties form a strongly hydrated interfacial layer that preserves mixed ionic-electronic transport while resisting nonspecific protein adsorption and cell/bacterial adhesion. PEDOT derivatives incorporating zwitterions, such as phosphorylcholine-functionalized PEDOT (PEDOT-PC) [95] and zwitterionic polythiophenes (e.g., PSBEDOT) have demonstrated antifouling properties in complex media, as well as compatibility with electrochemical transduction [96]. To balance antifouling with conductivity and capacitance, electrochemical copolymerization can be used to adjust zwitterionic content. Accordingly, the reported results should describe the proportion of zwitterionic components and the materials ionic-electronic conduction behavior under operating conditions [97]. In the context of thin-film bioelectronic arrays, where biofouling typically kills the signal, an antifouling OECT sensor was recently built from phosphorylcholine-functionalized PEDOT gates and thin-film arrays, leveraging zwitterionic polymers [95]. Additionally, cationic side chains (e.g., quaternary ammonium, guanidium) on conducting polymer backbones can achieve contact-killing via direct cell membrane disruption, thereby reducing biofilm formation without the need for antibiotics or metals. Several recent reviews summarize design rules and safety considerations for such cationic polymers, including those containing quaternary ammonium centers [98, 99]. Beyond mere prevention, the capacity to tune and regulate biofilm production offers a superior level of control in infection management. This was further illustrated by manipulating the availability of electron acceptors on redox-active conducting polymers to influence *S. Typhimurium* biofilm formation (Figure 6B) [66]. Image processing was used to quantify these effects, extracting consistent data on fluorophore distribution within the biofilm. This robust analysis reported significant variations in biofilms cultivated on PEDOT composites with different counterions and under varying electrochemical states, highlighting the precise control that conducting polymers can provide in infection prevention strategies. PEDOT surfaces, switching from oxidized to reduced state suppressed biofilm formation by 52%–58% compared with oxidized/neutral controls. These findings hold the potential to revolutionize how we approach the design of antimicrobial surfaces, pointing toward more effective solutions in clinical settings. Combining zwitterionic antifouling with redox-state control can reduce baseline fouling in protein-rich fluids, while enabling on-demand modulation of biofilm formation on electroactive surfaces. In addition to these preventive measures, understanding the dynamics of biofilm cooperation can lead to strategies for disruption. Biofilms exhibit phenotypic heterogeneity, enabling division of labor and cooperation for enhanced resistance toward stressors [100]. Inhibiting bacterial cooperation is a robust antibacterial strategy, as the spatial–temporal organization of specific structures and behaviors emerging in distinct regions within biofilm communities is crucial for their survival [101]. The realization that bacteria use electrical signaling both within and between biofilms to govern this organization has led to the emergence of the new field of bacterial biofilm electrophysiology [9]. Electrical communication between central and peripheral cells allows biofilms to manage metabolic stress through mechanisms similar to the propagation of electrical signals in the mammalian brain [11]. Just as the frequency and amplitude of calcium oscillations play specific signaling roles in neurons, bacterial ionic oscillations also have similar specificity. Ion pump devices can establish synthetic ionic oscillations at specified frequencies and amplitudes, enabling the delivery of cations and other positively charged molecules involved in signaling. In this regard, A bioelectronic K^+ ion pump integrated with *B. subtilis* biofilms used alternating pulses of +2 V for 300 s and −2 V for 30 s, producing an ionic current of 100 μA during K^+ delivery [94]. Spatial K^+ gradients were quantified with IPG-4 dye ($\Delta[K^+] = 49$ mM directly under the capillary outlet, =15 mM near the edge, and only 2 mM at 400 μm lateral distance) for tight, localized control

of extracellular K^+ that modulated membrane potential (V_{mem}) and growth dynamics in a spatiotemporal manner (Figure 6C). Therefore, OEIP-induced ionic oscillations could be used to disrupt bacterial electrical communication, interfering with bacterial cooperation in biofilms. This approach creates a new parallel between biology and electrical devices, comparable to a scrambler used in telecommunications, and highlights the potential for developing new strategies aimed at infection disruption. In the next section, we explore how the principles established in infection prevention using conducting polymers are being extended into infection intervention and treatment, focusing on innovative bioelectronic materials that enhance therapeutic efficacy and target biofilm-associated infections more effectively.

8 | Conducting Polymers in Infection Intervention/Treatment

The rapidly evolving field of bioelectronic medicine has taken significant steps in addressing the integration challenges between technology interfaces and biological tissues. Traditional materials such as metal and silicone electrodes frequently induce inflammatory responses, prompting researchers to seek organic bioelectronic materials that can mitigate foreign body reactions and enhance tissue compatibility. These organic materials, with their inherent biocompatibility, hold the potential to revolutionize infection treatment strategies, particularly in the context of biofilm-associated infections [18]. Biofilms, which can form on both biotic surfaces such as epithelial tissues and abiotic surfaces like catheters, are notorious for their ability to enable persistent and recurrent infections. These complex communities of microorganisms exhibit strong resistance to antibiotics through various mechanisms, including the protection of immunogenic bacteria, the formation of persister cells with reduced metabolic activity, and the production of ECM proteins that provide mechanical protection and facilitate adhesion. Consequently, biofilms pose a significant challenge not only for effective treatment but also for dynamic infection modeling, necessitating the development of improved methods for both prevention and intervention [102]. Organic bioelectronic materials offer a promising approach for the development of implants designed to combat infections through direct antibiotic release from their active surfaces generating high local concentrations of therapeutic agents at infection sites, thus minimizing systemic side effects. The electronically triggered release mechanisms utilized in organic conducting polymers are governed by redox-controlled ion exchange within the polymer matrix. An externally applied electrical potential triggers oxidation or reduction processes in the polymer, leading to conformational changes and the expulsion or uptake of charged drug molecules or dopants embedded within the film. The electrochemically mediated release provides spatial and temporal precision, allowing on-demand drug delivery only when and where needed. For instance, PEDOT-based coatings loaded with antibiotics have demonstrated controlled release in response to electrical stimulation, effectively inhibiting bacterial growth on medical device surfaces while reducing systemic exposure [103, 104]. These electroresponsive systems can thus act as stimuli sensitive systems, integrating detection and therapy within the same platform [105]. An efficient and scalable process for drug loading of PEDOT: PSS, which is independent of the drug size and charge has been reported using supercritical carbon dioxide (scCO2) impregnation of PEDOT:PSS with acetylcholine, facilitating its release upon electrical stimulation (Figure 7A,B) [106]. This process was carried out at 60°C and 3000 psi for 20 min, producing uniformly impregnated films containing 8–9 nm acetylcholine particles, which released 20–22 μg cm^{-2} within 6 h under ±1.0 V stimulation compared to ~2.6 μg cm^{-2} passive release at 0 V. Moreover, advancements in electrical methods have enabled rapid detection of bacterial activity at the single-cell level, enhancing the targeting of pathogenic bacteria. Research has shown that proliferative and inhibited bacterial cells exhibit distinct membrane polarization dynamics in response to the same electrical stimulus [54]. Specifically, while proliferative cells hyperpolarize, nonproliferative and antibiotic-treated cells undergo depolarization. This differential response allows for the precise identification and differentiation of bacterial states, enabling more targeted and effective treatment strategies. Unlike proliferative cells, nonproliferative and antibiotic-treated bacterial cells depolarize instead of hyperpolarizing, allowing them to be differentiated from proliferative bacteria for more specific treatment. Conducting polymers, due to their electrical conductivity and biocompatibility, can be utilized in detecting these polarization differences, offering a promising route for the targeted treatment of infections by selectively interacting with bacterial states. In addition to targeting bacterial infections, a multifunctional system has been developed that integrates PEDOT nanoparticles loaded with the antibiotic chloramphenicol, combining therapeutic and diagnostic capabilities within a single platform (Figure 7C) [107]. This system facilitates controlled antibiotic release through electrical stimulation (+1.0 V chronoamperometry or ±0.5 V CV, applied for 5–30 min), while simultaneously enabling real-time monitoring of bacterial growth via electrochemical detection of metabolites like NADH within the linear range of 250 μM–2 mM. The oxidation of NADH at +0.6 V produces a measurable current, which correlates with bacterial population growth, offering practical strategies to more effectively address biofilm-associated infections.

To transform conducting polymer drug release systems into successful medical devices for clinical applications, several limitations must be addressed. To overcome constraints in drug loading capacity several strategies have been used, such as nanostructuring for fabrication of nanoporous, nanofibrous, or nanotube architectures to increase the available surface area and free volume for drug incorporation [108]. Additionally, composite systems have been developed, where drug-loaded nanoparticles or micelles are embedded within the conducting polymer matrix and efficiently decouple conductivity from drug storage [109]. Hydrogels have also been explored as an effective solution [110]. Hydrogels also offer a possibility to protect drug release systems from physiological conditions with oxidative environments, pH fluctuations, and enzymatic activity. To overcome regulatory hurdles, manufacturing processes for conducting polymer-based drug release systems must meet reproducibility and scalability standards. To validate and benchmark efficacy of antibiotic release systems toward standard treatments, standardized antibiotic susceptibility tests must be used which address bacterial lifestyles present under conditions representing infections on indwelling devices.

The integration of optotracing-based biofilm antimicrobial susceptibility testing (AST) offers a valuable tool for improving

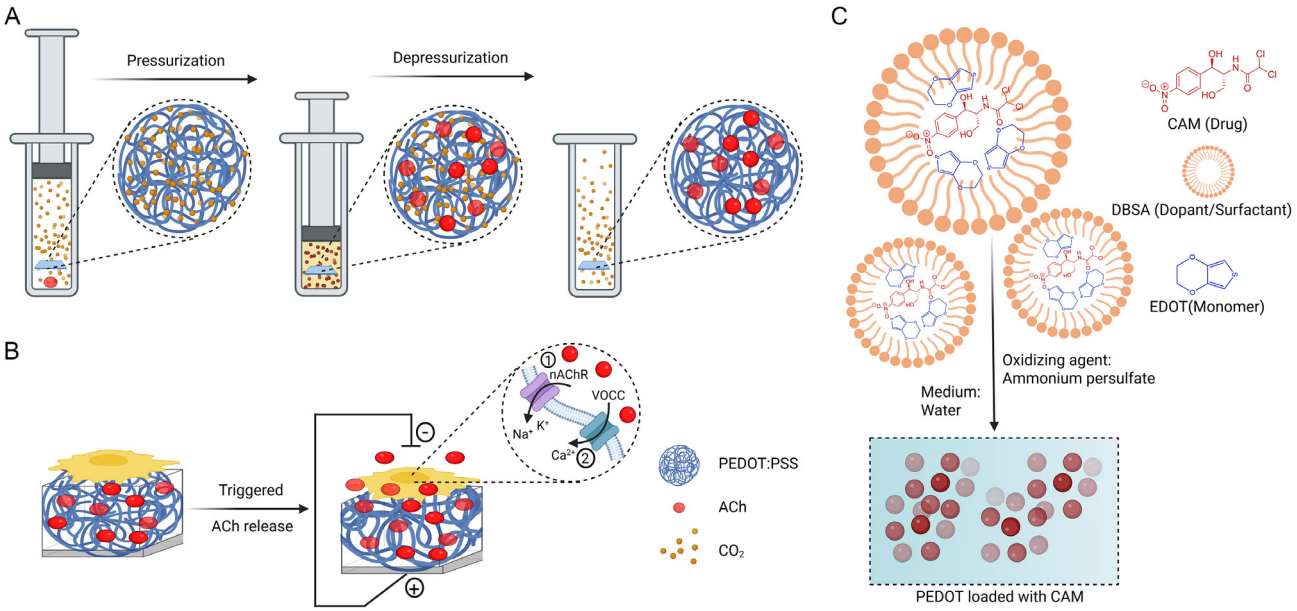

FIGURE 7 | Conducting polymer-based devices for infection treatment. (A) Preparation of conductive polymer PEDOT: PSS, impregnated with supercritical carbon dioxide ($scCO_2$) through a pressurized process. The acetylcholine (ACh) is incorporated into the polymer matrix during the impregnation. (B) The device for the electrochemical release of acetylcholine, where the release mechanism is triggered by electrical stimulation, evoking intracellular Ca^{2+} signaling in neurotypic cells. Adapted with permission from [106]. Copyright 2016, Elsevier. (C) Schematic illustration of the preparation process for antibiotic-loaded PEDOT nanoparticles (PEDOT/CAM NPs) designed for nanotheranostic applications. This diagram depicts the in situ emulsion polymerization method, where the conducting polymer PEDOT is synthesized in conjunction with chloramphenicol (CAM), a model antibiotic. Adapted with permission from [107]. Copyright 2020, Wiley-VCH.

infection treatment by addressing the limitations of traditional methods. Standard AST techniques primarily assess planktonic bacteria, neglecting the protective ECM that shields biofilm-embedded bacteria from antimicrobial agents. By enabling real-time detection of ECM components, optotracing allows for the confirmation of biofilm formation before antibiotic exposure, ensuring a more accurate evaluation of treatment efficacy. This approach has been utilized in broad-spectrum antibiotic screening, identifying compounds that either inhibit or promote ECM production [111]. Through dose–response assays, optotracing has provided critical insights into biofilm susceptibility and resistance mechanisms, complementing bioelectronic innovations in infection intervention. The combination of conducting polymers for controlled drug release and optotracing for biofilm-targeted AST offers a promising approach for developing more precise and adaptable treatment strategies aimed at reducing antimicrobial resistance and improving patient outcomes.

As discussed above, advances in the application of conducting polymers represent a key step forward in addressing the challenges of biofilm-related infections. These organic materials not only improve biocompatibility but also support precise, controlled antibiotic delivery, helping to enhance therapeutic outcomes while minimizing systemic side effects. Furthermore, the ability to monitor bacterial growth dynamics in real time offers valuable insights for infection management and supports the development of more personalized treatment approaches. As research in this area continues, incorporating conducting polymers into clinical practice may lead to more effective infection interventions and contribute to ongoing progress in bioelectronic medicine.

9 | Concluding Remarks and Future Perspectives

The integration of conducting polymers into infection modeling, detection, prevention, and treatment is revolutionizing biomedical research. These materials offer a unique combination of biocompatibility, electronic responsiveness, and adaptability, enabling the creation of biomimetic infection models, real-time bacterial biosensors, and antimicrobial surfaces with precise biofilm control. By bridging the gap between biology and electronics, conducting polymers enhance our ability to study infection dynamics and develop more targeted therapeutic strategies. While these advancements demonstrate the high potential of conducting polymers, several challenges must be addressed before applying these materials into clinical settings. The scalability and reproducibility in conducting polymers synthesis via chemical or electrochemical methods as well as in device fabrication are known as limiting factors. Small variations in polymer composition caused by, e.g., dopant or monomer concentrations greatly affect the performance of the final product. Additionally, stability of the synthesized materials and their long-term functionality in complex biological fluids are affected by delamination, degradation, and dopant loss, limiting their biocompatibility. Developing a device based on conducting polymers that is cost effective at large scale manufacturing process and survives under sterilization and implementation has remained an ongoing challenge. From clinical translation perspective, these technologies require complete in vitro and in vivo testing to confirm their safety and long-term biocompatibility. As discussed earlier, standard evaluation methods provided by ISO guidelines are essential to be applied in order to approve the device performance.

Looking ahead, the field is moving toward the development of autonomous biomedical devices that can detect and respond to infections in real time. These smart bioelectronic systems will be capable of secreting antimicrobial agents and peptides upon detecting infection, with structural changes in the polymer for wireless detection and monitoring. Additionally, electrical stimulation of the conducting polymer can enhance antimicrobial release, creating a self-regulated system that simultaneously senses, reports, and treats infections with high precision. Further advancements in bacterial biofilm electrophysiology and OEIPs could provide novel strategies for disrupting bacterial communication, addressing a critical challenge in antibiotic resistance. The refinement of electroactive materials, particularly PEDOT-based polymers, will expand their clinical applications, from infection-resistant implant coatings to dynamic, infection-responsive therapeutic platforms. As the field moves forward, interdisciplinary collaboration among researchers in materials science, microbiology, and clinical medicine will be essential for translating these innovations into practical healthcare solutions. Ongoing advances in organic bioelectronic materials and devices are making it possible to develop smarter, more adaptive, and minimally invasive approaches to infection management, offering promising directions in the fight against antibiotic-resistant infections.

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Conflicts of Interest

Susanne Löffler (S.L.) and Agneta Richter-Dahlfors (A.R.D.) are coinventors of patents related to this work. The intellectual property is owned by Richter Life Science Development AB, which was founded by A.R.D. Both S.L. and A.R.D. are involved with Ebba Biotech AB, a company that commercializes optotracers as outlined in this article.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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