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REVIEW

Bio-inspired Track-Etched Polymeric Nanochannels: Steady-State Biosensors for Detection of Analytes

Jian Wang, Yahong Zhou,* and Lei Jiang

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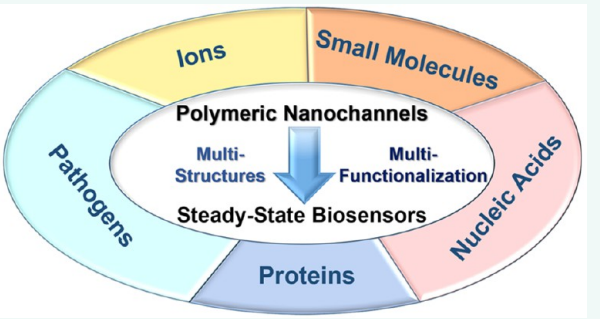
ABSTRACT: Bio-inspired polymeric nanochannel (also referred as nanopore)-based biosensors have attracted considerable attention on account of their controllable channel size and shape, multi-functional surface chemistry, unique ionic transport properties, and good robustness for applications. There are already very informative reviews on the latest developments in solid-state artificial nanochannel-based biosensors, however, which concentrated on the resistive-pulse sensing-based sensors for practical applications. The steady-state sensing-based nanochannel biosensors, in principle, have significant advantages over their counterparts in term of high sensitivity, fast response, target analytes with no size limit, and extensive suitable range. Furthermore, among the diverse materials, nanochannels based on polymeric materials perform outstandingly, due to flexible fabrication and wide application. This compressive Review summarizes the recent advances in bio-inspired polymeric nanochannels as sensing platforms for detection of important analytes in living organisms, to meet the high demand for high-performance biosensors for analysis of target analytes, and the potential for development of smart sensing devices. In the future, research efforts can be focused on transport mechanisms in the field of steady-state or resistive-pulse nanochannel-based sensors and on developing precisely size-controlled, robust, miniature and reusable, multi-functional, and high-throughput biosensors for practical applications. Future efforts should aim at a deeper understanding of the principles at the molecular level and incorporating these diverse pore architectures into homogeneous and defect-free multi-channel membrane systems. With the rapid advancement of nanoscience and biotechnology, we believe that many more achievements in nanochannel-based biosensors could be achieved in the near future, serving people in a better way.



KEYWORDS: *bio-inspired, track-etched, polymeric membranes, artificial nanochannels, ion transport, multi-structures, functionalization, biosensor, steady state, rectification*

Due to their similar or stronger functionality, superior stability, and robustness compared to biological ion channels, synthetic nanochannels (also referred as nanopores) have attracted great attention in the past decades with many potential applications, ranging from biosensors to energy harvesting.[1−5] Benefiting from the development of advanced micro-/nanofabrication techniques, a series of nanochannels with tunable pore sizes and various shapes have been produced from organic or inorganic materials, such as polyimide (PI),[6−11] polycarbonate (PC),[12,13] polyethylene terephthalate (PET),[14−19] silicon nitride,[20−22] carbon nanotube arrays,[23,24] and porous anodic alumina oxide (AAO).[25−28] As a representative application of the solid-state nanochannels, nanochannel-based biosensors have many advantages over other sensors, such as high sensitivity and specificity, inherent simplicity, quick detection and reversible response, label-free, and high signal-to-noise ratios.[29,30] Over the past decade, artificial nanochannel-based platforms for biosensing applications have been burgeoning and widely used as resistive-pulse and/or steady-state sensors for detecting proteins,[31−34] nucleic acid,[35−38] small molecules,[39−42] ions,[43−46] metal ion−molecular complexes,[47] and so on.[48−51] The resistive-pulse method,

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which is also referred as stochastic sensing, mainly focuses on the detection of molecules without labeling them as well as separation of particles by sizes, shapes, and surface charge densities. As the target passes through the channel, there is a momentary drop in the ionic current, generating a resistive pulse (a signal) which can then be used for the identification or the counting of targets.[22,52] Moreover, in the steady-state current method, the interior walls of the nanochannels are modified with functional molecules with recognition sites for the targets. The combination of functional probe and targets will induce changes in the effective pore size, wettability, and surface charge of the inner walls, causing a change of the ionic current. Consequently, by measuring the current−voltage (I−V) curves with/without addition of targets, the detection of analytes can be realized.[53] Compared with the resistive-pulse method, steady-state sensors have been widely used to detect various analytes including ions, small molecules, nucleic acids, proteins, and pathogens. This method has the features of high sensitivity, fast response, target analytes with no size limit, and extensive suitable range. The nanochannel-based devices, which have become a focus of current academic research in biomimetic materials, have grabbed considerable attention.

Polymer membranes, such as PET, PI, and PC, have been extensively utilized to fabricate single or multiple nanochannels with various geometries by the chemical etching method. The ion track-etching process is a relatively simple and economical technique, and it can result in the generation of negatively charged carboxyl groups on the inner channel walls. As-prepared nanochannels are selective for positively charged analytes, which are also suitable for surface functionalization to increase the selectivity toward target analytes and improve the efficiency of detection.[52,54] Due to these features, the polymer has the potential to develop nanochannel-based biosensors with excellent analytical performance.

It is generally known that minerals are essential constituents of body tissues and fluids, and they play a central role in the life of humans and other organisms to sustain certain physicochemical processes.[55] In reality, most of these chemical elements exist in the form of compounds and a few in the form of ions, such as Na^+, K^+, and Ca^{2+}, which play important roles in physiological and biochemical processes of living organisms and cells. In contrast to the essential ions, toxic ions (especially heavy ions) in aquatic ecosystems can affect the physiological and biochemical indexes and destroy the metabolism of living beings, even when just trace amounts are present. Therefore, to achieve sensitive detection of essential and toxic ions is of great significance. In addition, small molecules, which include lipids, monosaccharides, nucleosides, amino acid, neurotransmitters, and other natural products and metabolites, as well as drugs and xenobiotics, have critical roles at all levels of biological complexity.[56−60] Polymeric nanochannel-based biosensors have been developed for small molecules such as glucose,[61,62] hydrophobic biomolecules (Hoechst 33258 and Hoechst 33342),[63,64] chiral drugs,[65,66] and antibiotics.[67] Moreover, gas molecules like oxygen (O_2),[68] carbon monoxide (CO),[69,70] nitric oxide (NO),[71,72] and hydrogen sulfide (H_2S)[73,74] play vital roles in physiological and biochemical processes of living organisms and cells, and other gases like formaldehyde (HCHO),[75,76] as exogenous toxic agents, cause significant threats to the health of living organisms. Because the occlusion events of small analytes (for instance, small molecules and metal ions) cannot be observed by the resistive-pulse method, these biosensors rely on steady-state analysis approaches. Nucleic acids (including DNA and RNA) are important macromolecules found in all living cells and viruses, with the functions of storage and expression of genetic information for life.[77] Both biological and solid-state nanochannel-based sequencing and detecting of nucleic acids have been developed[78−80] into excellent single-molecule sensors in biophysics and nanobiotechnology.[36] Proteins are large, complex molecules that perform a wide array of functions with organisms and required for the structure, function, and regulation of cells, tissues, and organs in the body. Various kinds of nanochannels, such as α-hemolysin,[81] SiN,[22] and glass,[82] have been used to detect and analyze single-protein molecules.

Due to the high demand for high-performance biosensors for analysis of target analytes and the potential for development of smart sensing devices, we mainly review here the advances in bio-inspired polymeric nanochannels as sensing platforms for detection of important analytes in living organisms (Figure 1). To present the latest advances in this field, we mainly cover up-to-date research in the steady-state sensors based on polymeric nanochannels during the past 5 years. To provide the readers a more comprehensive view of the topic at hand, we also selectively cite representative literature prior to 2015. This Review is organized into four

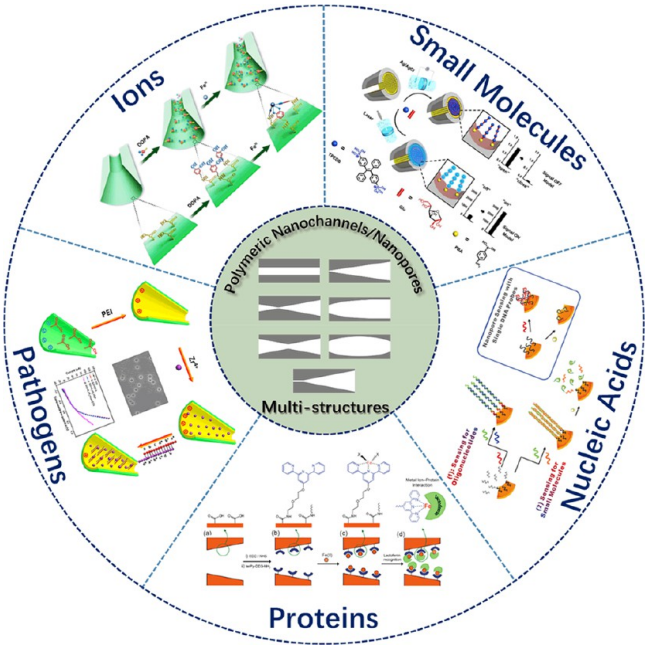

Figure 1. Schematic representation of various shapes and diverse applications in biosensors of polymeric nanochannels. Different shapes of nanochannels, including cylindrical, conical, asymmetric and symmetric hourglass, bullet, cigar, and funnel-shaped nanochannels, have been prepared by the track-etching method for polymer membranes. Diverse representative applications of polymeric nanochannel-based biosensors for related analytes in organisms, such as ions, small molecules, nucleic acids, proteins, and pathogens. Images for ions: Adapted with permission from ref 83. Copyright 2018 American Chemical Society. Images for small molecules: Adapted with permission under a Creative Commons CC-BY license from ref 84. Images for nucleic acids: Adapted with permission from ref 85. Copyright 2013 Wiley-VCH. Images for proteins: Adapted with permission from ref 54. Copyright 2011 American Chemical Society. Images for pathogens: Adapted with permission from ref 86. Copyright 2020 Elsevier.

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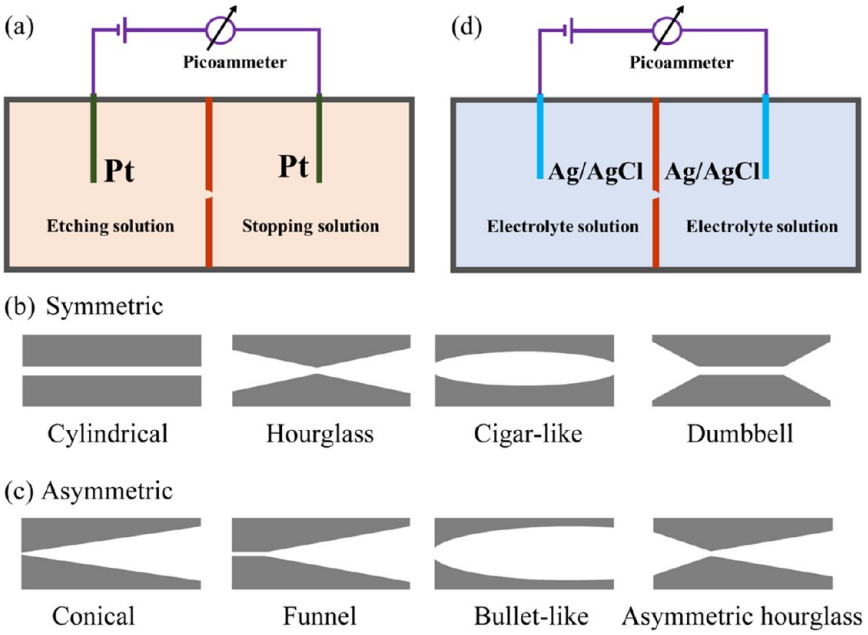

Figure 2. Polymeric nanochannels prepared by an ion track-etching technique. Scheme illustrations of the experimental setup for (a) fabrication and (d) electrical properties measurements of the polymeric nanochannels. By adjusting the etching conditions, (b) symmetrical and (c) asymmetrical geometries of polymeric nanochannels have been fabricated.

sections. First, in the preceding text, we gave a brief introduction of the polymeric nanochannels and the generic design strategy and potential applications of biosensors in living organisms. Next, we discuss the preparation techniques, the methods of functionalization, and the unique structural, chemical, and electrical properties of polymeric nanochannels that make them suitable for sensing platforms. In the third section, we mainly focus on various examples of the nanochannel-based biosensors for representative analytes in organisms, such as ions, small molecules, nucleic acids, proteins, and pathogens. Finally, we give an outlook for future challenges and perspectives on the development of polymeric nanochannel-based sensors. If not otherwise specified, all nanochannels mentioned in this Review are bio-inspired single/multiple polymeric nanochannels prepared by the ion track-etching technique.

FABRICATION, FUNCTIONALIZATION, AND PROPERTIES OF POLYMERIC NANOCHANNELS

Fabrication of Polymeric Nanochannels. According to the specific applications, various kinds of materials (e.g., biological, inorganic, organic, and composite materials) have been chosen to fabricate artificial single nanochannels and nanopores. As one of the types of materials widely used, polymeric films, including PET, PI, and PC, are selected to design different shapes of bio-inspired nanochannels by the ion track-etching technique.[52,87,88] The well-established method, which has been widely employed to produce different shapes of polymeric nanochannels, is based on the following process.[38] When a swift heavy ion passes through the polymeric membrane, it deposits energy uniformly along its trajectory, thus generating an individual damage zone, i.e., the latent track. The damaged polymeric material along the tracks can be removed more quickly than the bulk material by using the suitable etching solution, hence, developing the tracks into nanochannels. Under the appropriate conditions, channels down to a few nanometers in diameter can be prepared. Schematic representations of the electrochemical setup for fabrication and electrical properties measurements, and various geometries of the polymeric nanochannels, are shown in Figure 2. This method is a relatively simple and economical option which can accurately control the diameter and shape of the nanochannel.[89] By adjusting the etching conditions, such as etchant species, etchant concentration, etching time and temperature, and symmetrical or asymmetrical etching, various types of polymeric nanochannels could been fabricated, and the etching setup is shown in Figure 2a. Nanochannels having a symmetric geometry, including cylindrical, hourglass, cigar-like, and dumbbell structures, can be prepared by adding the same etchants in the two compartments of an electrochemical cell (Figure 2b). Alternatively, nanochannels with asymmetric shapes, such as conical, funnel, bullet-like, and asymmetric hourglass structures, can be fabricated by the asymmetrical etching method (Figure 2c).[17] The ion track-etching technique can generate negatively charged carboxyl groups on the inner channel walls, which are selective for positively charged analytes compared to negative ones.[90] Additionally, the track-etching polymer membranes are appropriate for surface functionalization, which could increase the selectivity toward certain target analytes and improve the detection efficiency.[52] This fabrication method for single nanochannels can further be used to prepare multi-nanochannels in polymeric membranes with pore density from 10^5 to 10^9 pores/cm^2,[89] which have potential applications such as drug delivery, hemodialysis, tissue regeneration, energy conversion, and biosensors.[2,91−93] The electrical conductivity, ionic current, and $I-V$ characteristics of single and multiple nanochannels are measured using Ag/AgCl electrodes in the same electrochemical setup filled with the electrolyte solution (for instance, KCl solutions of different concentrations), as shown in Figure 2d.

Functionalization of Polymeric Nanochannels. Functionalization of nanochannels can effectively respond to external stimuli and manipulate the nanofluidic transport properties, resulting in a wide range of practical applications in

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biosensors, drug delivery, environmental monitoring, filtration, and nanofluidic devices.[94−101] The biosensing capabilities of nanochannels obviously depend on the surface characteristics of the inner walls,[2] and a variety of physicochemical modification methods have been developed to achieve the expected functionality. The main methods of polymeric nanochannel functionalization can be roughly divided into the following four sorts: deposition techniques,[102−104] plasma modification,[105,106] chemical grafting in solution,[16,107−109] and self-assembly.[110−113] In particular, functionalization of nanochannels with functional molecules, such as dendrimers and peptide nucleic acids probes,[53,91] enables detection of target analytes with high selectivity and sensitivity (Figure 3). This

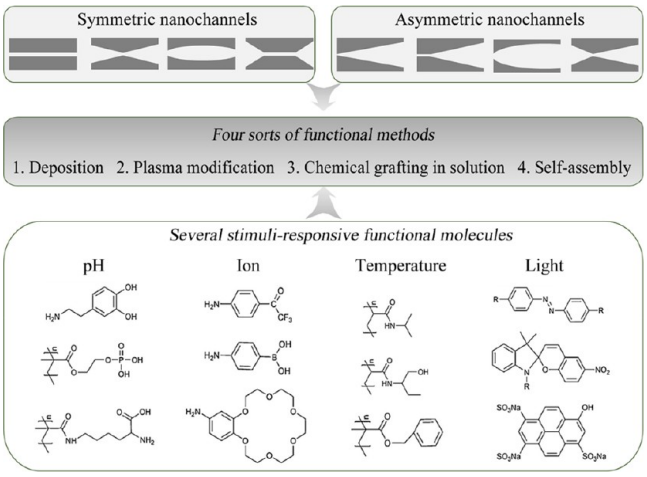

Figure 3. Physicochemical modifications of the interior surfaces of polymeric nanochannels with stimuli-responsive functional molecules. The functional approaches can be roughly divided into four sorts, namely deposition techniques, plasma modification, chemical grafting in solution, and self-assembly.

sensing principle, that is, the inner walls of nanochannels modified with functional molecules with specific recognition sites for analytes, is a steady-state analysis method.[89] The combination of functional probes and target analytes will trigger significant variations in the effective pore size, wettability, and surface charge of the pore walls, resulting in changes of the transmembrane ionic current. As a consequence, the detection of target analytes including ions, small molecules, nucleic acids, proteins, and pathogens can be achieved by measuring the current−voltage characteristics before and after addition of analytes. Actually, single nanochannel-based platforms have been also widely used as resistive-pulse sensors for detecting proteins and DNAs, that is, the target analytes driven by an applied external voltage to pass through the pores. If the analyte is large enough compared to the pore size, an obvious transient current dip can be observed, preoviding information on the target analyte.[114,115] In this Review, we mainly concentrate on polymeric nanochannel biosensors based on the steady-state analysis method. This type of sensor is primarily dependent on the change of ionic currents in an $I-V$ curve due to nanochannel blocking with a single or a few recognition events and thus shows unique detection sensitivity.[116]

Transport Properties of Polymeric Nanochannel. As is well known, functionalization of nanochannels is a widely used strategy for constructing bio-inspired stimuli-responsive nanochannels. The stimuli-responsive nanochannel has three key ion transport properties of the biological ion channels, including ionic selectivity,[117,118] ionic gating,[15,119] and ionic current rectification,[120] which make it highly desirable to be used as sensing platforms for detection of target analytes.

Ionic Selectivity. Ionic selectivity is one of the functional characteristics of biological ion channels that precisely controls the transport of ions/molecules across the cell membrane.[121] Inspired by the selectivity of biological pore proteins, artificial nanochannels with closely analogous ability to selectively transport specific ions or molecules can be constructed by modifying corresponding functional molecules on the channel inner walls.[17] As representative bionic products, however, the origin of ionic selectivity in artificial nanochannels is different from that of their biological counterparts. The ionic selectivity of solid-state channels is based on electrostatic interaction, while the selectivity in biological channels depends on fine fitting between the ions' size and the pore diameter.[122] The selectivity of ions and molecules inside the artificial nanochannels (as-prepared and functionalized nanochannels) can be classified into five types,[89] namely size-based selectivity, charge-based selectivity, wettability-based selectivity, selectivity based on multi-factor (size, charge, and wettability) collaboration, and selective recognition (Figure 4). In particular, the nanochannels modified with functional molecules, including antibodies, capture DNAs, and ligands as biosensors, specifically identify target analytes by well-designed interaction between functional probes and analytes.[53] In the following section, selective transports of ions/molecules by polymeric nanochannels, that is, bio-inspired nanochannel-based biosensing platforms for detection of ions or molecules, are reviewed in details.

Ionic Gating and Current Rectification. Ionic gating is also an important characteristic of biological ion channels, which can be opened and closed to regulate ionic conduction in response to specific external stimulus alternation.[119] Mimicking the smart gating properties of these biological structures, artificial functional nanochannels have been reconstructed to realize various responses to chemical and physical stimuli with corresponding responsive molecules, that is, single-, dual-, and multi-response ionic gates,[8,97,123−127] having potential applications in biosensing, drug delivery, and ionic circuit construction.[128] Functional molecules were immobilized on the inner walls of nanochannels to act as stimulus-driven artificial gates, which can undergo reversible conformational transitions in response to external stimuli, together with reversible changes of the effective size, the surface charge, and the wettability of the nanochannels at different states.[48,129] In recent years, many practical examples of artificial smart channel systems that exhibit pH,[16,96,105,128,130,131] temperature,[129,132] ion,[8,133,134] light,[135−137] voltage,[138,139] and magnetic[126,140] regulating ionic gating have been developed. Apart from the nanochannels demonstrating single-stimulus-activated ionic gating, nanochannels exhibiting multi-stimuli-induced ionic gating, such as light and voltage,[141] pH and light,[124] pH and temperature,[125] pH and voltage,[128] pH and salt,[142] pH and ion,[143] ion and molecule,[144] and even temperature, pH, and sugar triple-stimuli-responsive,[145] have been reported. These gating systems provide sensing platforms to recognize target analytes by regulating environmental stimulus and have potential applications for simulating the transport characteristics and gating features of specific biological ion channels.

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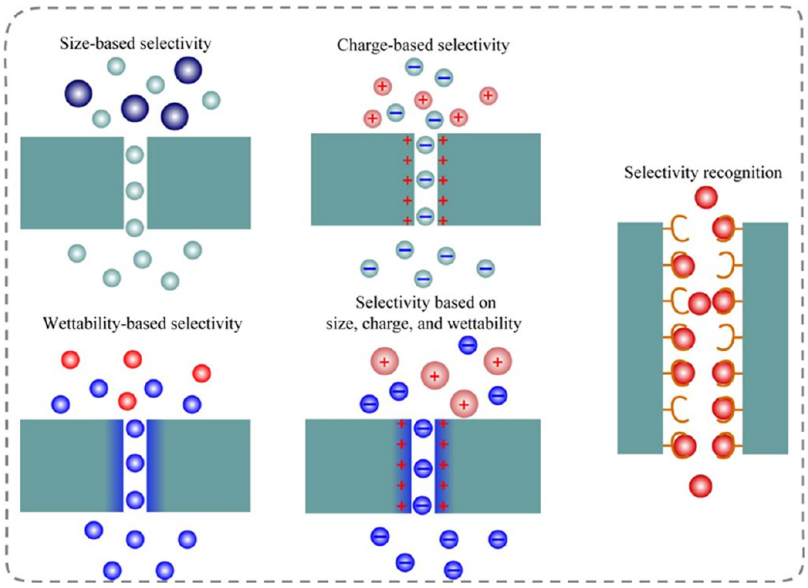

Figure 4. Schematic illustrations of the selectivity of the artificial nanochannels to ions, molecules, or particles based on the size, the charge, and the wettability. Size-based selectivity: The nanochannel only allows ions, molecules, or particles with size smaller than the diameter of the pore to pass through the membrane. Charge-based selectivity: The positively charged nanochannel allows anions or negatively charged molecules to transport through the membrane, while the negatively charged nanochannel preferentially transports cations other than anions. Wettability-based selectivity: The hydrophilic nanochannel selectively transports polar molecules, whereas hydrophobic nanochannel transports non-polar molecules faster than polar molecules. Selectivity based on size, charge, and wettability: The selectivity of the nanochannel could be enhanced by collaborating with small diameter, surface charge, and polarity. Selectivity recognition: The nanochannel functionalized with selective bonding sites has high selectivity of target analytes. Adapted with permission from ref 89. Copyright 2016 Elsevier.

Ionic current rectification, with the current recorded for one voltage polarity higher than that recorded for the same absolute value of voltage of opposite polarity, is observed as diode-like $I-V$ curves, indicating that there is a preferential direction for ionic flow.[120] Rectification is shown as high and low conductance states that approximate the "open" and "closed" conditions of electronic diodes, respectively.[1,146−148] The ionic current rectification ratio, defined as the absolute value of the quotient between the current obtained at one potential and the current obtained at the equal but opposite potential,[149,150] is used to characterize the degree of ionic rectification. Siwy has summarized several models that have been described to explain the ionic current rectification observed in artificial channel systems,[120] such as the electrostatic model based on the concepts of a rocking ratchet and an electrostatic trap,[87,151] Woermann mode,[152,153] and the quantitative model based on the Poisson and Nernst−Planck equations.[148,154,155] So far, ionic current rectifications have been achieved in the artificial nanochannels with asymmetries in the channel shapes, surface charge distributions, and external stimuli. For example, the ionic rectification behaviors were widely found in the conical,[156,157] bullet-like,[95,98] and asymmetric hourglass polymeric nanochannels,[158] showing diode-like asymmetric $I-V$ curves. Ramírez *et al.* have presented a completed theoretical study of the relationship between the asymmetric shape and the rectification properties of the single nanochannels based on the Nernst−Planck equations.[159,160] Ionic current rectification depends strongly on surface charge polarity and density, which can be regulated by pH and surface functionalization to construct nanofluidic sensors with high sensitivity and selectivity. When the surface charge polarity of single track-etched conical polymeric nanochannels changed, the channels demonstrated opposite asymmetric $I-V$ characteristics in the same electrolyte solutions,[146,161] and the level of the surface charge density of a channel also affected its ionic rectification behavior in qualitative and quantitative.[162] Additionally, external stimuli, such as pH,[163] pressure,[164] and ionic concentration gradients,[165−167] have been proved to control well the rectification properties of the asymmetric nanochannels. Apart from the asymmetrically shaped channels measured under the symmetric conditions, the symmetrically shaped nanochannels could also demonstrate ionic rectification features under the asymmetric pH stimuli.[123,168,169] Moreover, asymmetric modification of symmetric channels like cylindrical and hourglass nanochannels could also rectify ionic current as nanofluidic diodes under symmetric electrolyte conditions,[105,106,170] which provides another avenue to develop smart nanochannel systems.[171]

POLYMERIC NANOCHANNEL-BASED BIOSENSING PLATFORMS FOR DETECTION OF ANALYTES

In recent years, bio-inspired polymeric nanochannels have become powerful tools for detection of target analytes. In general, there are two major approaches to construct nanochannel-based biosensors: one is functionalizing the inner walls of nanochannels with recognition molecules for different target analytes, and the other is modifying recognition sites in channels to identify molecules.[172] The nanochannel-based sensors specifically recognize analytes through well-designed interaction between functional probes and targets, including covalent and non-covalent interactions.[53] In this section, we summarize the recent development of bio-inspired polymeric nanochannels as biosensors for detection of typical targets (ions, small molecules, nucleic acids, proteins, and pathogens) in living organisms.

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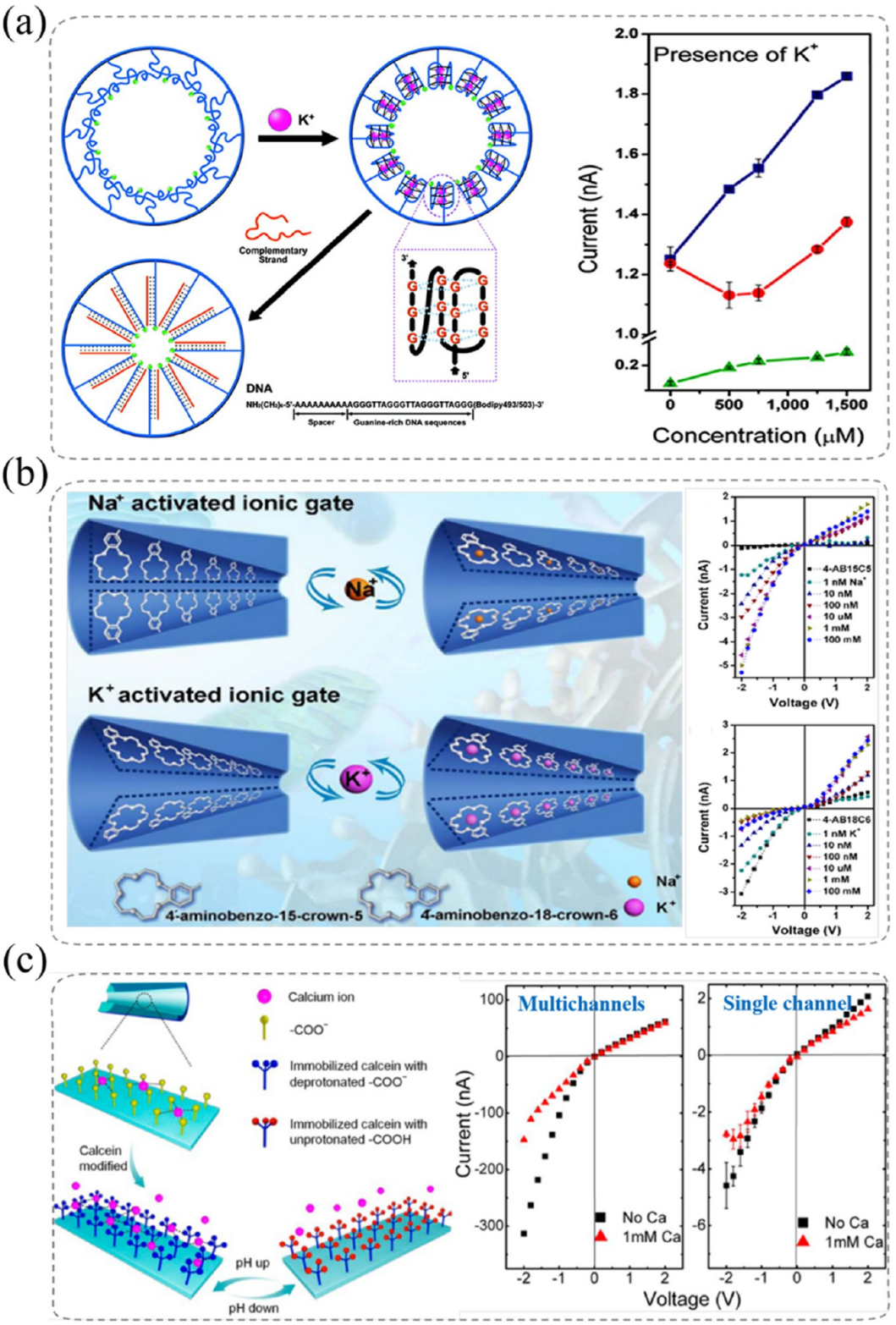

Figure 5. Polymeric nanochannel-based biosensors for detection of metal ions (cations). (a) A potassium ion (K^+) responsive nanofluidic device based on a G-quadruplex DNA-modified single conical PET nanochannel. Adapted with permission from ref 43. Copyright 2009 American Chemical Society. (b) Engineered ionic gates based on sodium and potassium activated conical PI nanochannels. Adapted with permission from ref 8. Copyright 2015 American Chemical Society. (c) Calcein-modified multi-nanochannels on PET films for calcium ions sensing. Adapted with permission from ref 182. Copyright 2014 American Chemical Society.

Detection of Ions. Numerous kinds of ions are indispensable for living systems and play crucial roles in physiological and biochemical processes of living organisms and cells. In recent years, nanochannel-based biosensors have been widely used as a promising platform to realize detection of various ions.

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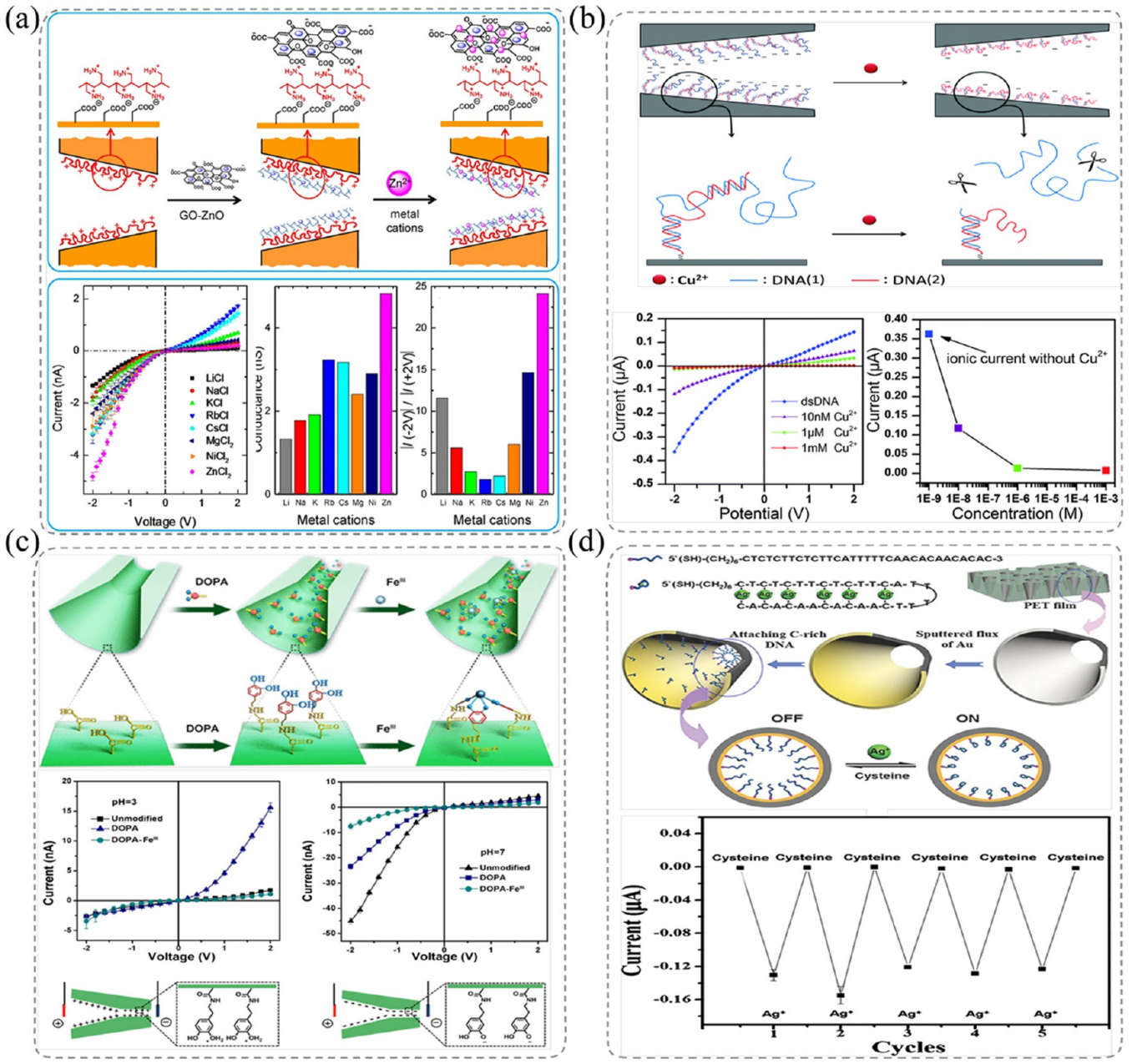

Figure 6. Polymeric nanochannel-based biosensors for detection of other metal ions. (a) A zinc ion (Zn^{2+})-sensitive bio-inspired nanofluidic device based on a single asymmetric nanochannel functionalized with a nanocomposite in PET membrane. Adapted with permission from ref 188. Copyright 2020 Elsevier. (b) An ion-gating PET conical multi-nanochannel system based on a Cu^{2+} responsive self-cleaving DNAzyme. Adapted with permission from ref 133. Copyright 2016 The Royal Society of Chemistry. (c) A platform based on funnel-shaped nanochannels for detecting trace amounts of Fe^{3+} ions. Adapted with permission from ref 83. Copyright 2018 American Chemical Society. (d) A silver ion (Ag^{+})-gated nanodevice constructed by immobilizing cytosine-rich ssDNA onto the inner surface of conical PET multi-nanochannels. Adapted with permission from ref 222. Copyright 2015 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim.

Detection of Metal Ions (Cations). Potassium (K) is crucial in modulating the activity of muscles and nerves, together with fast transfer of information by potassium ions.[173] In 2009, Jiang's group constructed a K^{+}-detection nanochannel system by grafting G-quadruplex DNA on a single PET nanochannel, and the artificial system provided a nonlinear response to K^{+} within the concentration ranging from 0 to 1500 μM (shown in Figure 5a).[43] This work can provide some meaningful guidance for the understanding of the responsive mechanism between metallic ions and channel systems, and has extensive potential in biomimetic nanofluidic devices. In 2015, Jiang *et al.* reported a dual-responsive double-gated nanodevice, that is, a bio-inspired potassium- and pH-responsive double-gated nanosystem, fabricated by immobilizing C-quadruplex and G-quadruplex DNA molecules onto the inner wall of the top and bottom tip sides of the cigar-shaped PET nanochannel, respectively.[143] In the same year, Azzaroni *et al.*[174] used single bullet-like PET nanopores decorated with crown ethers (18-crown-6 units) for developing a robust K^{+}-responsive chemical nanodevice, illustrating the potential and versatility of the integration of host−guest chemistry and asymmetric nanopores, as an essential enabler to achieve highly functional

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chemical devices for imitating the transport properties and gating functions of specific biological channels. In 2017, Wen and co-workers reported a voltage-gated ultrasensitive potassium-activated nanofluidic system by modifying the inner surface of a funnel-shaped PET nanochannel with 4′-aminobenzo-18-crown-6 molecules.[139] The crown ethers could combine with K^+ even at concentrations as low as 10^{-15} M, while the release of K^+ can be achieved by applying an external constant voltage. Sodium is the extracellular counterpart of potassium, which regulates blood pressure, blood volume and osmotic equilibrium in the body, and also fundamental for the electrical signaling in nerves.[175,176] In 2015, Wen *et al.*[8] reported biomimetic ionic gates for ion conduction based on Na^+ and K^+ activated nanochannels, which were developed by immobilizing the alkali metal cation-responsive functional molecules, that is, 4′-aminobenzo-15-crown-5 and 4′-aminobenzo-18-crown-6, respectively, onto the conical PI nanochannels. The constructed ionic gates enabled selective cation and anion conduction through the nanochannel, exhibiting great potentials in clinical medicine, biosensors and drug delivery (Figure 5b). Most recently, Ensinger's group reported an alkali metal cation-selective nanopores based on heavy ion-tracked PI membranes *via* the soft-etching (SE) technique, which selectively dissolved the latent ion tracks in the membranes by an organic solvent to form tiny pores.[177] The SE-PI nanoporous membranes could efficiently discriminate alkali cations from divalent metal cations and ammonium cations from tetraalkylammonium cations. The proposed system showed good stability and high selectivity toward target analytes, and this strategy could be used to miniaturize sensing devices for the discrimination of different analytes in biological fluids and also for energy conversion.

Calcium is the most abundant metallic element in the human body, particularly a major component of normal bones and teeth. Calcium ions (Ca^{2+}) play an essential role in the physiology and biochemistry of biological cells, for example, being involved in signal transduction pathways as a second messenger, in neurotransmitter release from neurons, and in the regulation of excitation−contraction coupling.[178−180] In 2012, Ali *et al.* presented an experimental and theoretical description of calcium binding to fixed charge groups (the covalent coupling of surface carboxylic acid moieties with 3-aminopropylphosphonic acid *via* carbodiimide coupling chemistry) confined in single conical PET nanopores and its influence on the ionic currents through a pore, and the effective Ca^{2+}-binding constant should be on the order of 10^5 M^{-1} in the proposed case.[181] In addition, Zhai's group developed a calcium-responsive nanofluidic sensing device by immobilizing calcein (2′,7′-bis[*N*,*N*-bis(carboxymethyl)-aminomethyl]fluorescein) on the channel wall, based on conical PET multi-nanochannels.[182] This sensing strategy could enhance the response of channels to Ca^{2+} and extend the responsive range. Compared to single nanochannels, calcein-modified multi-nanochannels demonstrated more significant responsiveness and higher stability of ionic current signals with an obvious reduction in variation (Figure 5c). It was found that the response of multi-channels to Ca^{2+} was a reversible process and the sensing range was $\geq 1 \times 10^{-5}$ M, covering the Ca^{2+} concentration level in the blood of human and other higher animals. Most recently, Zhai *et al.* also reported a cerium ion (Ce^{3+}) sensing device by immobilizing calcein onto the conical PET multi-channels, that is, detection of multivalent ions in an artificial calcium-responsive nanochannel (ACRN).[183] Ce^{3+} was introduced as the regulative factor, sharing several chemical properties with Ca^{2+}. The response of the ACRN to Ce^{3+} was fast and sensitive, with the sensing range of 0.001−1 mM.

The micronutrient zinc, which takes part in various enzymatic reactions, is essential for living organisms.[184] Zn^{2+} is a physiologically ubiquitous metallic ion which plays critical roles in biological systems, such as a catalytic role in hydrolysis, stabilization of small protein structural motifs, and a regulatory role among the redox-inert metal ions.[185,186] In 2010, Tian *et al.*[187] constructed a zinc-sensitive ion channel by functionalizing a single conical PET nanochannel with zinc finger peptides/proteins (Pro-Tyr-Ala-Cys-Pro-Val-Glu-Ser-Cys-Asp-Arg-Arg-Phe-Arg-Ser-Asp-Glu-Leu-Thr-Arg-His-Ile-Arg-Ile-His-Thr-Gly-Gln-Lys), which can undergo conformational changes in the absence or presence of Zn^{2+}. Based on the conformational transformation of zinc fingers, the channel system showed a highly sensitive response to Zn^{2+}. In addition, the presented system can realize excellent selectivity of Zn^{2+} detection due to specific interaction between zinc fingers and Zn^{2+}. Recently, Ali *et al.* reported a Zn^{2+}-sensitive biomimetic nanofluidic device based on a single conical PET nanochannel (pre-modified with poly(allylamine hydrochloride) (PAH) chains) functionalized with a nanocomposite (graphene oxide and zinc oxide (GO/ZnO) nanocomposite by electrostatic interactions).[188] The PAH-GO/ZnO-functionalized nanochannel demonstrated obvious changes in the current rectification when exposed to Zn^{2+} solution, and the proposed nanofluidic system exhibited more sensitive and selective toward Zn^{2+} compared to other divalent cations. This sensing strategy could provide a way to recognize a variety of metal cations by developing other nanocomposite systems in confined geometries (Figure 6a).

Copper is an essential microelement in living organisms, which plays a vital role in electron transfers in redox reactions and enzyme catalysis.[189,190] Free copper ions (Cu^{2+}) are found in human organisms with a very low concentration; however, excessive intake of copper in humans can generally lead to diseases, such as Wilson's,[191,192] Menke's, and Alzheimer's diseases.[193,194] Determination of Cu^{2+} in urine and serum can be used as a basis for a screening approach to early diagnosis and/or monitoring of diseases related to abnormal copper concentrations.[195−197] In 2016, Zhai *et al.* developed a Cu^{2+}-dependent nanochannel composite system by immobilizing a DNAzyme (DNA(1)), which can cleave into fragments with encountering Cu^{2+}, into PET conical multi-nanochannels.[133] The system was built by covalently attaching a short 26 base long oligonucleotide (DNA(2)), which was partly complementary to DNA(1) to form a double-stranded DNA (dsDNA), to the carboxyl groups on the inner surface of nanochannels for functionalizing (Figure 6b). The proposed nanodevice exhibited a gating function toward ion transport and could respond to Cu^{2+} highly selectively and sensitively at a wide concentration range from 10^{-8} to 10^{-6} M, showing potential applications in ion detection and toxicological testing. Furthermore, Tietze *et al.*[198] reported a robust nanopore-based Cu^{2+}-sensing system by crafting a fluorescent ATCUN-like peptide 5/6-FAM-Dap-*β*-Ala-His into conical PET multi-nanopores for ultrasensitive and selective detection of Cu^{2+}. The presented nanopore system enabled a selective, sensitive, and fast Cu^{2+} detection by either *I*−*V* measurements or fluorescence quenching. Compared with other current Cu^{2+} sensors, the nanodevice was significantly more robust and

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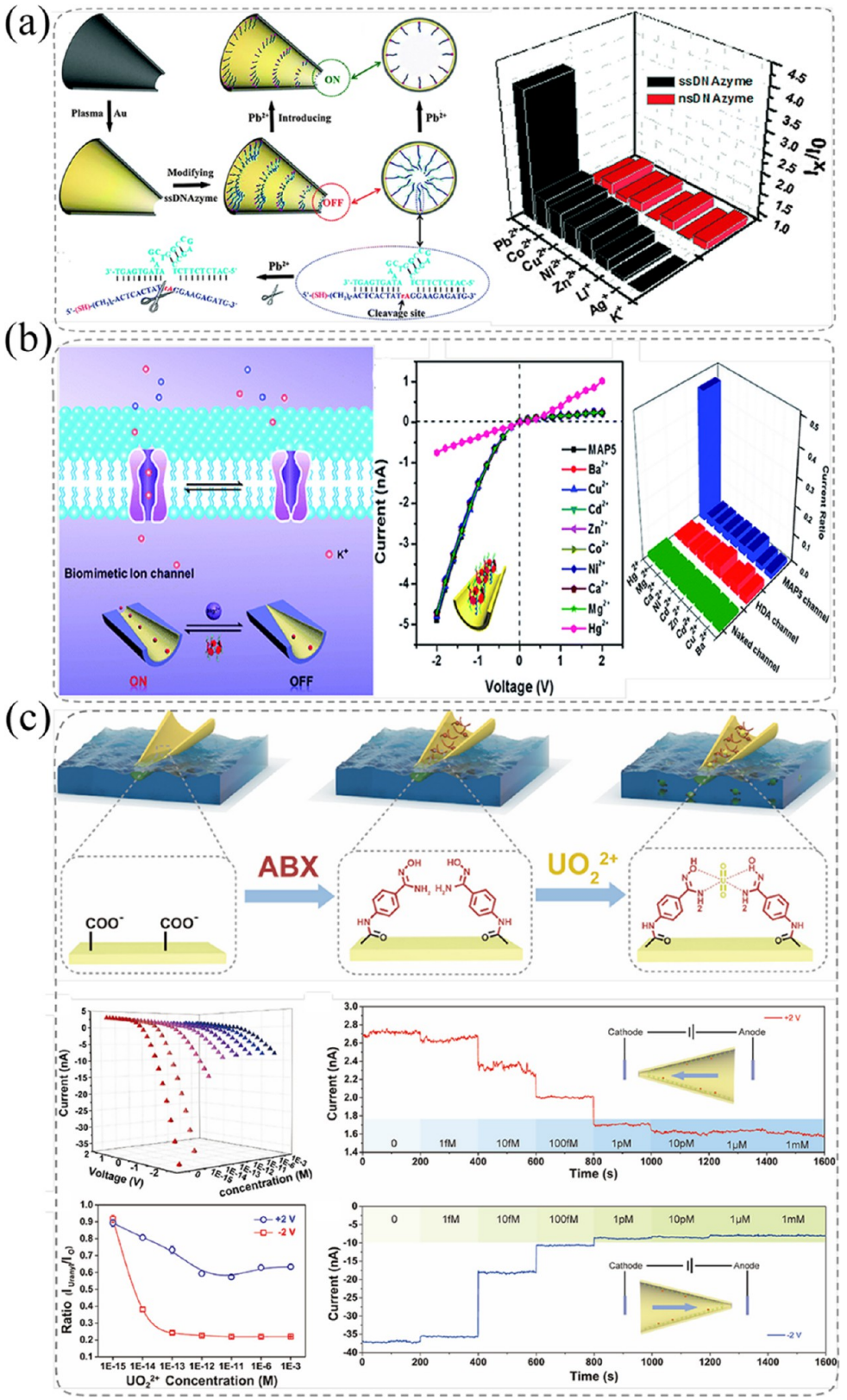

Figure 7. Polymeric nanochannel-based biosensors for detection of heavy metal ions. (a) A biomimetic smart nanodevice based on ion-track etched PET membranes showed high sensitivity and selectivity to lead ions. Adapted with permission from ref 229. Copyright 2015 The Royal Society of Chemistry. (b) A biomimetic tunable mercury(II)-gated nanochannel was developed by immobilizing MAP5 on an HDA-functionalized single conical PET nanochannel. Adapted with permission under a Creative Commons CC-BY license from ref 253. (c) A single conical PI nanochannel modified by 4-aminobenzamidoxime (ABX) for monitoring ultra-trace uranyl ions. Adapted with permission from ref 262. Copyright 2020 American Chemical Society.

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sensitive.[199,200] This sensing strategy could be developed for practical applications in on-bed diagnosis and monitoring Cu^{2+} levels in patients with copper dyshomeostasis.

Iron is an important trace element for fundamental metabolic processes in cells and organisms, particularly participating in synthesizing a series of enzymes relating to oxygen uptake, oxygen metabolism, and electron transfer.[201−203] Regular circulation of iron ions (Fe^{3+}) is a vital indicator of human health, and therefore efficient and sensitive detection of Fe^{3+} has been of wide concern for scholars.[204−210] These existing approaches have achieved the sensitive detection and even specific recognition of Fe^{3+}; however, they are generally costly or restrict the detection limits. In 2018, Wen *et al.*[83] reported a high-sensitivity, economic, and recyclable Fe^{3+} detection method by immobilizing dopamine (DOPA) into funnel-shaped PET nanochannels (Figure 6c). The funnel-shaped channel applied in this work with an extended critical section could enhance the ultrasensitive sensing ability,[211] and the proposed system realized the ultratrace Fe^{3+} detection with a concentration of 10^{-3} nM. This sensing platform could be well developed for practical applications in high-sensitivity ion detection fields, such as biological toxicity testing and water quality monitoring.

Silver is a type of precious metal that has many applications for human beings in daily life, such as jewelry, electronics, photography, and pharmacy.[212] Meanwhile, silver ions are greatly toxic to virus, bacteria, fungi, and algae, and such antibacterial activity of silver ions (Ag^{+}) has been widely applied in many application fields, such as toiletries, food, and medical materials.[213,214] A high concentration of Ag^{+}, however, may cause harmful effects to human health and the environment.[215] It is of great importance to sensitively and specifically detect Ag^{+} in environmental, biomedical, food, and other related fields. In recent years, numerous analytical strategies, including inductively coupled plasma mass spectrometry (ICP-MS),[216] electrochemical,[217,218] fluorescence,[219−221] *etc.* have been conventionally employed and well developed for sensing trace levels of Ag^{+} in aqueous solution. In 2015, Wen and co-workers[222] successfully built a bio-inspired Ag^{+}-gated nanodevice by immobilizing cytosine-rich single-stranded DNA (ssDNA) onto the inner surface of conical PET multi-nanochannels, which were sputtered with gold before modification with cytosine-rich ssDNA (Figure 6d). The thiol-terminated cytosine-rich ssDNA, which can bond Ag^{+} to form strong and stable C-Ag^{+}-C complexes,[223] was covalently attached onto the gold surfaces by Au-thiol chemistry. When Ag^{+} was added into the nanochannels, the cytosine-rich ssDNA changed from stretched structure to stable hairpin-like structure by forming C-Ag^{+}-C complexes, which resulted in increasing the effective pore size and high ionic current. The introduction of cysteine into the Ag^{+} bonding system, however, would pull Ag^{+} out from the C-Ag^{+}-C complexes, which led to the hairpin-like cytosine-rich ssDNA changed into random single-stranded structure, together with low ionic current. The proposed nanodevice appears highly selective and sensitive to Ag^{+} and has a good reversibility in cycles, showing potential application in sensing, pharmaceuticals, and sterilization fields.

Lead is a highly toxic metal affecting many organs and tissues of the human body, and Pb toxicity is a particularly insidious hazard with the potential to cause irreversible health effects, such as blood disorders and damage to the nervous system.[224−226] Infants and children are especially sensitive to even low levels of lead, which can severely affect mental and physical development.[227,228] Therefore, detection of lead ions (Pb^{2+}) is very important and highly desirable in clinical diagnosis and treatment. In 2015, Wen *et al.* developed a biomimetic smart nanodevice by modifying Pb^{2+} responsive DNAzymes onto the inner walls of the ion-track-etched conical PET multi-nanochannels, which showed high sensitivity and selectivity only to Pb^{2+} (Figure 7a).[229] The mechanism for this sensor is based on the conformational transition of DNAzymes in the presence or absence of Pb^{2+}, and the system exhibited an excellent Pb^{2+} sensing capability *via* the transformation from double-stranded portions to short single strands. This sensing strategy can provide a powerful platform for targeted ion response and smart gating, especially for specific toxic ion removal.

Mercury, present in a variety of different forms (including metallic, inorganic, and organic), is well known as a widespread bio-accumulative pollutant, and ionic mercury (Hg^{2+}) is a neurotoxin that can lead to serious damage to nervous tissues and organs, and also causes toxicity *in vivo*.[226,230−232] Consequently, it is of great importance to develop highly sensitive and selective biosensors for Hg^{2+} detection in environmental monitoring, food safety, and clinical therapy. So far, various methods for detecting Hg^{2+} have been reported, such as fluorescence sensors,[233−237] colorimetric sensors,[238−241] surface-enhanced Raman scattering,[242−245] and electrochemical sensors.[246−250] In 2013, Tian *et al.* developed a biomimetic Hg^{2+}-gated nanochannel by functionalizing thymine-rich ssDNA onto the inner surface of a single conical PI nanochannel, and the ssDNA bonded with Hg^{+} to form strong and stable T-Hg^{+}-T complexes.[251] The principle of this device was that the thymine-rich ssDNA would undergo conformational changes in the presence and absence of Hg^{2+}, and the sensor showed high sensitivity with a detection limit of 8 nM and high selectivity toward Hg^{2+}. In 2014, Wang and co-workers designed a Hg^{2+}-selective sensing platform based on a single conical PET nanopore in combination with single-walled carbon nanotubes (SWNTs).[252] The nanopore was modified with polyethylenimine (PEI) and Zr^{4+}, which can specially recognize Hg^{2+} in the presence of thymine-rich ssDNA with the assistance of SWNTs. The proposed sensor exhibited excellent sensitivity with a detection limit of 8.3 nM and high selectivity toward Hg^{2+}. Moreover, Li's group[253] reported a biomimetic tunable Hg^{2+}-gated nanochannel by immobilizing mercaptoacetic acid−pillar[5]arene (MAP5) on a 1,6-hexanediamine (HDA)-functionalized single conical PET nanochannel. By virtue of host−guest binding and release, MAP5 can assemble into the inner wall of the guest molecules-modified nanochannel, and Hg^{2+} can remove MAP5 from the host−guest complex, along with the changes of the surface charge and wettability of the nanochannel (Figure 7b). This device was demonstrated to be highly selective and sensitive to Hg^{2+} over other metal ions, with a detection limit of 1 nM, which could be developed for practical applications in biosensors and toxicological testing for Hg^{2+}.

Chromium(III) ion (Cr^{3+}) is a well-known mutagen and carcinogen which can damage DNA and induce a change in the cellular structure and components.[254] The conventional detection methods, such as atomic absorption, electrochemistry, and colorimetric, are always tedious and time-consuming, impeding their widespread usage in field analysis and diagnosis. In 2015, Wang's group reported a conical PET nanopore-based method to detect Cr^{3+} without functionaliza-

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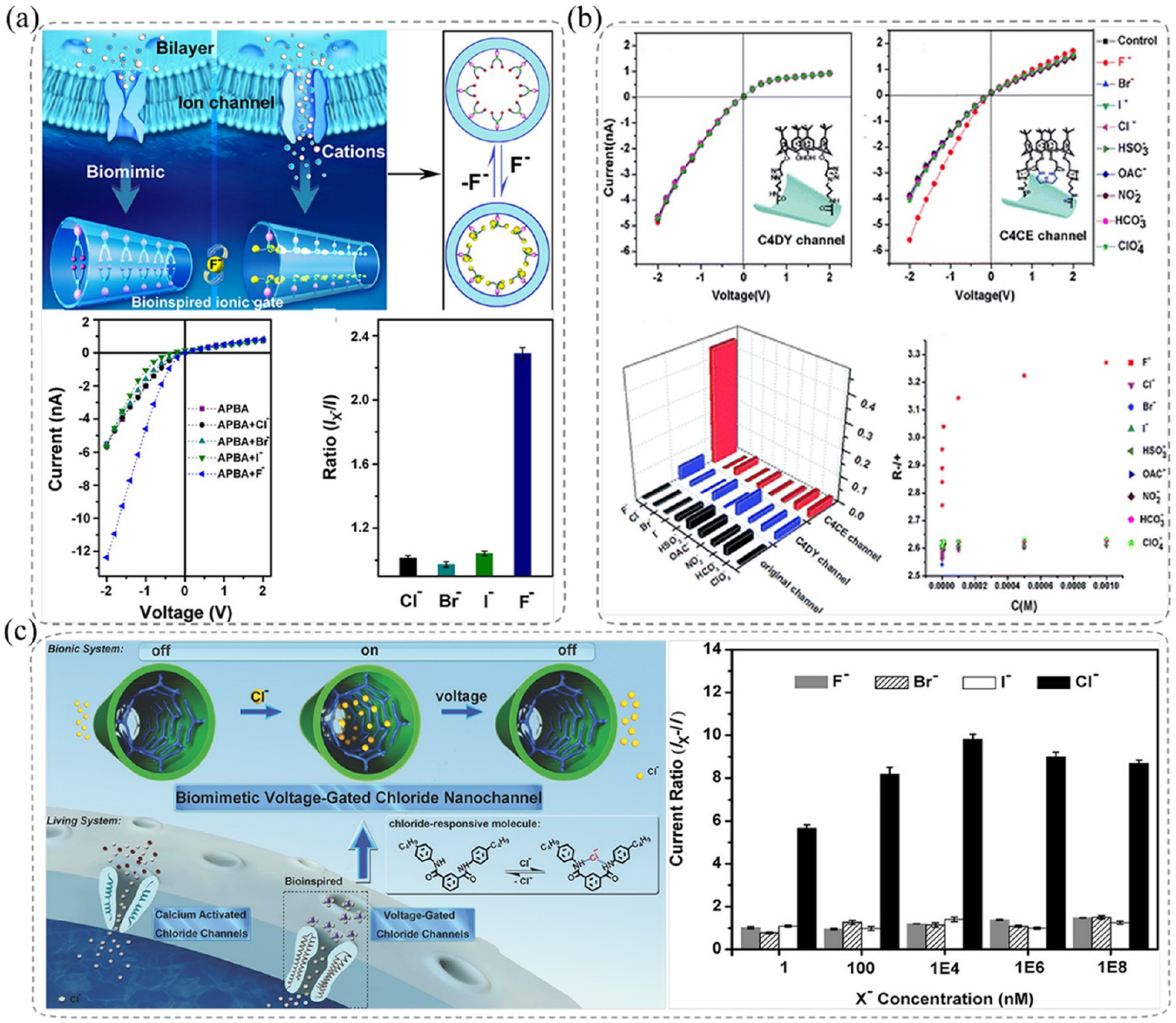

Figure 8. Polymeric nanochannel-based biosensors for detection of halide ions. (a) A fluoride-driven ionic gate based on a single conical PI nanochannel functionalized with 4-aminophenylboronic acid. Adapted with permission from ref 7. Copyright 2014 American Chemical Society. (b) A F^--responsive nanodevice designed based on a single conical PI nanochannel modified with C4CE by a click reaction. Adapted with permission under a Creative Commons CC-BY license from ref 267. (c) A biomimetic voltage-gated chloride nanochannel based on a single conical PI nanochannel modified with chloride-responsive molecules. Adapted with permission from ref 138. Copyright 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

tion of the internal surface of the channel.[255] A strong chelator, EDTA, was added to the solution to efficiently eliminate interference from other metal ions, and the detection of Cr^{3+} could be achieved while avoiding the tedious modification of functional groups. The presented sensor showed a high sensitivity, with a detection limit of 16 nM and significant specificity toward Cr^{3+}. Compared with the traditional detection methods, this proposed sensing strategy for easy regeneration of the nanopore surface allows elimination of the tedious functionalization steps, which can be developed universally in combination with a chelator specific for the detection of the desired metal ions.

Uranium is a heavy metal commonly used in the nuclear industry and for military applications, and the chemical toxicity of U can acutely damage human organs.[256−258] In air, U oxidizes easily and becomes coated with a layer of oxide; thus, it mainly occurs in oxidized form, such as uranite and pitchblende, in nature.[259] Among the different ionic forms of oxidation states of uranium, uranyl ion (UO_2^{2+}) is the most stable form in aqueous solutions, which can lead to adverse impacts on human health.[260,261] Most recently, Wen and co-workers reported a smart detection platform for ultrasensitive sensing of UO_2^{2+} by functionalizing a single conical PI nanochannel with 4-aminobenzamidoxime (ABX) (Figure 7c).[262] When the modified nanochannel comes into contact with UO_2^{2+} aqueous solution, the uranyl cation is adsorbed to the pore wall quickly, which changes the surface charge and wettability of the channel. The principle of this device was dependent on the coordination effect of specific adsorption and nanoscale domain, which made the nanochannel ultrasensitive to the incredibly small variation of UO_2^{2+} concentration, and thus displayed as the transmembrane

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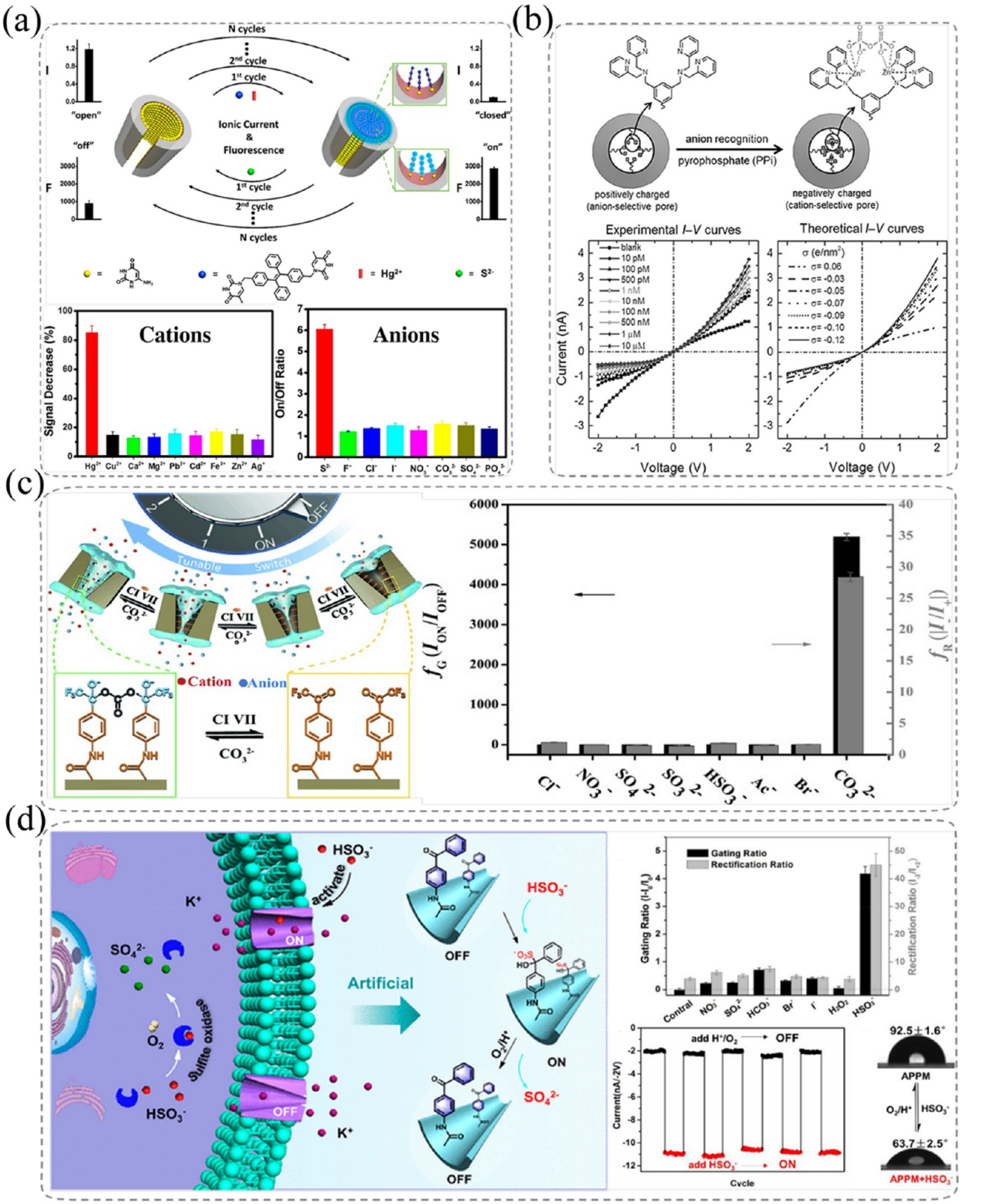

Figure 9. Polymeric nanochannel-based biosensors for detection of other anions. (a) A highly robust cylindrical PET multi-nanopores-based dual-signal-output ion detection system for Hg^{+} and S^{2-}. Adapted with permission from ref 277. Copyright 2016 American Chemical Society. (b) A nanofluidic sensing device for label-free detection of pyrophosphate (PPi) based on a single conical PET nanopore functionalized with bis(Zn^{2+}-DPA) complexes. Adapted with permission from ref 289. Copyright 2016 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim. (c) A bio-inspired switchable and tunable nanofluidic diode for detection of carbonate ions (CO_3^{2-}) based on a single conical PI nanochannel functionalized with APTE molecules. Adapted with permission from ref 298. Copyright 2015 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim. (d) A smart nanofluidic biosensor made through a reversible covalent bond strategy for high-efficiency HSO_3^{-} sensing and removal based on a single conical PET nanochannel. Adapted with permission from ref 316. Copyright 2020 American Chemical Society.

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current change measured by a picoammeter. The presented device exhibited ultra-sensitivity, with a detection limit of 1 fM and UO_2^{2+} removal property, providing a promising strategy for handing radioactive contamination of water.

Detection of Anions. Similar to cations, anions also play important roles in physiological and biochemical processes of living organisms and cells. In recent years, sensing strategies for anions based on bio-inspired polymeric nanochannels have been also well developed. Fluorine is one of the required trace elements in the human body, and fluoride ions (F^-) are utterly important to human beings' health because of their duplicitous nature.[263,264] Appropriate levels of fluorine can increase hardness of bones and give strength to the enamel tissues of the teeth, thus playing a role in the prevention and treatment of senior osteoporosis and dental caries.[55,265] Excessive intake of F^-, however, can cause a number of problems, such as teeth and bone deformities.[266] Therefore, sensitive and specific detection of F^- is very meaningful and highly desirable in clinical therapy. In 2014, Jiang's group[7] developed a fluoride-sensing system based on a single conical PI nanochannel, which was functionalized with a fluoride-responsive molecule, 4-aminophenylboronic acid (Figure 8a). The boron bound F^-, and thus the surface charge and wettability of the nanochannel changed in the presence of fluoride, resulting in a change of the transmembrane current. This device demonstrated high sensitivity and specific selectivity to F^- rather than other halogen ions and also showed excellent responsive switchability and stability. In the following year, Li *et al.* reported a fluoride-responsive nanodevice based on a single conical PI nanochannel modified with 1,3-dipropargylaza-*p*-*tert*-butyl calix[4]crown (C4CE) by a click reaction.[267] The mechanism for this sensor is based on N−H···F hydrogen-bonding interactions between the receptor C4CE and F^-. The C4CE channel displayed an obvious increase in the ionic current to F^- rather than other anions such as Cl^-, Br^-, and I^-, indicating a highly selective recognition of fluoride ions even in the presence of various interfering ions and serum samples (Figure 8b). The presented device also showed the useful property of recyclability on removal of F^- by Ca^{2+}. This proposed strategy could be developed for practical applications of sensing and real-time monitoring in the environment and living organisms.

Chloride ion (Cl^-) is the major anion in the human body which can maintain electrolyte homeostasis in both intracellular and extracellular compartments of the organism.[268,269] Consequently, monitoring of Cl^- in clinical diagnosis is needed and very important. For example, the level of Cl^- detected in sweat is a recognized biomarker for the genetic disorder cystic fibrosis.[270] In 2016, Wen and co-workers[138] developed a Cl^- sensing system based on a single conical PI nanochannel modified by 5-aminoisophthalic acid (AIPA) and 4-butylbenzenamine (BBA). The chloride-responsive molecules worked as probes for specific recognition of Cl^-. When the (AIPA-BBA)-modified nanochannel was driven by changes in voltage, surface charge and wettability changed accordingly, achieving the "on" and "off" states (Figure 8c). The proposed nanochannel displayed high sensitivity and good selectivity toward Cl^-, and this sensing strategy could be developed for practical applications in nanofluidic devices and biosensors.

Sulfide ion (S^{2-}) is widely used in industry and is also produced in biological systems.[271,272] However, S^{2-} is highly toxic and hazardous to human health, causing, for example, neurological damage, unconsciousness, and respiratory paralysis.[273,274] Meanwhile, the released S^{2-} can also readily convert into harmful H_2S at physiological pH in the living system, causing conjunctivitis and other related eye diseases.[275,276] Thus, developing efficient sensors for the detection of S^{2-} is very meaningful and desired. In 2016, Lou *et al.* reported a dual-signal-output (fluorescence and ion current signal) nanopore system based on cylindrical PET multi-nanopores modified with 6-aminouracil.[277] The principle of this system is dependent on the reversible plug−unplug processes, that is, Hg^{2+} inducing the plugged nanopores and S^{2-} inducing the unplugged nanopores. The proposed nanopore-detection system demonstrated high selectivity to Hg^{2+} and specific recognition of S^{2-} rather than other anions such as F^-, Cl^-, and I^- (Figure 9a).

Pyrophosphate (PPi) anion, which is a small, negatively charged analyte ($P_2O_7^{4-}$) produced in living organisms as the hydrolysis product of adenosine triphosphate (ATP), plays a vital role in a range of bio-energetic and metabolic processes.[278,279] PPi excess and deficiency in biological systems causes the calcium pyrophosphate deposition disease, correlated to calcium pyrophosphate dehydrate disease, and the deposition of calcium in arteries, respectively.[280] The monitoring and specific recognition of PPi is therefore of great importance in cancer and various disease research fields.[281] So far, a variety of analytical methods, such as fluorescent and colorimetric chemosensors,[282−285] electronic biosensors,[278,286,287] and surface plasmon resonance sensors,[280,288] have been developed for detection of PPi analyte. In 2016, Ali *et al.*[289] reported a nanofluidic sensing device for label-free detection of PPi anions based on a single conical PET nanopore functionalized with the complexation of two di(2-picolyl)amine (DPA) moieties with Zn^{2+}. The bis(Zn^{2+}-DPA) complexes were immobilized on the inner walls of the nanochannel, which served as recognition sites for PPi anions (Figure 9b). The proposed device showed high sensitivity with a detection limit of picomolar concentrations and specificity to PPi rather than other phosphate anions, such as HPO_4^{2-} and $H_2PO_4^-$. The presented sensing strategy could be developed for detecting anions and monitoring biological important reactions.

Biomineralization is a naturally occurring process which produces minerals in living organisms.[290,291] As a typical example, carbonate-based biominerals are the most abundant biogenic minerals found in freshwater and marine organisms and in natural hard tissues such as bones and teeth.[292−294] Carbonate plays a vital role in buffering action in human blood and seawater,[295] and $CaCO_3$ is also used as an antacid, calcium supplement in human medicine, and food additive in the food industry.[296] However, improper use of carbonates can lead to severe negative impacts on human health. For example, as a typical adulterant found in milk, carbonate may cause disruption in hormone signaling that regulates development and reproduction.[297] Detection of the carbonate ion (CO_3^{2-}) is of great importance in clinical diagnosis. In 2015, Wen *et al.* developed a bio-inspired switchable and tunable nanofluidic diode for sensing CO_3^{2-} based on a single conical PI nanochannel functionalized with hydrophobic 1-(4-aminophenyl)-2,2,2-trifluoroethanone (APTE) molecules (Figure 9c).[298] Carbonate operated as a trigger and regulator for the proposed device by specifically reacting with APTE. When a carbonate solution was added, the modified APTE molecules bound CO_3^{2-} and thus influenced the ion transport through the nanochannel.[299,300] After the addition of carbonate ionophore VII (CI VII) into this system, however, the

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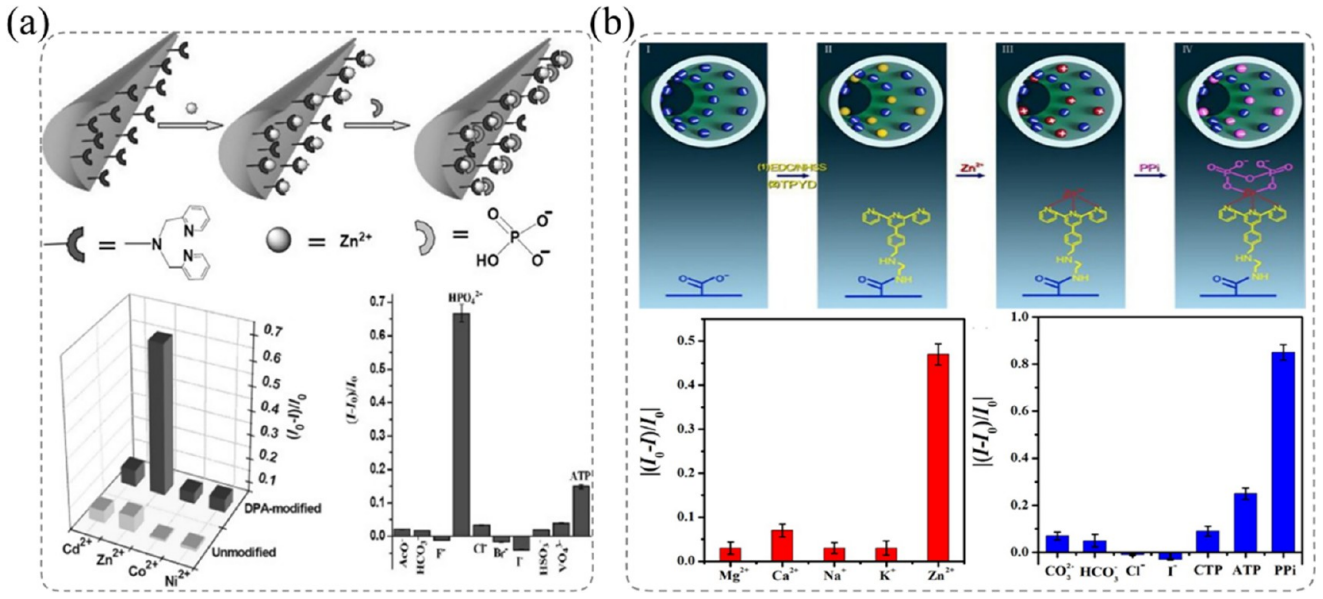

Figure 10. Polymeric nanochannel-based HSSSs for detection of multiple analytes. (a) A highly selective sequential sensor for Zn^{2+} and phosphate ions (HPO_4^{2-}) by covalently immobilizing DPA in track-etched conical PET multi-nanochannels. Adapted with permission from ref 323. Copyright 2013 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim. (b) A highly selective sequential recognition system for Zn^{2+} and pyrophosphate ions ($P_2O_7^{4-}$, PPi) by covalently functionalizing a single conical PET nanochannel with TPYD molecules. Adapted with permission from ref 324. Copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

bound CO_3^{2-} ions were removed,[301] and the device switched from the "on" to the "off" state. The presented nanodevice exhibited high sensitivity and excellent selectivity for carbonate ions, and the sensing strategy could be developed for practical applications in carbonate and carbon dioxide detection.

Bisulfite (HSO_3^-) anions have been widely used as crucial preservatives for foods, beverages, and pharmaceutical products due to their antimicrobial, bacteriostasis, and antioxidant properties.[302−304] However, extensive intake of HSO_3^- would induce detrimental effects to human health, triggering asthma and other allergic reactions in some individuals.[305] Consequently, the detection of HSO_3^- is of great significance and required in both food samples and biological system. Up to now, many detection methods, such as fluorescent probes and chromatometry,[306−315] have been utilized to determine HSO_3^- in living cells and in food samples. However, fluorescence techniques have limits such as low signal-to-noise ratio, false-positive (background) signals, and difficulty in labeling probes; the preparation of nanoparticles, complicated sample pretreatment, and low sensitivity of colorimetric sensors still restrict their applications. Therefore, the development of simple, convenient, and effective sensing platforms for HSO_3^- detection, such as nanochannel-based sensors, is needed. In 2020, Sun *et al.* reported a smart nanofluidic biosensor for high-efficiency bisulfite sensing and removal based on a single conical PET nanochannel modified with (4-aminophenyl)phenylmethanone (APPM).[316] The mechanism for this sensor is based on a reversible covalent bond strategy between APPM and bisulfite anions, and the proposed system displayed sensitivity with a detection limit of 1 μM and high selectivity to HSO_3^- rather than other anions (Figure 9d). Additionally, this biosensor demonstrated excellent reversibility and stability as well as high efficiency in removing excess HSO_3^- from L02 cells. This sensing strategy could be developed for practical biological applications of detection and removal of endogenous toxins.

Detection of Multiple Analytes. As previously described, many highly selective single-target chemosensors have been designed and reported in the past decades. Compared with the rapid development of single-target-responsive sensors, multifunctional chemosensors for two or more analytes with different responsive signals remain relatively rare, but they could simplify the detection of various environmental and biological analytes.[281,317−321]

There are two main strategies to realize the detection of multiple analytes. One is the combination of multiple binding site(s) and signal reporter(s),[322] and the other is the construction of ensembles based on various weak and noncovalent interactions.[271] The design of multi-functional chemosensors, such as highly selective sequential sensors (HSSSs), however, is a real challenge and highly required for multiple analytes. In 2013, Li's group constructed a biomimetic ion-responsive channel system by covalently immobilizing a metal-chelating ligand, 2,2′-dipicolylamine (DPA), in track-etched conical PET multi-nanochannels (Figure 10a).[323] The DPA-modified nanochannels showed specific recognition of Zn^{2+} over other metal ions, and the Zn^{2+}-chelated channels can be used as secondary sensors for detecting HPO_4^{2-} anions. The proposed sensing devices demonstrated significant specificity and high sensitivity, and this sensing strategy could be expanded for practical applications in disease-related molecular targets. Subsequently, Wen *et al.*[324] reported a highly selective sequential recognition system for Zn^{2+} and pyrophosphate ions ($P_2O_7^{4-}$, PPi) by covalently functionalizing a single conical PET nanochannel with *N*′-(4-((2,2′:6′,2″-terpyridin)-4-yl)benzy)ethane-1,2-diamine (TPYD) molecules (Figure 10b). The proposed sensor is based on the principle that the immobilized TPYD molecules used as a specific coordination site for Zn^{2+} to form strong and stable TPYD-Zn^{2+} complexes over other metal ions, and the complexes subsequently served as recognition elements to capture PPi by the coordination reaction between hydroxyl oxygen atoms of

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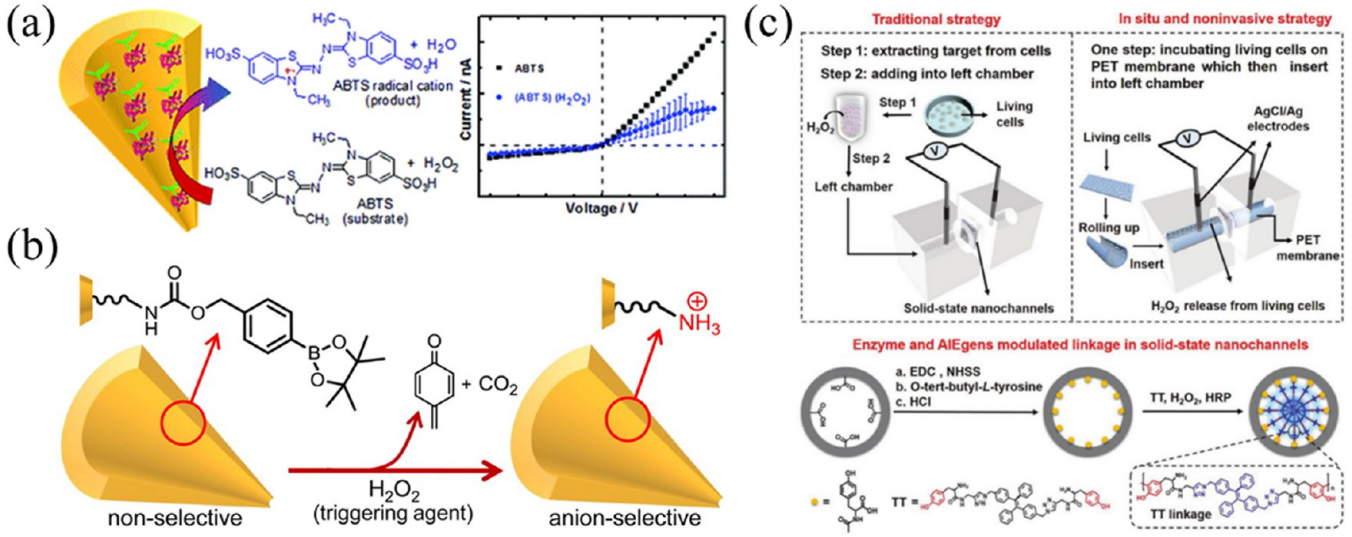

Figure 11. Polymeric nanochannel-based biosensors for the detection of hydrogen peroxide. (a) A biosensor for H_2O_2 detection based on a single conical PET nanochannel decorated with HRP enzyme. Adapted with permission from ref 329. Copyright 2011 American Chemical Society. (b) A sensing nanofluidic device for H_2O_2 detection based on conical PET nanopores modified with BEC-NH_2 moieties. Adapted with permission from ref 330. Copyright 2015 American Chemical Society. (c) *In situ* and noninvasive monitoring of H_2O_2 released from living cells based on cylindrical PET multi-nanochannels functionalized with phenolic hydroxyl groups (capture probes, using HRP and TT assistant oligomerization reaction). Adapted with permission from ref 332. Copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

pyrophosphate and Zn^{2+}. The presented device showed a good selectivity for Zn^{2+} and PPi, and can be used for recognizing multiple analytes by immobilizing different functional molecules, with potential applications in the fields of healthcare and the environment.

Detection of Small Molecules. Small molecules have a low molecular weight (lower than 900 Da), including inorganic and organic molecules, such as lipids, monosaccharides, second messengers, other natural products, and drugs.[50] Specifically, small molecules have vital roles at all levels of biological complexity, possessing clinical and commercial applications.[56,59] Some traditional detection methods, such as spectroscopic and colorimetric techniques,[325−327] are usually employed for small molecules recognition. However, these methods are considered to be tedious and expensive. As one of the promising alternatives, bio-inspired polymeric nanochannel-based biosensors for small molecules have generated considerable interests in recent years. In this section, we summarize the recent development of polymeric nanochannels as biosensors for detection of inorganic and organic small molecules in living organisms.

Detection of Inorganic Molecules. Hydrogen peroxide (H_2O_2), which is not only a toxic byproduct of the cellular metabolism but also a messenger in cellular redox signaling pathways and an agent significant for medical diagnostics.[328] In the past years, H_2O_2-sensitive sensors have been developed based on artificial polymeric nanochannels.

In 2011, Ali *et al.* described a sensing platform for the detection of H_2O_2 based on a single conical PET nanochannel functionalized with the horseradish peroxidase (HRP) enzyme (Figure 11a).[329] This small molecule can be detected *via* a redox reaction occurring in the presence of the 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) substrate and different concentrations of hydrogen peroxide, and the proposed sensor showed high sensitivity with a detection level of ∼10 nM. Moreover, Ali's group also reported a H_2O_2-sensitive nanofluidic device based on the surface functionalization of conical PET nanopores with amine-terminated boronic ester carbamate (BEC-NH_2) moieties (Figure 11b).[330] The changes observed in the *I*−*V* curves can be related with the presence of H_2O_2 in the external solution and thus monitoring it from electronic readouts. In 2016, Zhai *et al.*[331] produced another H_2O_2-responsive nanosystem by the modification of cytochrome C molecules onto the inner surface of cylindrical PET multi-nanochannels. The principle for this sensor was dependent on the mechanisms of redox reaction in biology. The device showed a switchable "on−off" function controlled by redox reaction, demonstrating good reversibility and stability. This sensing platform could be well developed for practical applications in H_2O_2 trace detection, energy conversion, and environmental field.

Furthermore, Xia *et al.*[332] reported a promising strategy to monitor H_2O_2 released from living cells, which was based on functionalized cylindrical PET multi-nanochannels with phenolic hydroxyl groups (Figure 11c). The combination of aggregation-induced emission luminogens and enzyme-responsive linkage properties in the modified nanochannels achieved *in situ* and non-invasive detection of H_2O_2, exhibiting high sensitivity and selectivity. The designed dual-signal-output (ionic current and fluorescence) sensing device can provide an available strategy for *in situ* and non-invasive detection of biological molecules *in vivo* and *in vitro*.

Besides the detection of H_2O_2, many inorganic gases artificial responsive polymeric nanochannels have also been designed and constructed. As is well known, carbon dioxide (CO_2) is one of the most important environmental stimulus and sensory cues that regulates living organisms' behaviors.[333,334] For example, mosquitoes can utilize odorant-gated ion channels in the olfactory sensory neurons (OSNs) to navigate the location of their hosts by detecting CO_2.[335,336] Actually, a population of OSNs is considered to be specialized and sensitive for CO_2 recognition.[337,338] Inspired from the

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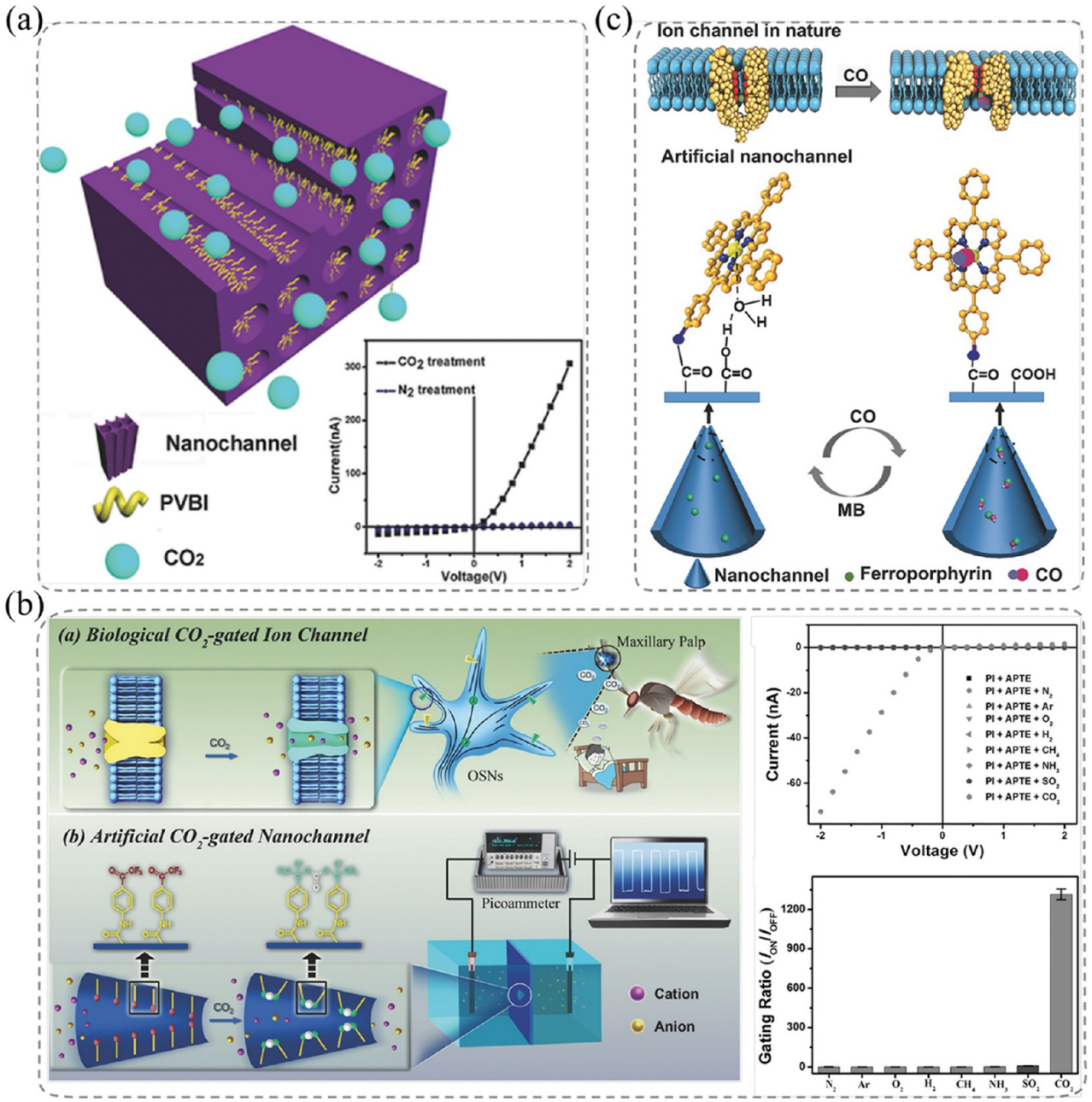

Figure 12. Polymeric nanochannel-based biosensors for the detection of inorganic gases. (a) A CO_2-responsive nanofluidic diode by modifying PVBI molecules onto the inner surface of conical PET multi-nanochannels. Adapted with permission from ref 339. Copyright 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) An OSNs-mimetic CO_2-responsive ionic gate based on a single conical PI nanochannel functionalized with APTE molecules. Adapted with permission from ref 340. Copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (c) A CO-gated nanodevice by grafting ferroporphyrin onto the inner surface of conical PET multi-nanochannels. Adapted with permission from ref 351. Copyright 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

CO_2-activated channels in nature, OSNs-mimetic CO_2-responsive artificial polymeric nanochannels have been produced in recent years. In 2015, Zhai's group[339] designed an OSNs-mimetic CO_2-activated nanofluidic diode by grafting poly[1-(4-vinylbenzyl)-1*H*-imidazole] (PVBI) molecules on the inner walls of conical PET multi-nanochannels. This proposed system showed the on/off switching function with bubbling CO_2 and N_2 alternatively, demonstrating high ion rectification ratio and high ion gating ratio (Figure 12a). The presented nanodevice exhibited the characters of reversibility and fast response rate, similar to the biological counterpart in the cell membranes of OSNs. This sensing strategy could be developed for practical applications in gas sensors, energy harvesting, and environmental fields. In addition, Wen *et al.*[340] also reported an OSNs-mimetic CO_2-activated nanogate by modifying CO_2-responsive APTE molecules on the inner walls of a single conical PI nanochannel. The APTE-modified nanochannel, with stability and selectivity, showed on/off switching property and excellent gating performance (Figure 12b). The proposed nanodevice could be used in CO_2-related sensing, gating, and nanofluidic systems. Moreover, Wang's group[341] fabricated a dual-responsive (CO_2 and temperature) nanochannel system by grafting poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) onto the inner surface of a single

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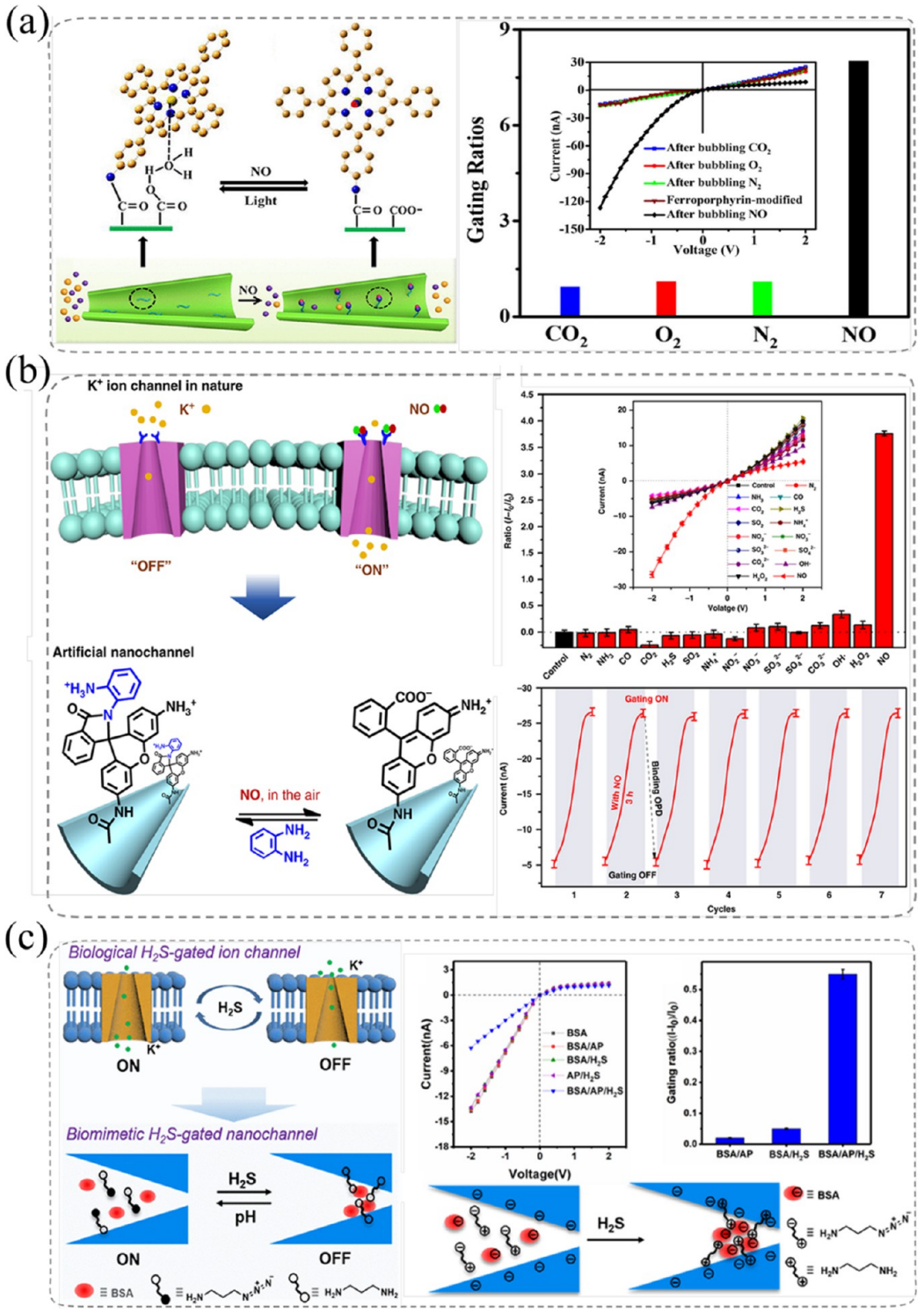

Figure 13. Polymeric nanochannel-based biosensors for the detection of other inorganic gases. (a) A nanofluidic sensing system for NO detection designed by functionalizing with ferroporphyrin *via* coupled reaction in conical PET multi-nanochannels. Adapted with permission from ref 355. Copyright 2018 American Chemical Society. (b) A NO-responsive system by modifying OPD and R-110 onto the inner surface of a single conical PET nanochannel *via* a spiro ring opening−closing reaction strategy. Adapted with permission under a Creative Commons CC-BY license from ref 356. Copyright 2019 Nature Publishing Group. (c) A bio-inspired H_2S-responsive biosensor based on a single conical PET nanochannel *via* an azide reduction reaction controlled BSA aggregation. Adapted with permission from ref 362. Copyright 2019 American Chemical Society.

conical PET nanopore through the technique of self-initiated photografting and photopolymerization. The PDMAEMA-modified nanochannel showed a good response to CO_2, exhibiting highly reversible property and stability.

As one kind of gasotransmitter molecules (including CO, NO, and H_2S), CO is firmly regarded as an important intracellular signaling molecule, participating in the regulation of many biological functions like neurotransmission, anti-

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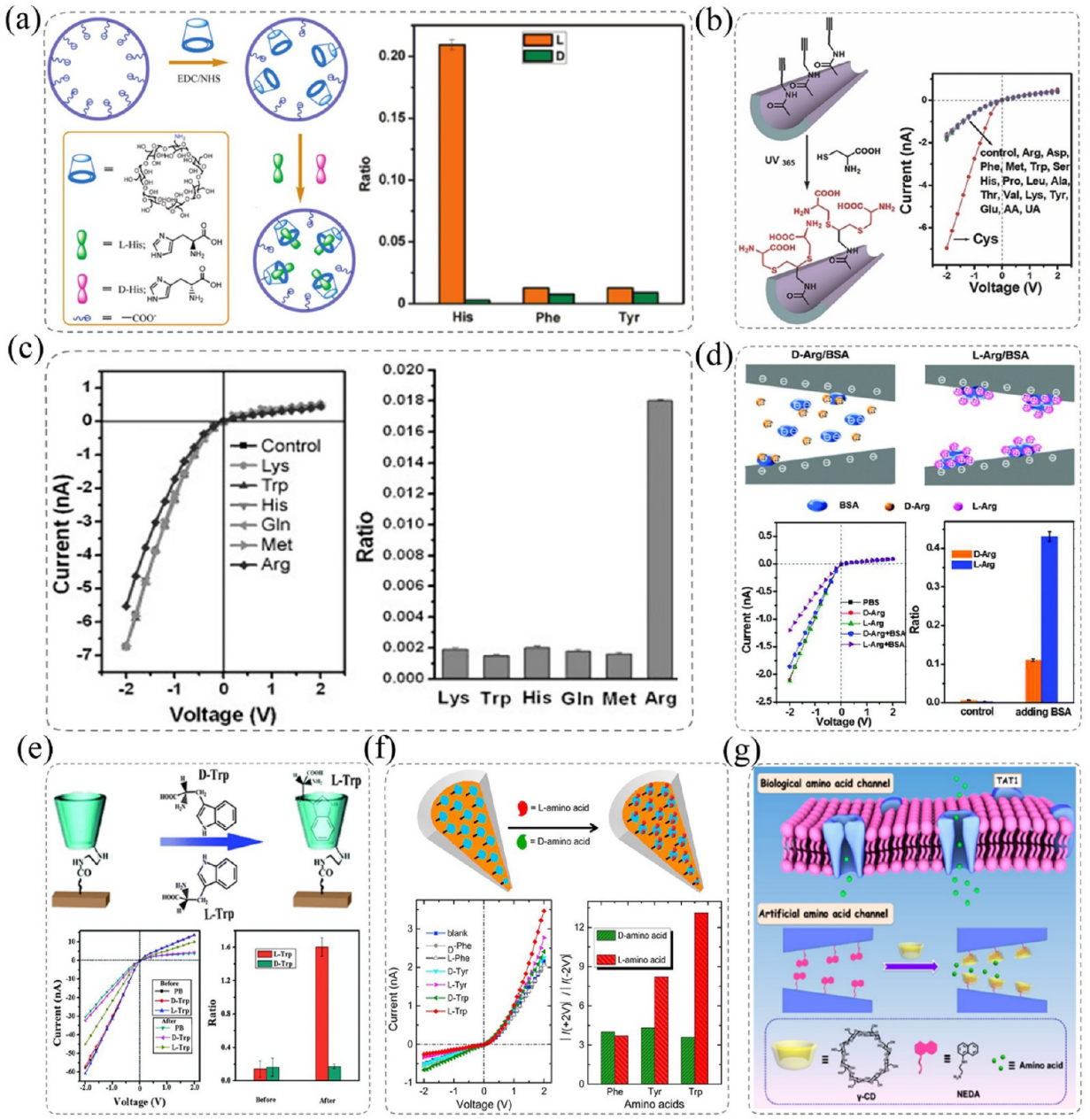

Figure 14. Polymeric nanochannel-based biosensors for detection of amino acids. (a) A chiral L-His sensing nanodevice based on a single conical PET nanochannel modified with mono-6-amino-β-cyclodextrin molecules. Adapted with permission from ref 364. Copyright 2011 American Chemical Society. (b) A cysteine-responsive platform based on a propargylamine-functionalized single conical PET nanochannel. Adapted with permission from ref 365. Copyright 2014 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim. (c) An arginine-responsive nanofluidic device based on a single conical PET nanochannel functionalized with calix[4]arenes. Adapted with permission from ref 366. Copyright 2014 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim. (d) A label-free single conical PET nanochannel for enantioselective recognition of arginine by adding BSA as chiral selector. Adapted with permission from ref 367. Copyright 2015 The Royal Society of Chemistry. (e) Chiral recognition of L-Trp based on a β-CD-modified single conical PI nanochannel. Adapted with permission from ref 368. Copyright 2015 The Royal Society of Chemistry. (f) Stereoselective detection of L-tryptophan based on a BSA-modified single conical PET nanopore. Adapted with permission from ref 370. Copyright 2016 Elsevier. (g) A sensing platform for the chiral detection of L-phenylalanine based on a single conical PET nanochannel functionalized with *N*-(1-naphthyl)ethylenediamine. Adapted with permission from ref 371. Copyright 2019 American Chemical Society.

inflammatory, and vasodilation.[342,343] In recent years, much attention has been paid to develop convenient and effective approaches, such as colorimetric,[344−346] fluorescence,[347,348] and electrochemical,[349,350] for detecting gasotransmitter molecules in living systems. Particularly, polymeric nanochannels have attracted increasing interests as promising platforms for gaseous messenger sensors. In 2016, Zhai's group constructed a CO-gated nanodevice by modifying ferroporphyrin onto the inner surface of conical PET multi-nanochannels (Figure 12c).[351] In the proposed system, CO was used as trigger for regulating the "on−off" function. The presented platform demonstrated reversibility and fast response rate to CO, providing the potential applications in CO sensors. Recently, Sun *et al.* developed a smart CO-

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responsive nanosensor through the redox reaction strategy, demonstrated an outstanding CO specificity and selectivity as well as excellent stability and reversibility.[352] This sensing strategy endows the design of nanochannel-based sensors for future practical and biological applications, including understanding the natural function of CO in life.

As a secondary messenger molecule, NO in guard cells plays vital roles in K^+ nanochannels by direct binding to the heme-containing enzymes.[353,354] In 2018, Zhai and co-workers reported an artificial NO and light cooperative nanofluidic device by modifying ferroporphyrin onto the inner surface of conical PET multi-nanochannels.[355] NO and light cooperative triggered the on/off switching function in the nanofluidic system, relying on the higher NO affinity of ferroporphyrin compared to carboxyl groups on the nanochannel surface (Figure 13a). On the basis of this mechanism, the nanodevice can be applied in the fields of NO detection, exhibiting excellent stability and reversibility. Furthermore, Li *et al.* designed an NO-responsive system by grafting *o*-phenylenediamine (OPD) and rhodamine (R-110) onto the inner walls of a single conical PET nanochannel using a spiro ring opening-closing reaction strategy.[356] The proposed device exhibited a highly specific and sensitive NO response without interference, as well as excellent reversibility and stability (Figure 13b). This sensing strategy could be well-developed for real-world applications in NO biosensors. As the third endogenous gaseous signal molecule in organisms, H_2S is involved in many physiological and pathological activities,[74,357−359] and H_2S-specific detection is of great consequence for early disease diagnosis.[360,361] In 2019, Li *et al.* reported an artificial H_2S-responsive biosensors based on a single conical PET nanochannel by an azide reduction reaction controlled bovine serum albumin (BSA) aggregation (Figure 13c).[362] The device demonstrated highly selective and reversible response to H_2S without interference, as well as excellent stability and a fast response rate.

Detection of Organic Molecules. In addition to the detection of inorganic molecules, strategies for sensing organic molecules based on bio-inspired polymeric nanochannels have been also developed. The nanochannel-based biosensors have been used as promising platforms for the detection of organic small molecules, such as amino acids, glucose, drugs, and other small molecules.

Amino acids are the building blocks of proteins, which serve both to nourish and signal in cells.[363] Therefore, the direct and sensitive detection of amino acids is of significant importance for life sciences research. In 2011, Jiang *et al.*[364] reported a convenient and robust chiral sensing device based on a single conical PET nanochannel modified with mono-6-amino-*β*-cyclodextrin molecules (Figure 14a). On the basis of rectified ionic currents, the modified nanochannel offered a sensing platform for the detection of L-histidine (L-His). The proposed nanochannel system showed high sensitivity and selectivity toward L-His, which could be developed for practical chiral-sensing nanodevices in living organisms. In 2014, Jiang and Li *et al.* fabricated a cysteine-responsive platform based on a propargylamine-functionalized single conical PET nanochannel *via* the photo-initiated thiol−yne click reaction strategy (Figure 14b).[365] The reaction-based biosensor exhibited a high cysteine (Cys)-selective response under UV light (365 nm) and excellent sensitivity with a detection limit of 10 nM. Intriguingly, the proposed device when applied to complex matrices and urine samples also displayed high Cys specificity and robust non-interference. The sensing strategy could be further developed for applications in drug metabolism monitoring, energy conversion, and biomolecule transport processes. Later on, the same group[366] further reported a nanofluidic device for the detection of arginine (Arg) based on a single conical PET nanochannel, which was modified with calix[4]arenes by using a click reaction. The functionalized nanochannel offered a promising sensing platform to detect Arg, showing an excellent response and a highly selective recognition for Arg (Figure 14c). The biosensor had a detection limit of 0.1 μM, and which also exhibited high selectivity for Arg even in the presence of interfering substances and serum samples. In 2015, Li's group[367] designed a chiral recognition system based on a label-free single conical PET nanochannel, with the addition of BSA as chiral selector for enantioselective recognition of D- and L-Arg (Figure 14d). The interaction of L-Arg with BSA is stronger than that of D-Arg; thus BSA bonds much more L-Arg. L-Arg/BSA complexes were easily absorbed on the inner surface and partial blockage of nanochannel, resulting in a significant decrease of ionic current. The proposed system also displayed high selectivity on chiral detection of D- and L-Arg in the presence of interfering chiral amine acids. This sensing strategy expanded a universal applicability platform for construction of an enantioselective detection nanodevice. Moreover, Wen's group[368] reported a stable system to enantioselectively recognize L-tryptophan (L-Trp) based on a *β*-cyclodextrin (*β*-CD)-modified single conical PI nanochannel (Figure 14e). The modified *β*-CD would selectively bind with L-Trp, thereby changing the surface charge and wettability of nanochannel. The ionic current of the modified nanochannel decreased obviously with the addition of L-Trp; however, it remained unchanged in the presence of D-Trp or the other aromatic amino acids.[369] The presented nanodevice showed good chiral selectivity and sensitivity to L-Trp, and the sensing strategy could be developed for practical applications in chiral recognition, drug detection, and analysis. In 2016, Ali *et al.* reported a BSA-dopamine-modified single conical PET nanopore for the stereospecific recognition of Trp enantiomers (Figure 14f).[370] The immobilized BSA molecules served as chiral receptor on the inner surface of nanopore, which would selectively bind with L-Trp, resulting in measurable changes in the ionic current. The proposed biosensor detected L-Trp in the range from 100 μM to 1.5 mM, and exhibited a good selectivity to L-Trp over D-Trp and other amino acids. The principle of this device is based on specific protein-drug interactions, and the sensing strategy could be developed for the recognition of various pharmaceutical molecules. In 2019, Li and co-workers constructed a switchable chiral recognition system for L-phenylalanine (L-Phe) based on a single conical PET nanochannel functionalized with *N*-(1-naphthyl)ethylenediamine (NEDA).[371] The principle of this system is dependent on the host−guest interaction, and *γ*-cyclodextrin (*γ*-CD) acted as the host while NEDA served as the guest (Figure 14g). The device achieved the highly selective L-Phe molecules transport, exhibiting a pH-responsive switching ability and stability.

Glucose, commonly called "blood sugar", is the most abundant monosaccharide in nature.[372,373] As a star molecule for health, glucose provides the principle energy source for the mammalian brain and contracting muscle.[374,375] In recent years, much attention has been drawn to develop bio-inspired polymeric nanochannel-based biosensors for detecting glucose *in vitro*. In 2009, Alfonta *et al.*[116] reported a glucose biosensor

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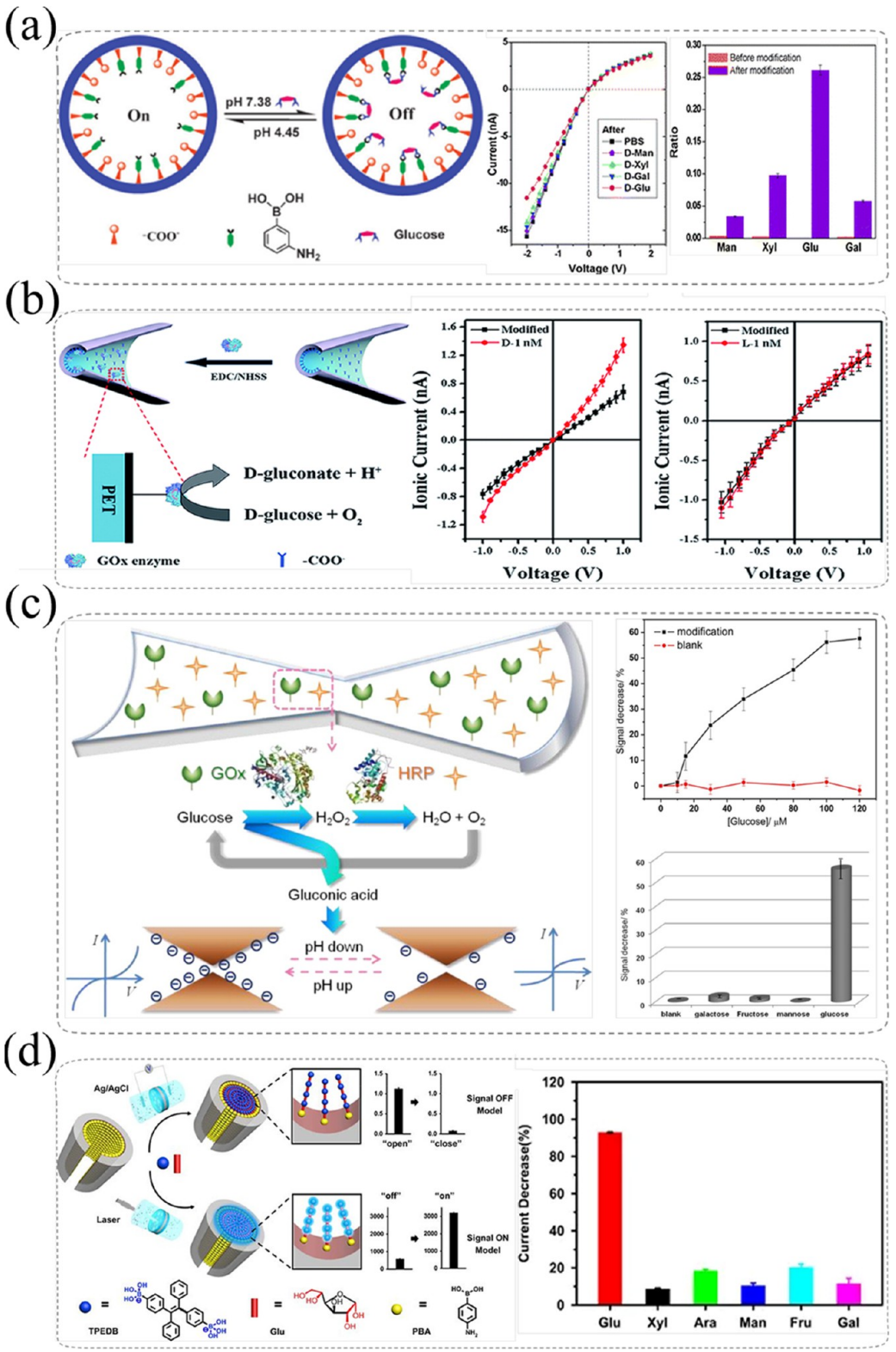

Figure 15. Polymeric nanochannel-based biosensors for glucose detection. (a) A pH-gated glucose biosensor based on a single conical PET nanochannel modified with 3-aminobenzeneboronic acid. Adapted with permission from ref 61. Copyright 2012 The Royal Society of Chemistry. (b) A sensitive nanodevice for D-glucose detection prepared by modifying a single conical PET nanochannel with GOx enzymes. Adapted with permission from ref 62. Copyright 2014 The Royal Society of Chemistry. (c) A glucose-responsive nanoreactor constructed based on cascade enzymatic catalysis and cation-selective system from a single hourglass PI nanochannel. Adapted with permission from ref 41. Copyright 2014 American Chemical Society. (d) An AIE molecule-functionalized biosensor for the detection of glucose based on cylindrical PET multi-nanochannels. Adapted with permission under a Creative Commons CC-BY license from ref 84. Copyright 2016 Nature Publishing Group.

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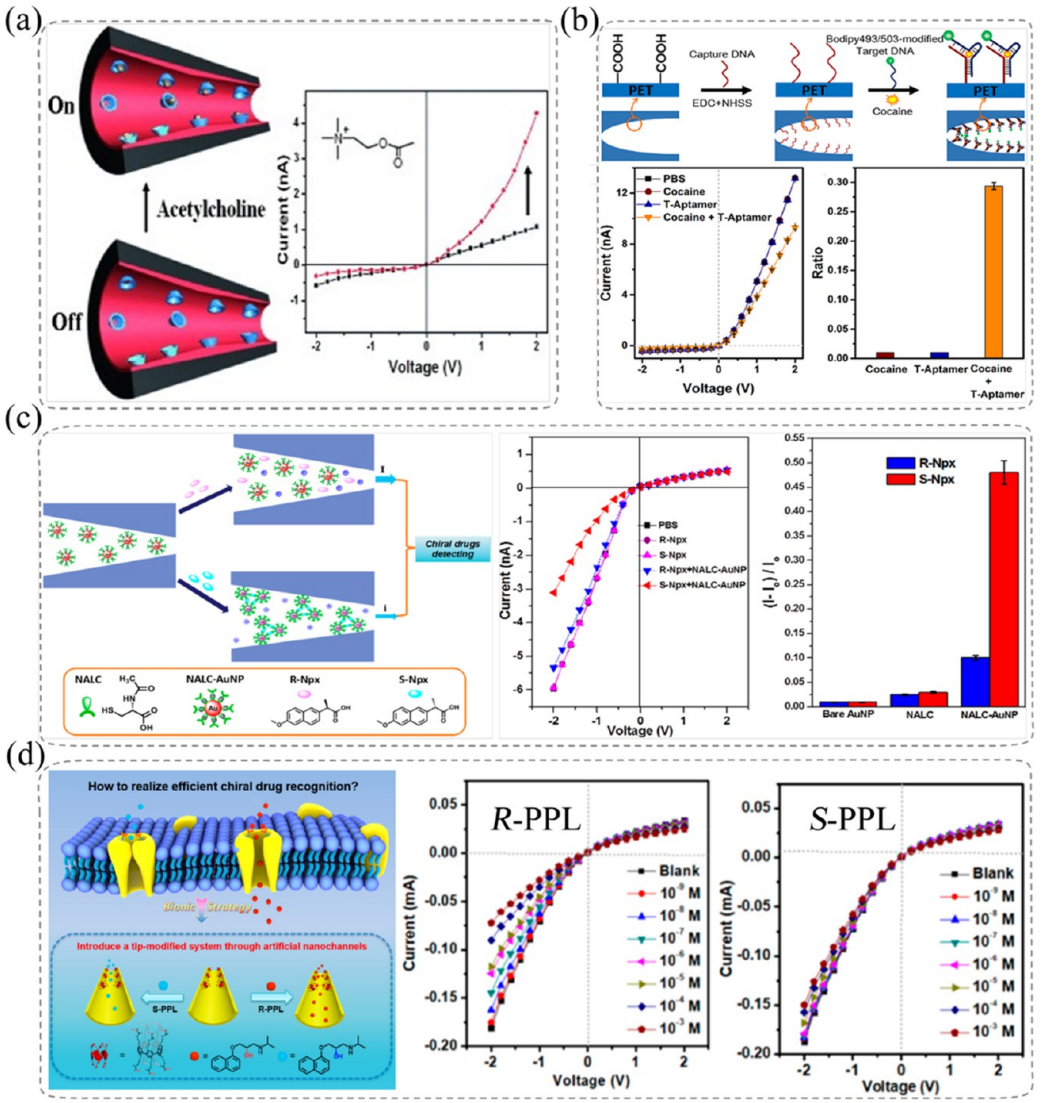

Figure 16. Polymeric nanochannel-based biosensors for detection of neurotransmitters and drugs. (a) An acetylcholine sensing nanodevice fabricated by layer-by-layer assembly within a single conical PET nanochannel. Adapted with permission from ref 376. Copyright 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) A high-sensitive cocaine biosensor based on a single bullet-like PET nanochannel coupled with DNA aptamers. Adapted with permission from ref 377. Copyright 2018 American Chemical Society. (c) Chiral detection of *S*-naproxen (*S*-Npx) from *R*-naproxen (*R*-Npx) using *N*-acetyl-L-cysteine-capped Au nanoparticles as a chiral selector in a modification-free single conical PET nanochannel. Adapted with permission from ref 65. Copyright 2017 American Chemical Society. (d) A strategy for simulating biological channels to selectively recognize *R*-PPL in tip-modified conical PET nanochannels. Adapted with permission from ref 379. Copyright 2021 American Chemical Society.

based on the enzyme glucose oxidase (GOx) covalently linked to conical PET nanopores. The catalytic sensor showed good sensitivity toward glucose in the range from 10 μM to 1 M, which can be reused as least 10 times. In 2012, Li's group designed a pH-gated glucose biosensor based on a single conical PET nanochannel functionalized with 3-aminobenzeneboronic acid (Figure 15a).[61] The modified nanochannel exhibited a high glucose selective response, even in the presence of interferents such as ascorbic acid, glycine, and urea. Additionally, the proposed system showed on/off switching property with pH changes for glucose recognition, which provided a sensing platform to detect glucose by regulating environmental stimulus. In 2014, Tian and co-workers[62] developed a sensitive nanodevice for ultratrace D-glucose detection based on a GOx-modified single conical PET nanochannel (Figure 15b). The modified nanochannel demonstrated ultra-sensitivity with a detection limit of 1 nM and excellent specific recognition toward D-glucose rather than its enantiomer. This presented biosensor also showed good reproducibility, which could be developed for practical applications in clinical therapy, fermentation monitoring, and food analysis. Moreover, Li *et al.*[41] reported a glucose-responsive nanodevice by modifying GOx and horseradish peroxidase on the inner wall of a single hourglass PI nanochannel (Figure 15c). The mechanism for this sensor is based on that different concentration of glucose created different amount of gluconic acid and thus induced the pH change inside the nanochannel to various degrees. The proposed device exhibited high sensitivity and robust selectivity toward glucose through monitoring ionic current signatures, which could be expanded for potential applications in clinical diagnosis, drug discovery, and biological process. In

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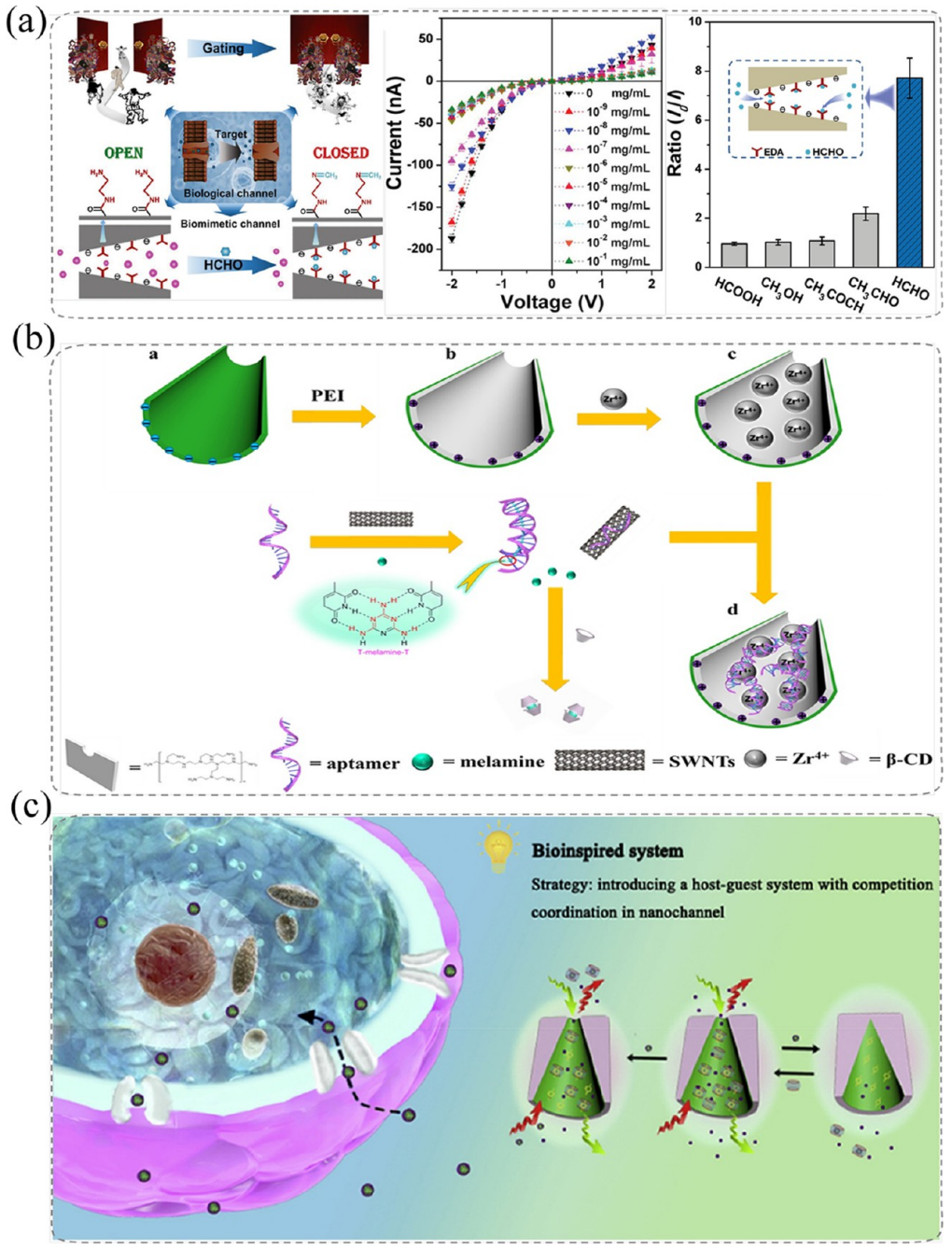

Figure 17. Polymeric nanochannel-based biosensors for detection of exogenous toxic agents and medicines. (a) A smart responsive platform for HCHO detection designed and fabricated by functionalizing the inner surface of conical PET multi-nanochannels with EDA. Adapted with permission from ref 381. Copyright 2019 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim. (f) A sensing platform for the detection of melamine based on a single conical PET nanochannel modified with PEI and Zr^{4+}, in combination with β-CD and SWNTs. Adapted with permission from ref 382. Copyright 2019 Elsevier. (g) A single conical PET nanochannel-based ADA sensor constructed by functionalizing the channel surface with *p*-toluidine and then assembled with CB[7]. Adapted with permission from ref 383. Copyright 2020 Elsevier.

2016, Lou *et al.* presented a dual-signal-output PET multi-nanochannel-based biosensor for glucose detection by the combination of ionic current with fluorescence (Figure 15d).[84] The principle of this device is dependent on the oligomerization reaction between the aggregation-induced emission (AIE) molecule and glucose. This presented sensor demonstrated high sensitivity and specific recognition for glucose, and the sensing strategy could be developed for the potentials of smart nanofluidic devices in many fields such as biomolecule delivery, drug metabolism monitoring, and clinical diagnosis in complex microenvironments.

As one of promising sensing platforms, artificial polymeric nanochannel-based biosensors can also be implemented for highly sensitive recognition of other small molecules, such as neurotransmitters, drugs, exogenous toxic agents, and medicines. In 2013, Li's group developed an acetylcholine (Ach) sensing nanodevice fabricated by layer-by-layer assembly within a single conical PET nanochannel (Figure 16a).[376] The principle of this sensor is dependent on directly exploiting

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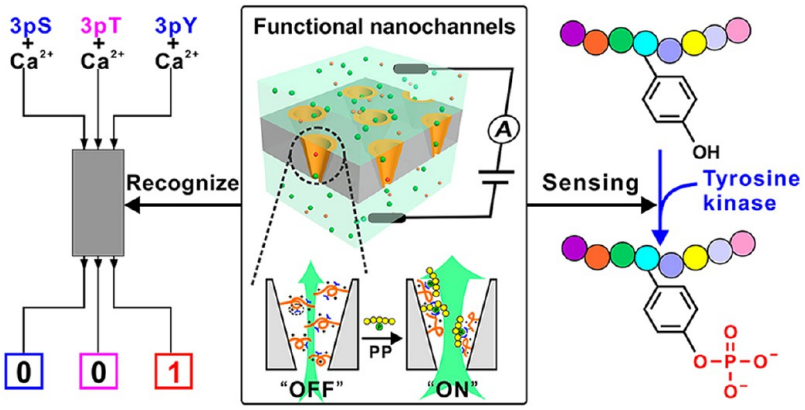

Figure 18. A pTyr-specific nanofluidic logic sensing device based on conical PET multi-nanochannels, which were functionalized by guanidinium-rich polyethylenimine-*graft*-phenylguanidine. The nanochannel platform performed simple logic operations by introducing Ca^{2+} as an interferent. Adapted with permission from ref 387. Copyright 2020 American Chemical Society.

the charges on PEI and *p*-sulfonatocalix[4]-arene to yield electrostatic assembly on the inner walls of channel. The proposed device demonstrated high sensitivity with a detection limit of 1 nM to Ach, which was evaluated by measuring the rectified ion flux across the channel. In addition, our group reported a high-sensitive biosensor for cocaine detection based on a single bullet-shaped PET nanochannel coupled with DNA aptamers (Figure 16b).[377] Single-stranded capture DNA was first modified onto the channel walls and then fold into double-stranded structures after binding of cocaine and target–aptamer molecules,[378] changing the surface properties of the channel and reducing the ionic current. The biosensor exhibited excellent sensitivity with a detection limit of 1 nM and good selectivity toward cocaine rather than other drugs with similar chemical structures. Moreover, the presented device displayed better cocaine sensitivity and specificity than traditional sole aptamer-based sensors. This sensing strategy could be developed for ultrasensitive and selective illicit drugs testing in many fields such as medicine, healthcare, law enforcement, and environment. In 2017, Li and co-workers designed a modification-free single conical PET nanochannel platform for selectively detecting *S*-naproxen (*S*-Npx) from *N*-naproxen (*N*-Npx) by using *N*-acetyl-L-cysteine-capped Au nanoparticles as a chiral selector (Figure 16c).[65] The mechanism for this biosensor is based on preferential interaction between the chiral molecules and the ligand, which leads to the aggregation of inter-nanoparticles and thus reduces ion flux through the nanochannel. This sensing strategy could be developed for monitoring drug metabolism and biomolecule enantioselective transport. Recently, Li's group reported a chiral nanosensor based on an artificial tip-modified nanochannel system that allowed efficient selective recognition of *R*-propranolol (*R*-PPL).[379] In the proposed system, L-alanine-pillar[5]arenes as selective receptors were introduced on the tip side of a conical PET nanochannel to form a "gate" to perform efficient enantioselective response to *R*-PPL, showing a higher selective coefficient than the traditional fully modified nanochannels (Figure 16d). Moreover, Li *et al.* developed artificial hourglass-shaped PET nanochannels with antiporter behavior for chiral sensing and separation of naproxen (Npx) enantiomers.[380] Multi-ligand-modified asymmetric nanochannels, which were constructed by introducing tyrosine enantiomers *via* two-step modification, exhibited spontaneous transport of Npx enantiomers with high enantioselectivity and opposite directions. The proposed detecting strategies could be effectively developed for potential applications in chiral discrimination and drug delivery.

As is well known, formaldehyde is an exogenous toxic agent that poses a severe threat to human being's health. In 2019, Wen's group[381] designed and fabricated a formaldehyde-sensitive device based on conical PET multi-nanochannels by modifying the inner surface of channels with ethylenediamine (EDA) (Figure 17a). The interaction of HCHO molecules with EDA induced the changes in ionic current, and the sensing platform exhibited excellent sensitivity and high selectivity rather than volatile organic compounds in indoor environments. Moreover, the designed system showed effective HCHO removal even in complex matrices. This detecting strategy could be applied to develop bio-inspired nanochannel-based biosensors for harmful organic compounds recognition and removal. In the same year, Wang and co-workers[382] reported a biosensor for melamine recognition based on a single conical PET nanochannel functionalized with PEI and Zr^{4+}, in combination with β-CD and SWNTs (Figure 17b). The proposed sensor possessed high sensitivity with a detection limit of approximately 4.3 nM and excellent selectivity toward melamine over other interfering substances. This strategy for polymeric nanochannels could be used as versatile and universal platforms for the detection of other possible targets in real samples. Later on, the same group also established a sensitive biosensor for the rapid quantitative recognition of adamantanamine (ADA) based on a single conical PET nanochannel, which was modified with *p*-toluidine and was then assembled with cucurbit[7]uril (CB[7]) (Figure 17c).[383] The melamine-responsive sensor exhibited high sensitivity with a detection limit of 4.54 nM, and also showed excellent reproducibility and high specificity. This sensing strategy could be effectively applied to practical applications for the detection of small drugs in the fields of medicine and food safety.

Tyrosine phosphorylation (pTyr), which can initiate cellular signaling pathways, regulate signal transduction, and govern cellular functions, plays vital roles in human health and disease.[384−386] Most recently, Qing and Liang *et al.* developed a pTyr-specific nanofluidic logic sensing device based on polyethylenimine-*graft*-phenylguanidine (PEI-PG)-modified conical PET multi-nanochannels (Figure 18).[387] Guanidinium-rich PEI-PG polymer was designed to anchor onto the

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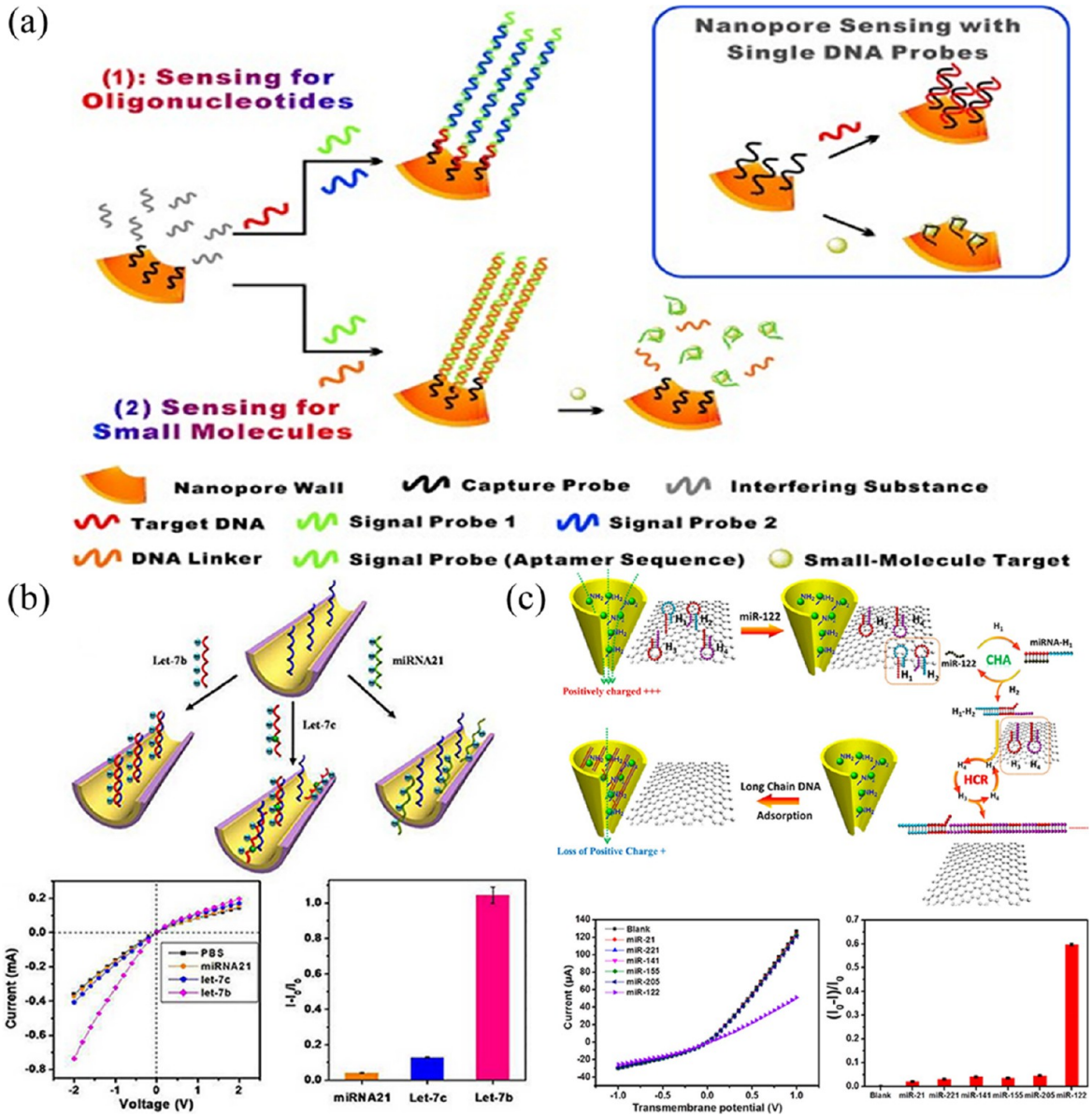

Figure 19. Polymeric nanochannel-based biosensors for the detection of nucleic acids. (a) A highly sensitive and selective nanofluidic sensing device for both DNA and ATP based on cylindrical PET multi-nanopores *via* the modulation of supramolecular DNA nanostructures. Adapted with permission from ref 85. Copyright 2013 Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim. (b) A phosphorodiamidate morpholino oligos (PMO)-functionalized conical PET nanochannel-based biosensor for label-free recognition of microRNAs. Adapted with permission from ref 393. Copyright 2017 American Chemical Society. (c) A label-free nanofluidic device for miRNA detection based on conical PET nanochannels modified with PEI and Zr^{4+} in combination with graphene oxide. Adapted with permission from ref 394. Copyright 2020 American Chemical Society.

inner surface of nanochannels, in which the multiple PG components acted as recognition receptors for pTyr, and PEI chains experienced the recognition-induced conformational change. The PEI-PG-modified nanochannels could recognize phosphorylated peptide (PP) from non-modified peptide, and the mechanism for this sensor is based on the binding-induced shrinkage of the anchored polymer in nanochannels and the corresponding ion flux "off−on" change. The specific sensing of pTyr peptides was also achieved by simple logic operation based on the functionalized nanochannels by introducing Ca^{2+} as an interferent. Specifically, the designed nanofluidic device showed potential applications in the real-time monitoring of pTyr by kinase and in the kinase inhibitor screening assay.

Detection of Nucleic Acids. Nucleic acids, which are macromolecules found in cells and viruses, play essential roles in diverse biological processes, such as the storage, transport, processing, and expression of the genetic information.[388] The detection of nucleic acid molecules in solution has attracted increasing interest over the past decade. Nanochannel-based sensing (including biological and solid-state nanochannels)[36,78,389−391] is attractive for DNA and RNA detection applications, which are mainly based on the temporal fluctuations in the recording ionic current through the channel.[392]

Compared with the resistive-pulse method, these biosensors, relying on steady-state analysis approaches for detection of nucleic acids, are lagging behind the development of the

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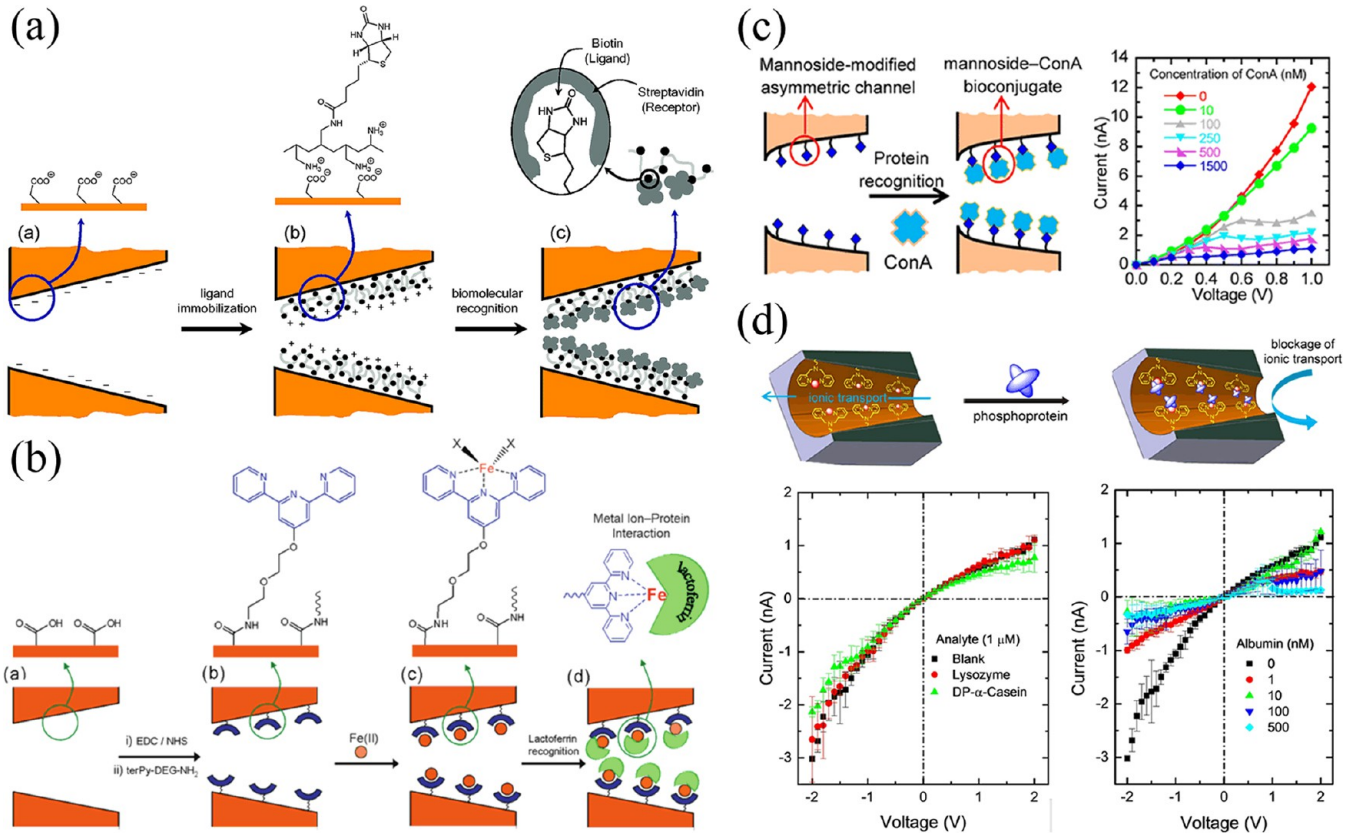

Figure 20. Polymeric nanochannel-based biosensors for the detection of proteins. (a) A protein-responsive platform for specific recognition of streptavidin based on a single conical PET nanopore by electrostatic self-assembly of b-PAH inside the channel. Adapted with permission from ref 397. Copyright 2008 American Chemical Society. (b) A nano-biosensor for the selective lactoferrin recognition through metal–protein specific interactions based on the immobilization of metal–ligand complexes inside a single conical PET nanopore. Adapted with permission from ref 54. Copyright 2011 American Chemical Society. (c) Reusable nanofluidic biosensors for reversible Con A protein detection based on the APMP-modified single bullet-like PI nanochannel and cylindrical PET multi-nanochannels. Adapted with permission from ref 399. Copyright 2013 American Chemical Society. (d) A DPA-Zn^{2+} chelates-functionalized conical PET nanochannel-based biosensor for the label-free recognition of PPn. Reproduced with permission under a Creative Commons CC-BY license from ref 400.

competitors. In 2013, on the basis of conventional DNA-based nanopore sensors, Jiang's group constructed a nanofluidic sensing device for sequence-specific detection of sub-nanomolar DNA and sub-micromolar ATP in complex matrices by integrating DNA supersandwich structures within the cylindrical PET nanopores (Figure 19a).[85] The sensing principle for this device is dependent on turning off or turning on an intelligent nanofluidic switch by self-assembly and disassembly of supermolecular DNA nanostructures in nanopores. The designed sensor possessed high selectivity and excellent sensitivity for target DNA and ATP, with detection limits of 10 fM and 1 nM, respectively. This sensing strategy could be developed into real-time detection method for disease-related molecular targets in biotechnology and life science.

In addition, Zhang *et al.* demonstrated a conical PET nanochannel array functionalized with phosphorodiamidate morpholino oligomers, used to prepare a biosensor for label-free recognition of microRNAs (miRNAs) (Figure 19b).[393] The mechanism for this sensor is based on observing changes of the surface charge density when PMO/miRNAs hybridization occurred. The proposed system displayed highly sensitive and specific for target miRNA (Let-7b), achieving sensitivity as high as 1 fM in PBS and 10 fM in serum sample, respectively. This sensing strategy can be developed for miRNA detection in clinical diagnosis. Most recently, Han and co-workers constructed a label-free nanofluidic sensing platform for miRNA detection based on conical PET nanochannels modified with PEI and Zr^{4+} in combination with graphene oxide (Figure 19c).[394] The principle of this biosensor is also based on the change of the surface charge density of the channel, which was originated from DNA cascade signal amplification in solution. The nanofluidic device demonstrated high selectivity toward target miRNA (miR-122) with a detection limit of 97.2 aM and excellent selectivity even in the presence of interferents such as miR Let-7a. This proposed strategy could be developed for practical applications in the detection of liver cancer-related miRNAs.

Detection of Proteins and Pathogens. In the past decade, polymeric nanochannel-based devices have become a powerful tool to detect biomolecules at the single-molecule level. For example, Martin *et al.*[395] constructed a poly(ethylene glycol) (PEG)-functionalized conical Au nanotube in a PET membrane for a selective resistive-pulse sensing of BSA molecules, using the protein/antibody interaction between BSA and Fab fragment from a BSA-binding antibody. The result showed that the pulse durations were proportional to the size of the BSA/anti-BSA-Fab complex, and the key to obtaining current pulses for the analytes was the comparable diameters between the protein molecules and the nanochannel (or Au nanotube) mouth.[15,396] Protein molecules are generally

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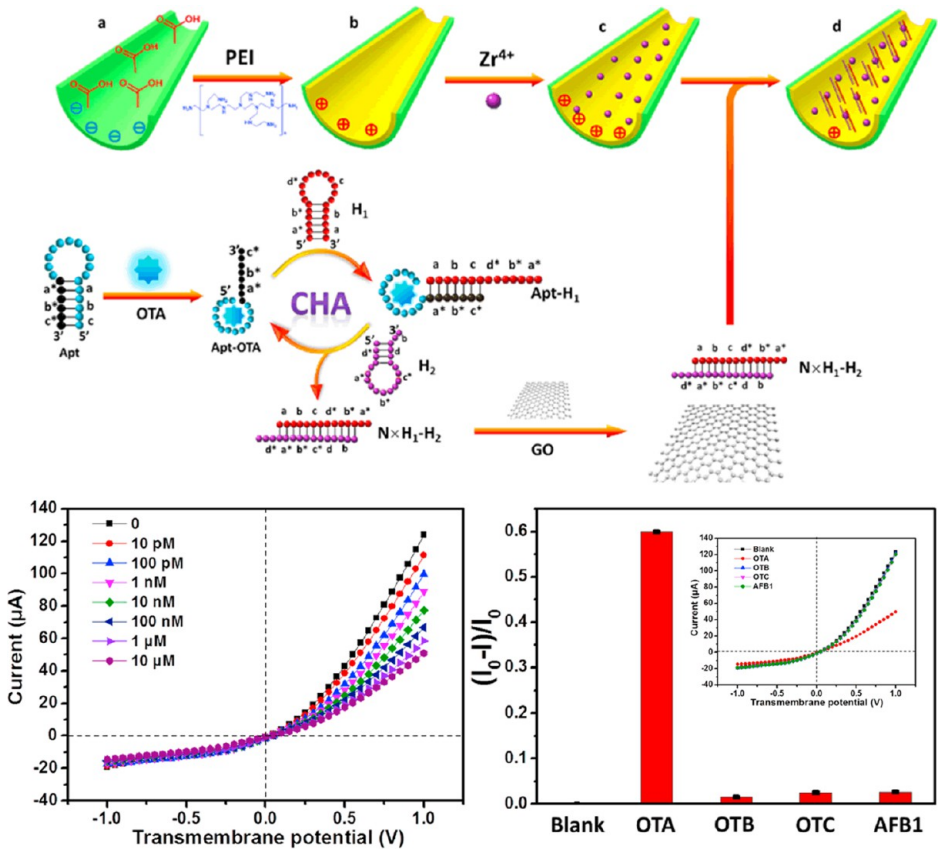

Figure 21. An ultrasensitive biosensor for the label-free detection of OTA assay based on conical PET multi-nanochannels in combination with graphene oxide (GO) and catalyzed hairpin assembly (CHA). Adapted with permission from ref 86. Copyright 2020 Elsevier.

quite challenging to detect rather than the long-chain nucleic acids by the resistive-pulse method, due to smaller size and fast-traveling through the nanopore with poor signal-to-noise ratio of the induced transport signals.[115]

These bio-inspired polymeric nanochannel-based biosensors for detection of proteins by steady-state analysis approaches have been developed in the past years. In 2008, Azzaroni and Ali *et al.*[397] constructed a nano-biosensor for specific recognition of streptavidin by using a bifunctional macromolecular multivalent ligand, that is, biotinylated poly(allylamine) (b-PAH), to electrostatically assemble biorecognition sites into the wall of a single conical PET nanopore (Figure 20a). The biosensor showed excellent specificity and high sensitivity with a detection limit of 1 pM toward streptavidin. In 2011, the same group[54] reported a biosensing platform based on the immobilization of metal−ligand complexes inside a single conical PET nanopore for the selective recognition of lactoferrin (LFN) by metal−protein specific interactions. The immobilized iron−terpyridine complexes acted as recognition elements, and the sensing principle is based on specific non-covalent interactions between LFN and chelated metal (iron) ions in the grafted terpyridine monolayer (Figure 20b). The designed biosensor exhibited high biospecificity and non-fouling properties. The detection limit of LFN by using this nanodevice can reach down to 1 pM. The sensing strategy could be further extended for the molecular detection of other proteins possessing specific receptors for coordination with metal ions in their polypeptide backbone. The same group also explored the biomolecular conjugation of concanavalin A (Con A) protein with glycoenzyme horseradish peroxidase (HRP) inside single conical and cylindrical PET nanopores, which was achieved through the biospecific mannose−lectin interactions.[47] The immobilization of HRP inside nanopores led to a significant reduction of the available area for ionic transport, and the blocking effect can be developed for tuning the conductance and selectivity of the nanopores. Furthermore, the same group then demonstrated monosaccharides (glucose and fructose) and glycoprotein (ovalbumin) sensors based on single conical PET nanochannels functionalized with 3-aminophenylboronic acid.[398] The sensing principle is dependent on the reversible binding occurring between boronic acid and diols of saccharides or glycoprotein molecules, inducing a sensible change in the ionic flux through the nanochannel. It is known that the design and miniaturization of reusable channel/pore-based biosensing devices has still been a challenge in nanoscience and biotechnology. In 2013, Ali and Ensinger *et al.*[399] constructed reusable nanofluidic biosensors for reversible recognition of Con A protein based on the *p*-aminophenyl α-D-mannopyranoside (APMP)-modified single bullet-like PI nanochannel and cylindrical PET multi-nanochannels (Figure 20c). The sensing principle rests on reversible lectin−carbohydrate interactions, and the biosensors selectively recognized Con A protein with a detection limit of 10 nM. Most recently, the same group reported a conical PET nanochannel-based biosensor for the label-free recognition of phosphoprotein (PPn) analytes (Figure 20d).[400] A metal ion chelator, namely 4-[bis(2-pyridylmethyl)aminomethyl]aniline ($DPA\text{-}NH_2$) compound, was first immobilized on the inner surface of the nanochannel, followed by Zn^{2+} complexation to

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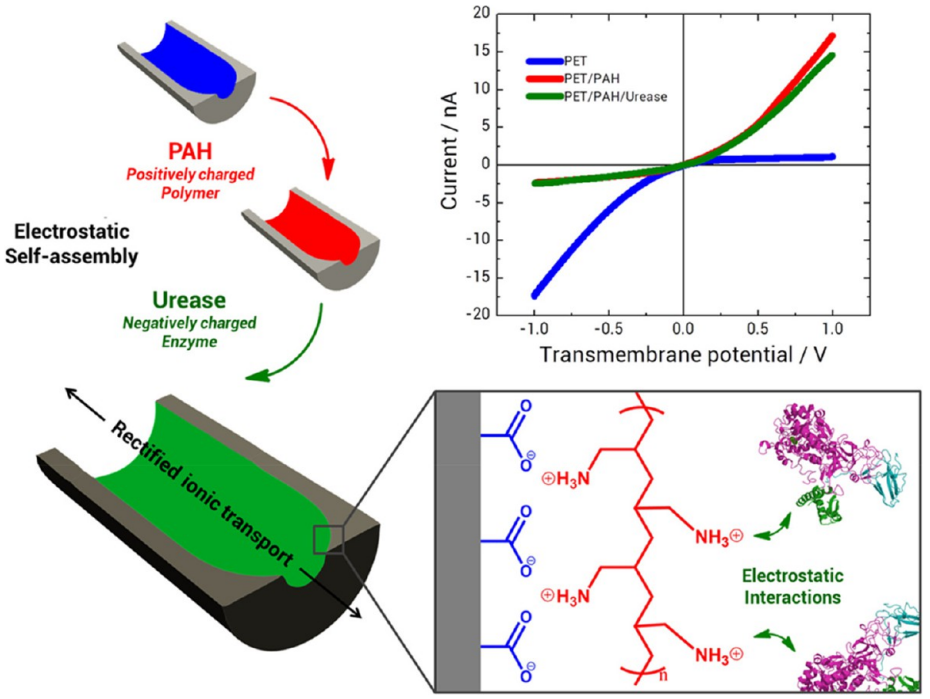

Figure 22. An ultrasensitive enzymatic biosensor based on PAH-modified bullet-like PET nanochannels employing "reactive signal amplifiers" as key elements coupled to the transduction mechanism. Adapted with permission from ref 410. Copyright 2018 American Chemical Society.

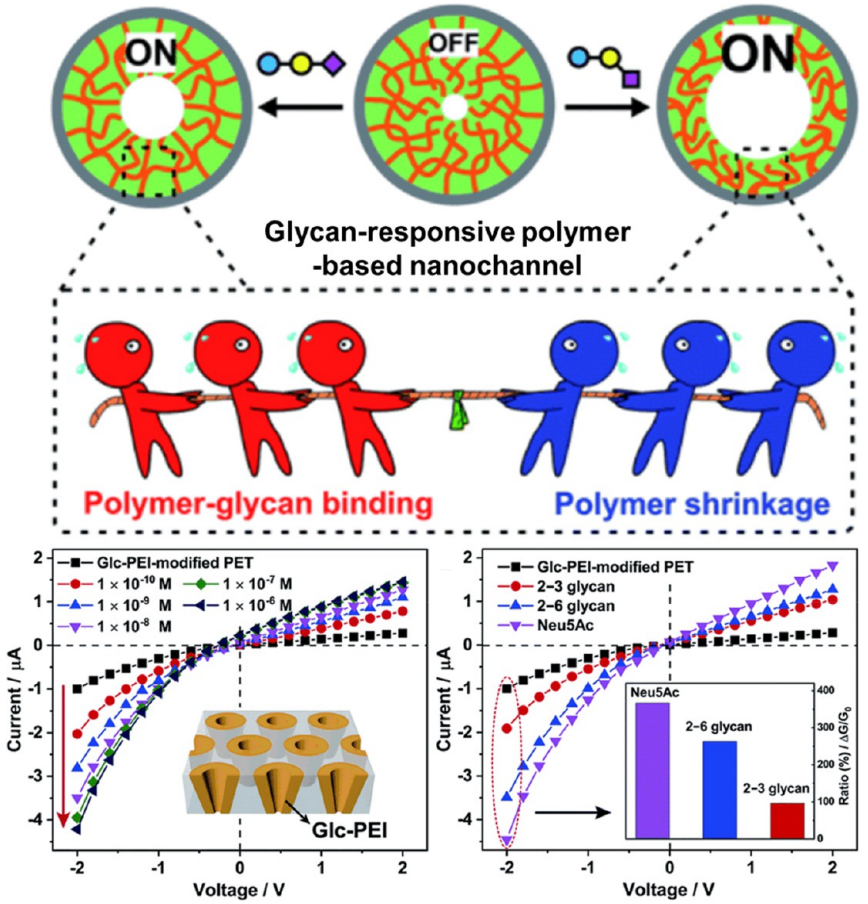

Figure 23. A biomimetic glycan-responsive nanochannel system, which is based on conical Glc-PEI-modified PET multi-nanochannels, for precise recognition and discrimination of sialylated glycan linkage isomers *via* dramatic "off−on" ion flux changes. Adapted with permission under a Creative Commons CC-BY license from ref 414.

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afford DPA-Zn^{2+} chelates, which served as ligand moieties for the specific binding of phosphoproteins. The biomolecular recognition process occurring in the channel was monitored through $I-V$ measurements. The proposed nanofluidic biosensor exhibited excellent specificity and high sensitivity with a detection limit as low as 1 nM toward PPn proteins (albumin and α-casein), and the sensing strategy could be developed for differentiating between phosphoproteins and dephosphoproteins.

Mycotoxins occurring in food commodities are toxic secondary metabolites of filamentous fungi, which can contaminate many types of food crops and then cause a variety of toxic effects to mammals.[401] A number of analytical methods, such as chromatography,[402−404] capillary electrophoresis,[405,406] and fluorescence polarization,[407,408] have been developed for mycotoxin detection. Recently, Han *et al.* reported a label-free nanofluidic device for the detection of ochratoxin (OTA) assay based on conical PET multi-nanochannels in combination with graphene oxide (GO) and catalyzed hairpin assembly (CHA) (Figure 21).[86] The nanochannels were functionalized with PEI and Zr^{4+}, which could monitor the concentration of OTA by detecting the dsDNA in solution. The proposed biosensor showed high sensitivity with a low detection limit of 6.2 pM and excellent specificity toward OTA over other toxins, and this sensing strategy could provide an excellent universal sensing platform for different molecules determination in real samples.

In recent years, manipulating the selective and specific properties of solid-state nanochannels with enzymatic architectures available to catalyze specific biochemical reactions has attracted much attention.[62,409,410] In 2011, Alfonta and Fink *et al.* described a highly sensitive urea biosensor based on conical PC multi-nanopores, which were modified with enzyme amino residues.[411] The sensing principle is dependent on specific interactions between the enzyme urease and urea in the solution. The proposed biosensor showed high sensitivity with a detection limit as low as 10^{-7} M toward urea. In 2018, Azzaroni *et al.*[410] designed a nanofluidic biosensor based on the iontronic amplification of an enzymatic reaction by electrostatically assembling poly(allylamine) (PAH) into the bullet-like PET nanochannels as "reactive signal amplifiers" and subsequently grafting urease on the PAH layer (Figure 22). The surface charge state of the inner walls of the nanochannels changed due to the enzymatic reaction in the presence of urea, leading to the generated ionic signals. The proposed enzymatic biosensor was highly reproducible and reversible, showing excellent sensitivity with a limit of detection of 1 nM toward urea. This work can provide meaningful guidance for the molecular design of ultrasensitive nanochannel-based biosensors as well as (bio)-chemically addressable nanofluidic elements.

Sialylated glycans, which are attached to mammalian cell surfaces, serve as critical binding sites for mediating numerous cellular processes, such as immune responses, pathogen binding, and cancer progression.[412,413] Precise recognition of sialylated glycans, particularly their linkage isomers can benefit both the understanding of disease progression and the improvement of early diagnoses and targeted treatments.[292] Most recently, Qing and Liang *et al.*[414] constructed a nanochannel platform based on conical PET multi-nanochannels integrated with the responsive polymer polyethylenimine-*graft*-glucopyranoside (Glc-PEI) for precise discrimination of sialylated glycans (Figure 23). The sensing principle depended on dramatic "off−on" ion flux changes, which was attributed to the result of tug-of-war competition between Glc-PEI-glycan binding and the shrinkage of polymer itself. The proposed biosensor showed high selectivity, excellent sensitivity and label-free features toward sialylated glycans, broadening the application of nanochannel systems in biosensing and bioanalysis.

CONCLUSIONS AND PERSPECTIVES

In this Review, we have summarized the main advances of biosensing applications for detection of important analytes in life and healthcare based on bio-inspired track-etched polymeric nanochannel relied on steady-state analysis approaches. The preparation, functionalization, and ion transport properties of polymeric nanochannels have been discussed.

In the past decade, bio-inspired nanochannel-based sensors have been widely studied due to their high sensitivity, excellent selectivity, rapid response, and easy test. Part of the attractiveness of nanochannel-based sensors relies on the great potential for the detection of a wide range of target analytes, which is mainly attributed to the unique transport properties of these nanoarchitectures.[415,416] Significant achievements and great potential have been shown in the past few years; however, there are still many challenges in the development and applications of bio-inspired polymeric nanochannel-based biosensors. As a general method for the preparation of polymeric nanochannels, the ion track-etching technique can develop the tracks into channels/pores with various geometries in a few minutes by simply making changes in the etching conditions. However, it is difficult to open as desired asymmetric nanochannels with an exact pore diameter, thus affecting the construction of high-accuracy biosensors for detection of analytes.[417] Developing emerging techniques to fabricate artificial nanochannels with precise and known structure, therefore, is essential for the design of highly selective biosensors. It is widely known that there are two routes to construct bio-inspired stimuli-responsive nanochannels, including the direct approach for fabrication by employing functional materials and the indirect method by modifying the as-prepared artificial nanochannels with various functional molecules. In particular, the symmetric/asymmetric modification of the inner surface of channels/pores offers much flexibility in changing their physicochemical properties, which is a primary approach to build smart nanochannels. Nevertheless, the physicochemical modification always suffers from unclear and uncontrollable grafting density, especially in confined spaces. Moreover, the lack of the theoretical basis and models to explain the ionic transport mechanisms in nanochannels inhibits the understanding of the complex ion and molecular transport behaviors, which obviously has unfavorable significance for the design of future nanofluidic devices. But fortunately, molecular dynamic simulation has achieved a plethora of valuable insights. To acquire a deep understanding of the ion transport in nanoconfinement, considering a combination of various approaches including molecular dynamics, statistics, and emerging concepts such as quantum-confined superfluidics, which shows a promising path to investigating controlled ion transport across the nanochannels, is indispensable.[418,419]

Most of the polymeric nanochannel-based biosensors reviewed here are much more sensitive and efficient than the conventional detection methods, such as colorimetric and

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electrochemical techniques. Some challenges in the detection of analytes based on polymeric nanochannel systems, however, still lie in the stability, durability, and *in situ*, fast, and real-time for real-world applications with high accuracy and excellent specificity. The design and miniaturization of reusable channel/nanopore-based biosensors are also challenges in nanoscience and biotechnology.[399] The lack of other direct characterizing techniques except for electrical current makes it difficult to understand the sensing principle of nanochannel-based biosensors, which can affect the design, fabrication, and application of the promising sensing platforms. As we have discussed, achieving multifunctional biosensors, such as HSSSs, is perhaps one of the greatest challenges. Polymeric nanochannel-based HSSSs for detection of multiple ions have been designed and applied in the past decade, however, which still remains at the infant stage. Furthermore, it is essential to design and fabricate nanochannel-based sensor arrays, which hold promises for the high-throughput single entity sensing in electrical measurement, improving the capture rate, sensing efficiency, and target analyte diversity.[420] Virus detection using artificial ion channels mainly relies on the resistive-pulse method; however, the steady-state sensors may also have the potential application for detecting viruses such as coronavirus[421] by choosing functional molecules with recognition sites for the targets.

After witnessing the recent development of steady-state nanochannel-based sensors, more efforts are expected to develop precisely size-controlled, robust, miniature, and reusable, multifunctional, and high-throughput biosensors for practical applications. Future efforts should aim at deeper understanding of the principles at the molecular level and incorporating of these diverse pore architectures into homogeneous and defect-free multi-channel membrane systems.[422] Furthermore, synergistically enhanced ionic signals have been realized through the orchestration of different functions into the nanochannels, for example, the iontronic detection of analytes in charged nanochannels.[423] The iontronic characteristics of the artificial nanochannels enable precise and reliable quantitative analysis for various target analytes with excellent sensitivity, breaking through the limits of other detection methods.[415] Beyond the exploration of advanced yet low-cost micro/nanofabrication, the introduction of materials with meso- and micropores, for example, metal–organic frameworks, should advance the nanochannel-based sensors.[424,425] Moreover, with the rapid development of emerging technologies such as artificial intelligence, machine learning, big data, and data visualization, an underlying trend is rising that integrates these technologies with nanoconfinement effect-based analyzing and sensing technologies. Consequently, more sensitive and higher throughput sensing can be obtained with the in-depth use of data.[426] Undoubtedly, the development of bio-inspired nanochannel-based sensors is far from complete. With the rapid advancement of nanoscience and biotechnology, we believe that many more achievements in artificial nanochannel-based biosensors would be achieved and used for practical commercial applications in the future, serving people in a better way.

AUTHOR INFORMATION

Corresponding Author

Yahong Zhou − *Key Laboratory of Bio-inspired Materials and Interface Science, Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, People's Republic of China; Key Laboratory of Bio-inspired Smart Interfacial Science and Technology of Ministry of Education, School of Chemistry, Beihang University, Beijing 100191, People's Republic of China;* orcid.org/0000-0002-2482-1976; Email: zhouyh@mail.ipc.ac.cn

Authors

Jian Wang − *College of Materials and Chemistry & Chemical Engineering, Chengdu University of Technology, Chengdu 610059, People's Republic of China;* orcid.org/0000-0002-4271-3485

Lei Jiang − *Key Laboratory of Bio-inspired Materials and Interface Science, Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, People's Republic of China; Key Laboratory of Bio-inspired Smart Interfacial Science and Technology of Ministry of Education, School of Chemistry, Beihang University, Beijing 100191, People's Republic of China;* orcid.org/0000-0003-4579-728X

Complete contact information is available at: https://pubs.acs.org/10.1021/acsnano.1c08582

Notes

The authors declare no competing financial interest.

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VOCABULARY

Biological ion channels, protein-based pores embedded into biological membranes that allow selected ions to pass through the membrane; **nanochannel-based biosensors**, artificial nanochannel systems which are inspired by biological ion channels for detecting various analytes; **steady state**, a situation in which all state variables are constant in spite of ongoing processes that strive to change them; **ionic gating**, an important characteristic of ion channels which can be opened and closed to regulate ionic conduction in response to specific external stimulus alternation; **ionic current rectification** (also referred to as ionic rectification), when the ionic current for one voltage polarity is higher than that recorded for the same absolute value of opposite polarity

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