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From symmetric to asymmetric design of bio-inspired smart single nanochannels

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Biological nanochannels, such as ion channels and ion pumps, existing in cell membranes and intelligently controlling ions through the cell membrane serve as a big source of bio-inspiration for the scientists to build artificial functional nanochannels. In this Feature Article, a general strategy for the design and synthesis of bio-inspired smart single nanochannels is presented, and put into context with recent progress in constructing symmetric and asymmetric smart single polymer nanochannels with single/double artificial gates which can respond to single/multiple external stimuli, e.g., pH, ions, temperature, light, and molecules. This article is intended to utilize specific stimulus-dependent ionic transport properties inside the single nanochannel as an example to demonstrate the feasibility of the design strategy, and provide an overview of this fascinating research field.

1. Introduction

The transport of ions across cell membranes is a prerequisite for many of vital processes including maintaining cellular ion homeostasis, signal transduction, and energy conversion.¹ Various kinds of biological nanochannels embedded within cell membranes are used to intelligently regulate ions across cell membranes (Fig. 1a).^{1–4} Biological nanochannels generally fall into two general classes: ion channels and ion pumps.⁴ The transport of ions through the ion channel is usually controlled by a single gate for which opening and closing is modulated by appropriate signals (Fig. 1b), while ion pumps generally refer to

two cooperative response gates that are located separately at two ends of the pathway. The two gates can open and close alternately or simultaneously, which makes ion pumps possess many more functional ionic transport features (Fig. 1c).^{2,3}

Ion channels and ion pumps are membrane protein complexes, in which a “gate” can be considered to be the part of the protein that precludes ion movement along the translocation pathway in the prohibitive conformation, but conducts ions in the permissive conformation. Based on the functional gates, the regulation of ionic transport inside biological nanochannels is mainly composed of three characteristic features including ionic selectivity, ionic rectification and gating. Inspired by biological nanochannels, the generation of bio-inspired nanochannels is delightfully varied in the scientific research field, due to which such bio-inspired materials as a basic platform could potentially spark experimental and theoretical efforts to simulate the process of ionic transport in living organisms as well as the enhancement of the

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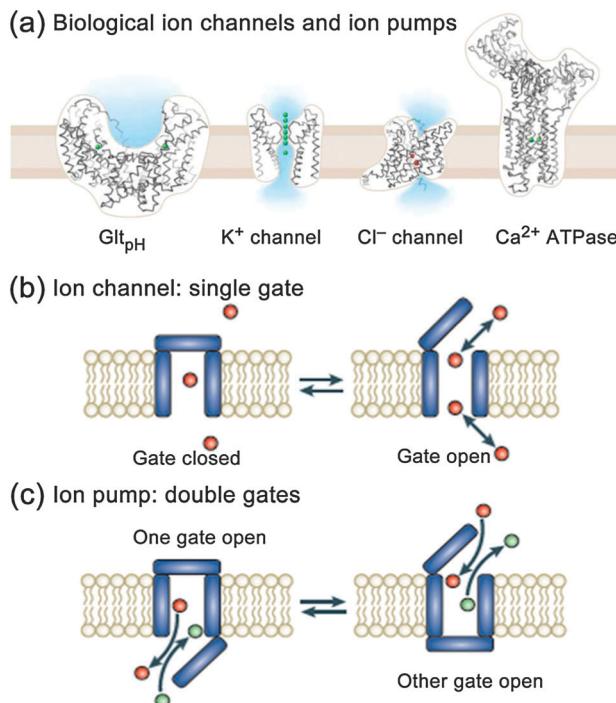


Fig. 1 Biological nanochannels. (a) Architectures of different ion channels and ion pumps.⁴ Copyright 2005 Science. (b) Schematic representation of an ion channel through which ion (red spheres) movement is controlled by a single gate that opens and closes by ambient stimuli.² (c) Schematic representation of an ion pump with double gates which open and close alternately to actively exchange red for green ions across the membrane.² Copyright 2009 Macmillan Publishers Ltd.

functionality of biological nanochannels and boost the development of bio-inspired smart nanochannel apparatus such as biosensors,^{5–8} nanofluidic devices,^{9–13} and molecular filtration.^{14–16,103}

In this Feature Article, we are mainly concerned with single/multiple stimuli responsive symmetric and asymmetric bio-inspired smart single nanochannels with single/double artificial functional gates embedded in polymer films. This article is organized into five sections. The first section gives a brief introduction to bio-inspired functional single nanochannels including the strategy for the design



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and synthesis of the symmetric and asymmetric shaped single nanochannels, the classical approaches for symmetric and asymmetric functionalization of single nanochannels with single/dual responsive functional molecules, and the common symmetric and asymmetric stimuli for tuning the surface properties of the nanochannels. The second section summarizes a comprehensive overview of the symmetric and asymmetric, single and dual stimuli responsive single-gate nanochannels in recent years, while the third section further provides much more functional asymmetric responsive single nanochannels regulated by double gates. The fourth section presents an overview of potential applications of smart nanochannel materials. Finally, there is an outlook for future challenges in the development of bio-inspired smart nanochannel materials.

As shown in Fig. 2, we suggest design and preparation processes for developing bio-inspired smart single nanochannels. Four design routes including the symmetric-asymmetric design for the shapes of the single nanochannels, the classical approaches for asymmetric and asymmetric functionalization of the inner surface of the single nanochannels, the symmetric and asymmetric external stimuli, and a co-design strategy of the above three, lead to various kinds of bio-inspired symmetric and asymmetric smart single nanochannels. In these four routes, the idea of asymmetric design provides more flexible approaches for building various functional nanochannels.

A variety of techniques have been used to fabricate single artificial nanochannels/nanopores in diverse synthetic materials, such as biomolecules self-assembly,^{17,18} electrochemical etching,¹⁹ anodic oxidation method,²⁰ electron beam technology,^{21,22} laser technology,²³ and ion-track-etching technology.^{24–28} The single inorganic and thin nanopores have been widely used to study DNA and protein sensing, which have been described in detail by Gyurcsányi,⁷ Matile *et al.*,²⁹ Dekker,⁵ and Martin *et al.*^{6,9} and will not be considered in this review. Here the examples of ion-track-etching single polymer nanochannels with different shapes (Fig. 3) are used to demonstrate the feasibility of the shape design for building functional nanochannels. The ion-track-etching technology has become a well-developed technology to create very uniform insulators, and is based on the following process.^{24–26,30} The first step entails bombarding the polymer (*e.g.*, poly(ethylene terephthalate) (PET) and polyimide (PI)) film with a high-energy particle from a nuclear reactor or cyclotron. This process creates a linear damage track that spans the entire thickness of the film (Fig. 3a, i). Then, by using suitable wet etchants, the damaged material along the track can be removed more quickly than the bulk material, thus developing the track into nanochannel (Fig. 3a, ii). Under suitable conditions, channels down to a few nanometers in diameter can be produced. For example, to produce a conical nanochannel (Fig. 3b), etching was performed only from one side of the polymer membrane (left side), the other (right) side contained a solution that is able to neutralize the etchant as soon as the channel opens, thus slowing down the further etching process. The large opening of the conical nanochannel was called the base, while the small opening was called the tip. Details of chemical etching procedures which lead to symmetric (cylinder,^{27,31,32} hour glass,^{33–37} and cigar^{28,38,39}) and asymmetric (cone^{24,25,40} and bullet^{41–43})

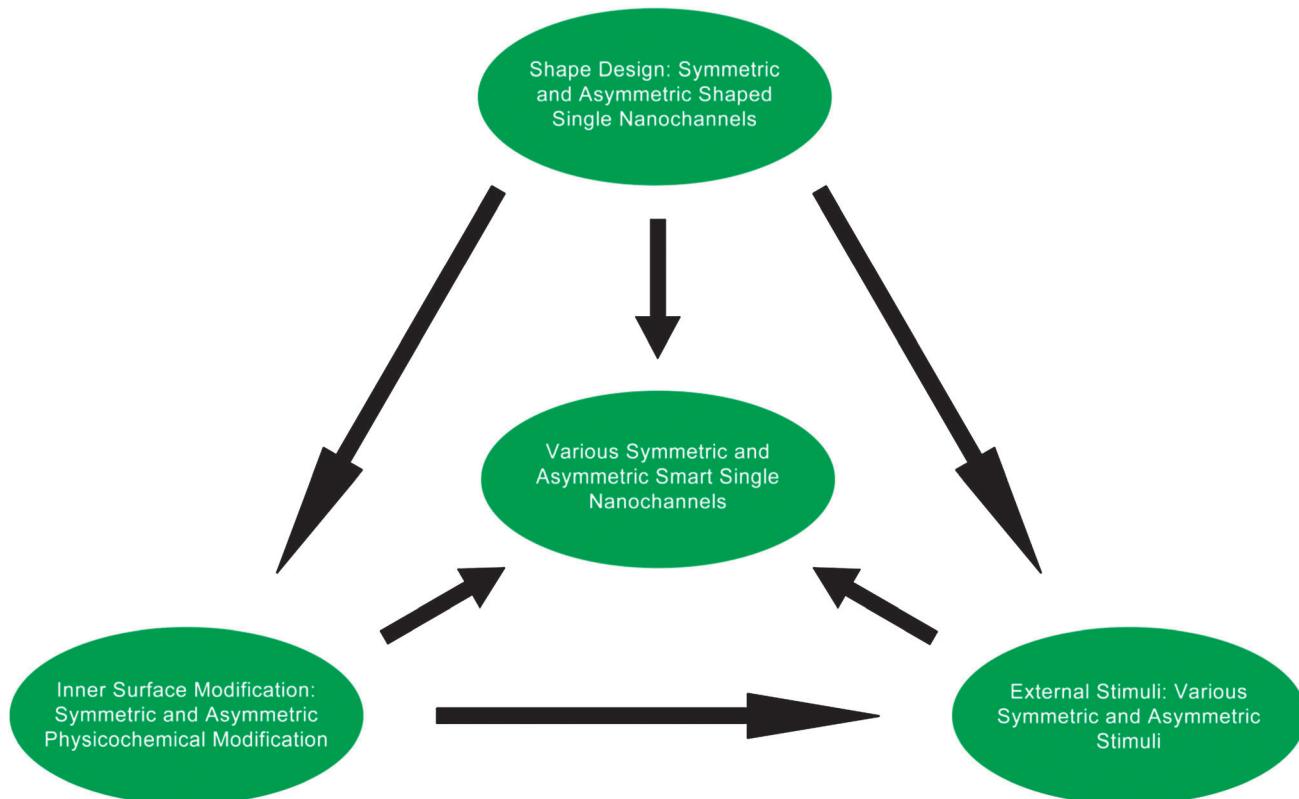


Fig. 2 The symmetric and asymmetric design and preparation of bio-inspired smart single nanochannels.

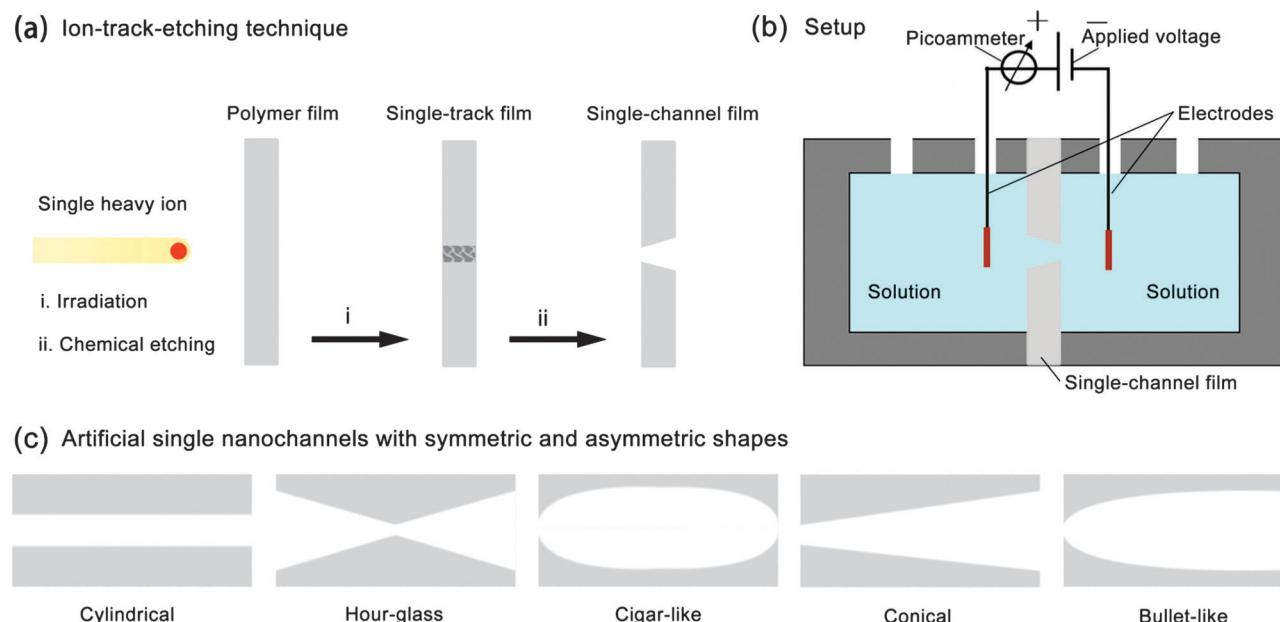


Fig. 3 Artificial single polymer nanochannels. (a) Principle of the ion-track-etching technique. (b) Experiment setup for the chemical etching and ionic current measurements of the nanochannels. (c) Symmetric and asymmetric shapes of the polymer nanochannels.

shaped single nanochannels (Fig. 3c) have been studied and described in detail by Apel, Siwy, and Jiang *et al.* These symmetric and asymmetric shaped nanochannels provide a useful platform for the further development of smart nanochannels with single/double functional artificial gates by chemical

modifications of the inner surface of the nanochannels with functional molecules.

Here we show two classical approaches in the chemical modification⁴⁴ of the interior surfaces of single polymer nanochannels as an example to illustrate the chemical modification

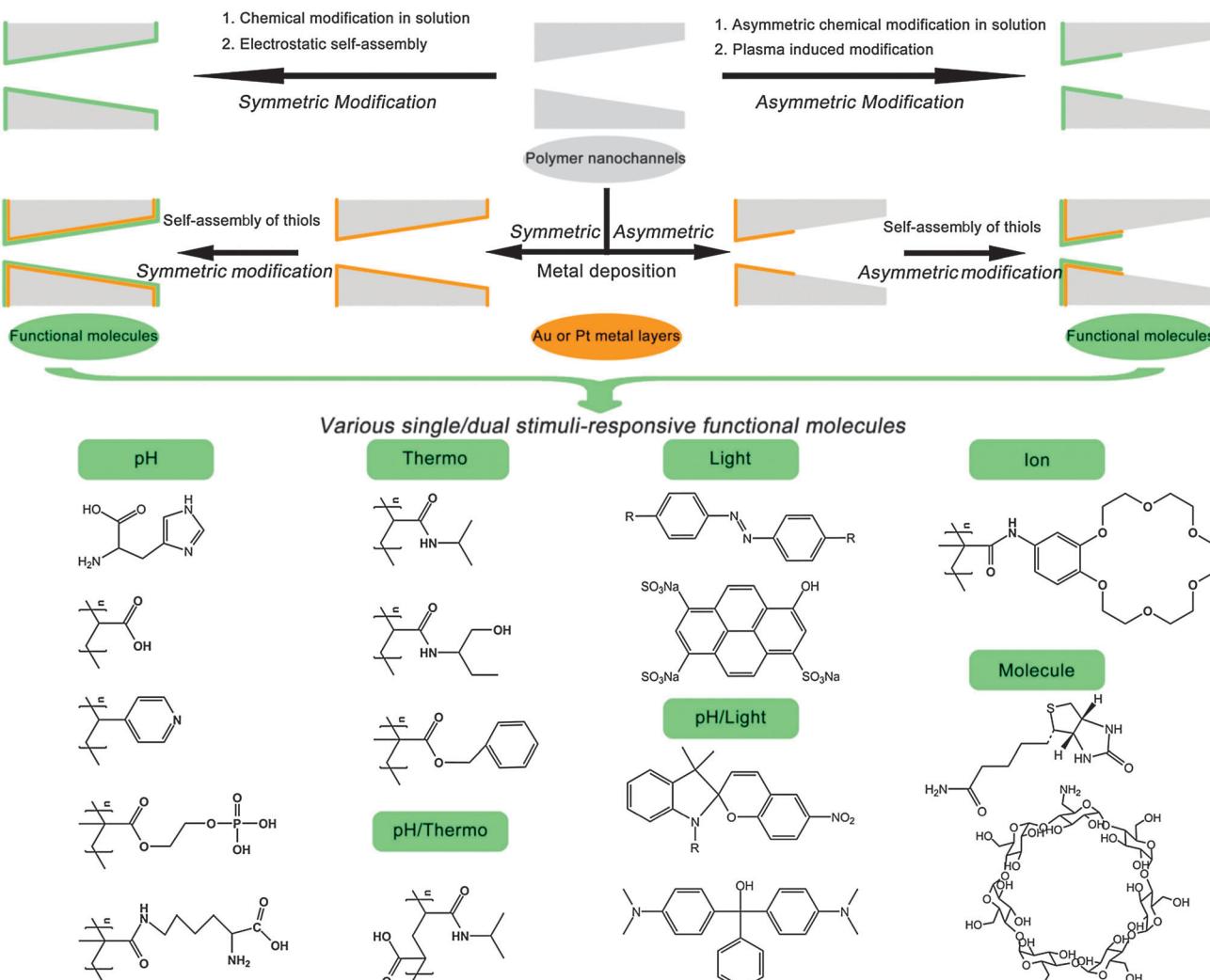


Fig. 4 Symmetric and asymmetric physicochemical modifications of the interior surfaces of the single polymer nanochannels with functional molecules which can respond to the diverse stimuli including pH, temperature, light, ions and molecules and so on.

part of the design strategy, which may also be extended to other nanochannel materials (Fig. 4). The first approach is the symmetric modification of the nanochannel. The symmetric modification method is the most commonly used method because it has the advantage of very simple implementation of overall modification or functionalization of the inner surface of the nanochannel to finally develop an artificial gate on the nanochannel. It is universally suitable for the modification of a variety of materials. It is also noteworthy that this modification method can take advantage of the nanochannel's symmetric-asymmetric shape itself to achieve the symmetric-asymmetric ionic transport regulation inside the nanochannel. The major symmetric modification methods include electroless deposition modification,^{45,46} chemical modification by functional molecules in solution,^{27,30,47–58} and self-assembly modification.^{59,60}

The second approach is asymmetric modification of the nanochannel. Asymmetric functional modification of nanochannels is still in its early stages. In general, the asymmetric modification methods are also adequate for the symmetric

modification. However, the asymmetric modification could potentially provide new ideas to spark experimental efforts to develop smart nanochannel systems, because the asymmetric modification approaches can precisely functionalize diverse specific local areas of the channel with different functional molecules to build multiple artificial functional gates on the nanochannel. It provides more design ideas for building multiple functional nanochannels. The typical asymmetric modification methods include ion sputtering modification,^{37,61} physical/chemical evaporation modification,⁶² plasma-induced modification,^{35,36,39} and asymmetric modification by functional molecules in solution.^{34,63,64} As already mentioned above, chemical modification of the nanochannel with functional molecules to build artificial functional gates is a primary approach to make nanochannels "smart". Thus, the design and synthesis of functional molecules is a key factor to develop bio-inspired smart nanochannels. Several single (pH, thermo, light, ions and molecules) and dual (pH/light and pH/thermo) responsive molecules described in the literature are listed in Fig. 4.

2. Smart single-gate nanochannels

There has been rapid progress in developing artificial functional nanochannels with single/double functional gates, by the opening and closing of which ionic currents inside the nanochannels can be intelligently controlled as in biological nanochannels. An artificial gate on the single nanochannel is an abstract concept of the functional groups or molecules immobilized on the channel wall, which could act in response to single/multiple external stimuli such as pH, temperature, light, electric potential, ions and molecules. Based on the artificial functional gates, the regulation of ionic transport inside the single nanochannels could well reproduce the three features including ionic selectivity, ionic rectification and ionic gating in biological nanochannels. The ionic gating feature could be directly illustrated by the stimuli responsive current–voltage (*I*–*V*) curves of the nanochannels (Fig. 5a). The ionic rectification is observed as asymmetric *I*–*V* curves (Fig. 5b, blue line), while the ionic selectivity is defined as the ratio of the ionic current of anions (or cations) to the total ionic current. According to the symmetric and asymmetric ionic transport properties, the nanochannels could be divided into the symmetric and asymmetric nanochannels. Symmetric nanochannels demonstrate stimuli-dependent symmetric ionic current gating properties, which generally characterize symmetric and linear *I*–*V* curves (Fig. 5a), while the asymmetric nanochannels possess both stimuli-tunable ionic current gating and ionic rectification properties, and exhibit non-linear and asymmetric *I*–*V* curves on the open state (Fig. 5b). It has been experimentally and theoretically proved that the shape and surface properties are key factors to influence the ionic transport inside the nanochannels, and the ionic rectification is caused by the broken symmetry in electrochemical potential of the nanochannel system.^{10,13} Therefore, symmetric nanochannels may generally refer to the nanochannels with symmetric shapes, symmetric modifications, and the symmetric external stimuli. However, asymmetric nanochannels can be attributed to the asymmetric shape, the asymmetric modification and the asymmetric external stimuli of the nanochannels. In addition, according to the number of artificial gates they have, the nanochannels could be further classified into single-gate and double-gate nanochannels. In the following, the symmetric single-gate nanochannels, the asymmetric single-gate nanochannels, and

the much more functional double-gate nanochannels are illustrated in detail.

2.1. Symmetric single-gate nanochannels

Single nanochannels integrated with single artificial gates have been widely developed by creating one kind of functional group or molecules on the inner surface of the nanochannels by the symmetric–asymmetric modification methods shown in Fig. 3. At present, symmetric ionic transport features have mainly been obtained in the symmetric shaped nanochannels, and some asymmetric shaped nanochannels without surface charge. In the following, pH, molecule, temperature, and ion-responsive single nanochannels with symmetric ionic transport features are illustrated in detail.

2.1.1. pH-responsive single-gate nanochannels. At present, pH-responsive nanochannels have been extensively studied for two main reasons. First, pH is very significant for all electrochemical reactions, and the change of pH is recognized as one of the most important signals for ion channels in life processes. Second, pH values can be easily changed by a simple acid and alkali regulation approach.

The unmodified PET and PI single nanochannels could demonstrate symmetric pH gating properties because their inner surface is coated with pH-responsive carboxylate groups after chemical etching. A direct consequence of the presence of carboxylate groups is the possibility of regulating the channel surface charge by immersing the membranes in electrolyte solutions buffered to various pH values (Fig. 6a, right). For example, at neutral and basic conditions, the carboxylate groups are deprotonated and the net surface charge is negative. Lowering the pH to values close to the isoelectric point of the track-etched surface neutralizes the surface charge. As shown in Fig. 6a, *I*–*V* curves were recorded through a single hour-glass PET nanochannel at 0.1 M KCl concentrations with a pH range from 3.7 to 9,³⁴ and the change of the pH of 0.1 M KCl between 3.7 and 9 changed the current value by $\geq 40\%$. The symmetric pH gating functionalities of the cylindrical and cigar-like PET nanochannels have also been experimentally and theoretically confirmed by Siwy's, Jiang's and Azzaroni's groups.^{27,35,36,38,39,65}

Similar to the original symmetric shaped nanochannels, the pH-responsive molecules-modified symmetric nanochannels also exhibit symmetric pH gating ability under symmetric pH stimuli. A single cylindrical polymer nanochannel modified with pH-responsive polyvinylpyridine (PVP) brushes was developed to achieve the more effective symmetric ionic current gating characteristics, and its transmembrane ionic current can be accurately controlled by manipulating the proton concentration in the surrounding environment. This allows the creation of a pH-switchable and tunable single nanochannel displaying ionic transport properties similar to the typical behavior observed in many biological channels that fulfil key pH-dependent transport functions in living organisms. That is, the nanochannel can be switched from a "closed" state to an "open" state in response to a pH drop. Fig. 6b depicts the *I*–*V* curves of this single nanochannel modified with PVP brushes at different pH values. By increasing the pH from 2 to 4, and finally to 10, a significant decrease in the transmembrane ionic current was observed

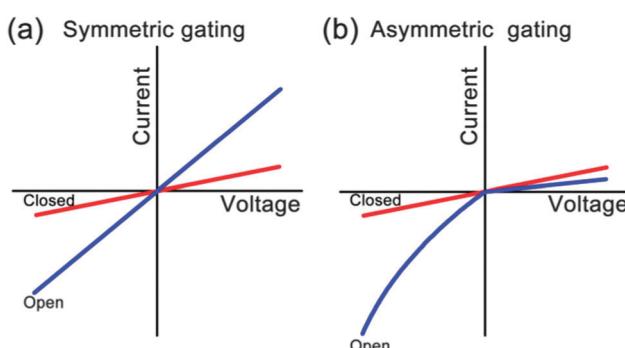


Fig. 5 *I*–*V* curves of the stimuli responsive symmetric (a) and asymmetric (b) nanochannels.

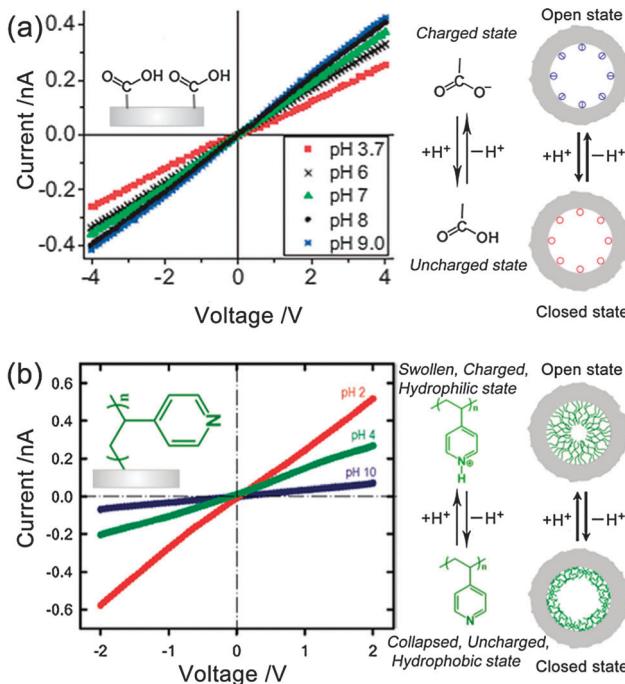


Fig. 6 pH-responsive symmetric single-gate nanochannels. (a) I - V curves of an hour-glass PET nanochannel as a function of pH were studied at 0.1 M KCl and cartoon describing the surface charge in response to pH.³⁴ Copyright 2007 Wiley-VCH Verlag GmbH & Co. KGaA. (b) I - V characteristics of a cylindrical PVP-modified nanochannel in 0.1 M KCl at different pH and cartoon describing the pH-responsive conformation transition of the polymer brushes.⁶⁵ Copyright 2009 American Chemical Society.

under the same applied bias.⁶⁵ The “open/close” switching was based on the manipulation of the surface charges of the channel walls *via* the protonation of the PVP brush layer, which in turn controls the channel conductivity (Fig. 6b, right).

2.1.2. Molecule-responsive single-gate nanochannels. Bio-inspired molecule-responsive nanochannels attract increasing interest for their potential applications in molecular sensors. Symmetric single-gate nanochannels for molecule sensing are based on the specific binding of protein molecules inside the channel wall, which symmetrically change the transmembrane ionic currents by reducing the effective channel diameters after binding. For instance, Martin, Siwy *et al.* reported a protein analyte that binds to a biochemical molecular-recognition agent (MRA) immobilized on a single conical gold nanochannel.⁴⁸ Because the protein molecule and the nanochannel mouth have comparable diameters, the binding of protein molecules effectively plugs the nanochannel, which correspondingly shows a molecule-responsive blockage of the ionic current (Fig. 7a). I - V curves for the biotinylated nanochannel before and after exposure to a solution that contains 100 nM lysozyme are identical, indicating that the channel does not respond to a protein that does not bind to the biotin MRA. In contrast, the ionic current is completely shut off after exposure to a solution with 180 pM streptavidin (Fig. 7b). Total ionic current blockage occurs because the diameter of the streptavidin molecule, about 5 nm, is comparable to the mouth diameter for the biotinylated nanochannel.

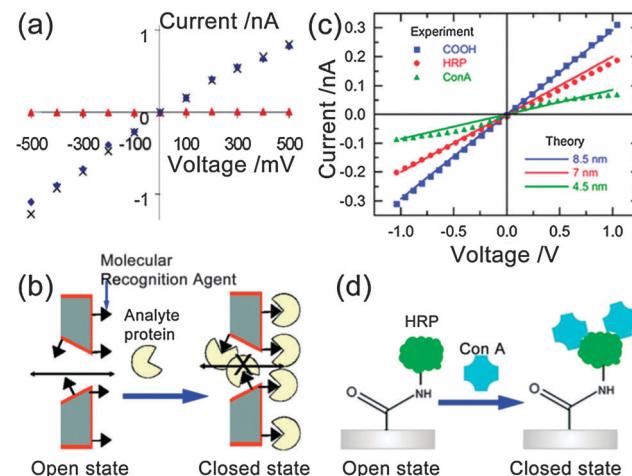


Fig. 7 Molecular-responsive symmetric single-gate nanochannels. (a) I - V curves for the streptavidin responsive conical Au nanochannel in the presence of no protein (x), 100 nM lysozyme (■), and 180 pM streptavidin (▲).⁴⁸ (b) Schematic representation of the process of streptavidin binding. Copyright 2005 American Chemical Society. (c) I - V curves for the case of a cylindrical PET nanochannel with COOH, HRP and Con A groups. (d) Schematic representation of the Con A binding process.²⁷ Copyright 2011 Royal Society of Chemistry.

Ali *et al.* further demonstrated a symmetric molecule-responsive nanochannel by supramolecular bioconjugation of concanavalin A (Con A) protein with glycoenzyme horseradish peroxidase (HRP) inside a single cylindrical nanochannel (Fig. 7c).²⁷ Firstly, the HRP-enzyme was covalently immobilized on the inner wall of the channel using carbodiimide coupling chemistry. The immobilized HRP-molecules bear sugar (mannose) groups available for the binding of Con A protein. Secondly, the bioconjugation of Con A on the channel wall was achieved through its bio-specific interactions with the mannose residues of the HRP enzyme. The immobilization of biomolecules inside the nanochannel leads to the reduction of the available area for ionic transport, and this blocking effect can be exploited to tune the conductance and selectivity of the nanochannel in aqueous solution. The significant changes in the I - V curves resulting from the binding of different molecules clearly demonstrate that a detecting system was established based on the decrease in the electrical conductance due to the blocking of the channel upon protein bioconjugation (Fig. 7d).

2.1.3. Thermo-responsive single-gate nanochannels. The physiological process of thermo-sensation is carried out by the direct activation of thermo-gated ion channels in the surface membranes of sensory neurons. Ion channels activated by temperature changes are based on thermo-responsive molecular conformational changes that open and close the channels. Inspired by these ion channels, Azzaroni's group reported a temperature-driven single-gate nanochannel based on a single conical PI nanochannel that was symmetrically modified with temperature-responsive poly(*N*-isopropylacrylamide) (PNIPA).⁵² PNIPA brushes neutralize the surface charge of the channels resulting in the loss of the ionic rectification behaviour, and the channel consequently exhibits linear I - V characteristics (Fig. 8). At room temperature (23 °C) PNIPA brushes remain in a swollen state, thus decreasing the effective diameter of the nanochannel,

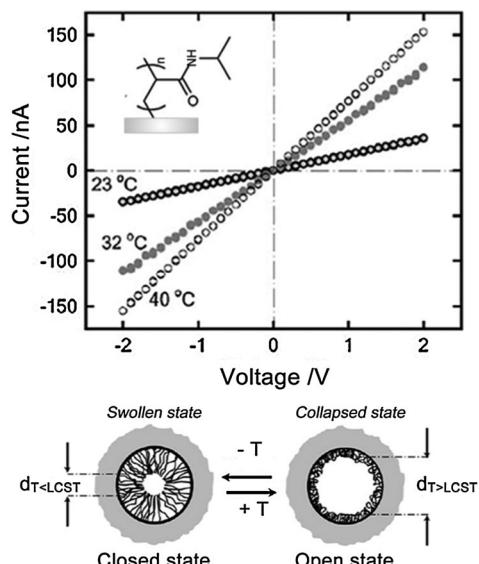


Fig. 8 A thermo-responsive single-gate nanochannel. I - V curves in 1 M KCl for a PI conical nanochannel after modification with PNIPA brushes at different temperatures. The cartoon describes the thermally driven nanoactuations of the PNIPA brushes in the nanochannel.⁵² Copyright 2009 Wiley-VCH Verlag GmbH & Co. KGaA.

which is described by the low slope of the I - V curve and is associated with a low conductance of the nanochannel (closed state). Raising the temperature above the lower critical solubility temperature (LCST) undergoes a sharp change in the PNIPA brushes' conformational state, which suffers a transition into a collapsed state, leading to an increase of the effective cross-section of the nanochannel. The conformational transition into a more compact state promotes the widening of the diameter of the nanochannel, which is evidenced as an increase in conductance, as derived from the slope of the I - V plots at 40 °C. The thermo-responsive brushes are acting as a thermo-driven gate, effectively controlling the ionic flow through the nanochannel. Moreover, this thermo-responsive nanochannel is completely reversible, due to the reversibility of the thermally triggered conformational changes of the PNIPA brushes. This work further demonstrates the versatility of polymer brushes to achieve an accurate and reversible control of the topological characteristics of nanoconfined environments with dimensions comparable to biological channels.

In a similar vein, many studies have reported that the ionic transport behaviour of nanoporous membranes directly grafting thermo-responsive hydrogels⁶⁶ or polymer brushes^{52,67,68} is symmetric in both directions, showing no ionic rectifying properties. It was thought that the native charged groups on the inner surfaces of the nanochannels are replaced by the uncharged thermo-responsive polymer chains after chemical modification.

2.1.4. Ion-responsive single-gate nanochannels. Metallic ions are crucial in modulating the activity of muscles and nerves whose cells have specialized ion channels for transporting these ions, such as sodium, calcium and potassium. Normal body function is extremely dependent on the regulation of metallic ion concentrations inside the ion channels within a certain range. For life science, ion-responsive single nanochannels promote a

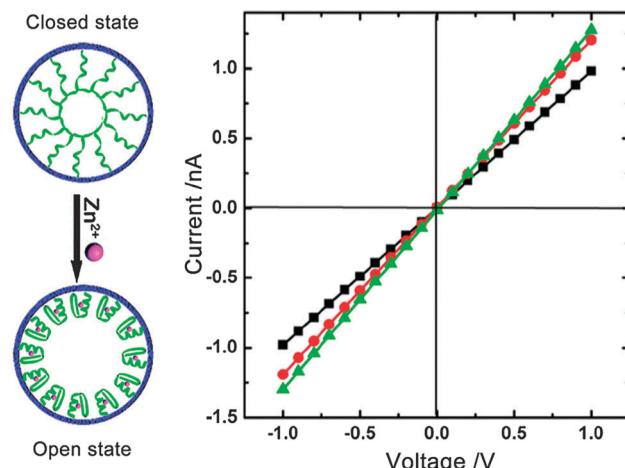


Fig. 9 Ion-responsive single-gate nanochannel. I - V characteristics of a zinc fingers-immobilized nanochannel in 0.1 M KCl with 0 μ M (■, black) 10 μ M (●, red) and 100 μ M (▲, green) Zn^{2+} .⁵¹ Copyright 2010 Royal Society of Chemistry.

potential platform to study and simulate these processes happening in living organisms by a convenient artificial system.

Jiang *et al.* recently developed a Zn^{2+} -responsive single nanochannel showing a symmetric ionic gating feature in the absence of surface charges after modification. A biomimetic zinc-activated nanochannel was obtained by immobilizing zinc finger peptides into a single conical nanochannel.⁵¹ Similarly to the zinc-activated ion channel, this nanochannel is activated by zinc, which contributes to the conformational changes of the zinc fingers (Fig. 9). Compared with simple responsive organic molecules, the biomolecule-modified nanochannel is more complicated and moves one step farther for the development of "smart" nanochannel materials.

2.2. Asymmetric single-gate nanochannels

Asymmetric single-gate nanochannels with the broken symmetry in their electrochemical potential could show asymmetric ionic transport properties. The asymmetric shape integrated with symmetric-asymmetric surface properties including surface charge and wettability could bring out asymmetric electrochemical potential. Thus asymmetric responsive properties are mainly obtained in the original/modified asymmetric shaped polymer nanochannels, and in some symmetric shaped nanochannels integrated with asymmetric modification and asymmetric external stimuli. In the following, both single stimulus (*i.e.*, pH, temperature, electric potential, ions and molecules) and dual stimuli (pH/light, pH/temperature, and pH/molecule) responsive single-gate nanochannels with asymmetric ionic transport features are illustrated in detail.

2.2.1. pH-responsive single-gate nanochannels. The asymmetric pH-responsive ionic current gating phenomenon is originally observed from biological ion channels. Later, the ionic rectification could also be found in the micro/nanochannels. Different from other artificial channels, the asymmetric (cone and bullet) shaped single PET nanochannels could show asymmetric pH-responsive properties because carboxyl groups were created on the channel inner surface during the etching process.^{26,43,69} As shown in Fig. 10a, a single conical PET nanochannel behaves

with asymmetric *I*-*V* character when the channel surface is negatively charged under neutral and basic conditions.⁷⁰ For lower pH values, however, the surface is protonating the groups by the adsorption of protons, and it shows a loss of the rectification properties. Many other materials also have similar properties, such as PI nanochannels⁴⁰ and glass pipettes.⁷¹ Siwy has also developed a pH-responsive asymmetric nanochannel whose inner surface was patterned after asymmetric chemical modification to partially transform carboxyl groups into amino groups so that a sharp boundary between positively and negatively charged regions was created.⁶³ The rectification property is not a typical pH-responsive change of the original conically shaped nanochannel, and there is a maximum value in the middle range of the pH change from acidic to alkaline.

Azzaroni, Ali *et al.* reported several pH-tunable asymmetric single nanochannels by the integration of pH-responsive polymer brushes or amphoteric molecules into the inner surfaces of the channels.^{54–56,72} The growth of zwitterionic polymer brushes provides a useful approach to finely tune the asymmetric ionic transport features of the nanochannels. They demonstrate that manipulation of ion transport through the channel by simply varying the environmental pH is achievable and enables a higher degree of control over the ionic transport properties inside the channel. They describe the construction of a pH-responsive asymmetric single nanochannel whose permselectivity and rectifying properties are enhanced by using polyprotic polymer brushes as highly tuneable building blocks. Poly(methacryloyl-L-lysine) brushes (PMALL) as amphoteric chains were immobilized onto the inner surface of the single conical nanochannel to finely tune the ionic transport by presetting the environmental pH.⁵⁵ At low pH values, the ionized amino groups are positively charged due to protonation, while the protonated carboxylic groups are neutral (Fig. 10b). The nanochannel is then selective to anions and shows the rectification properties characteristic of the conical channel with positive fixed charges. Conversely, at high pH values, the deprotonated amino groups are in neutral form, while the carboxylic groups are ionized. The transition between these two rectification regimes occurs close at the isoelectric point, and at this pH value the carboxylic and the amino groups are charged, but the nanochannel net charge is zero, and the *I*-*V* curve shows a linear behavior.

As mentioned above, the pH-tunable asymmetric ionic transport properties of the nanochannels have already been successfully developed based on the asymmetric shaped nanochannels modified with pH-responsive molecules. Jiang's group further developed the asymmetric pH responsive nanochannel material by using a plasma-induced asymmetric modification of a symmetric hour-glass single nanochannel with polyacrylic acid (PAA) brushes.³⁵ Compared with previous materials, this responsive nanochannel has the advantage that it provides simultaneous control over the pH-tunable asymmetric and pH gating ionic transport properties inside the symmetric shaped nanochannel. There was a remarkable difference in that significant rectifications were observed as asymmetric *I*-*V* curves (Fig. 11a). A significant asymmetric increase in the transmembrane ionic current could be observed when the pH changed from 2.8 to 10 in both ion transport directions under the same ion concentration. This asymmetric ionic current gating property is

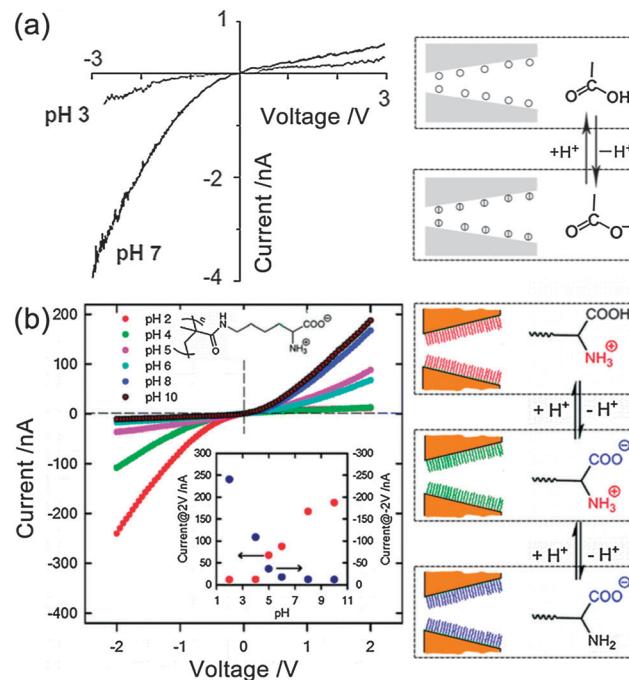


Fig. 10 pH-responsive asymmetric single-gate nanochannels. (a) *I*-*V* characteristics of the single conical PET nanochannel recorded in 0.1 M KCl at different pH.⁴⁰ Copyright 2003 Elsevier. (b) *I*-*V* curves corresponding to a single conical nanochannel modified with PMALL brushes measured at different pH values (using 1 M KCl as electrolyte). The inset describes the changes in the rectified currents upon variation in the environmental pH.⁵⁵ Copyright 2009 American Chemical Society.

caused by PAA brushes inducing the structural asymmetry and the asymmetric surface charge distributions on the both sides of the nanochannel (Fig. 11a, left).

In addition to the asymmetric shape design and asymmetric modification method, the asymmetric pH stimuli are also effective approaches to obtain the asymmetric pH-responsiveness inside the nanochannels. The asymmetric pH stimuli-induced asymmetric pH gating properties were first obtained in biological ion channels.⁷³ After that, the asymmetric pH stimuli have been used in a single cylindrical PET nanochannel to observe asymmetric ionic transport properties inside a symmetric nanochannel.^{38,74–76} Ali *et al.* further used the asymmetric pH stimuli in a lysine-modified cigar-shaped nanochannel and thus the nanochannel showed functional asymmetric pH gating properties.³⁸ The curves of Fig. 11b show diode-like *I*-*V* characteristics with well-defined on and off conductance states due to the asymmetric fixed charge distributions generated by the applied pH gradients (see the cartoons above the curves). The case of $pH_L = 5$ and $pH_R = 10.5$ corresponds to a neutral/negative fixed charge distribution similar to that of the pristine nanochannel under asymmetric pH conditions. The channel is in the on state for $V < 0$ when the positive mobile ions enter first the channel tip with opposite fixed charges. Conversely, for $pH_L = 5$ and $pH_R = 2.5$, the fixed charge distribution is neutral/positive and the nanochannel shows the on state when the negative mobile ions enter first the channel tip with positive fixed charges ($V > 0$). Finally, the case of $pH_L = 10.5$ and $pH_R = 2.5$ gives a negative/positive fixed charge distribution similar to

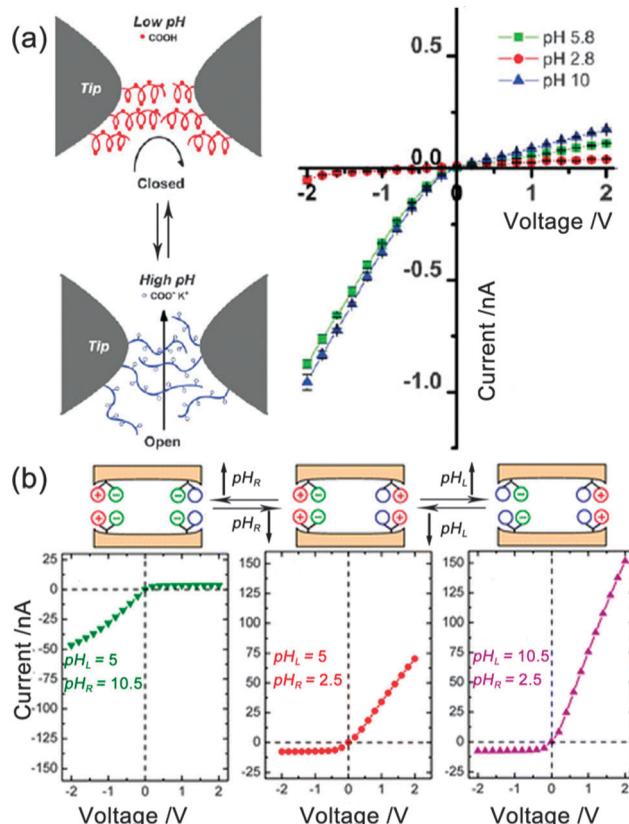


Fig. 11 Asymmetric pH-driven single symmetric shaped nanochannels. (a) I - V properties of the PAA asymmetrically modified single hour-glass nanochannel under different pH conditions.³⁵ Copyright 2010 Wiley-VCH Verlag GmbH & Co. KGaA. (b) I - V curves of a cigar-shaped single nanochannel functionalized with lysine chains at 0.1 M KCl and asymmetric pH conditions. The cartoons above each curve illustrate the distribution of fixed charges in the regions close to the pore tips.³⁸ Copyright 2012 American Chemical Society.

that found in solid-state n-p diodes, bipolar ion-exchange membranes, and conical nanochannels with alternating regions of positive and negative fixed charges. The resulting I - V curve shows the on state for when the negative and positive mobile ions first enter the respective channel tips with opposite fixed charges.

2.2.2. Ion-responsive single-gate nanochannels. Different from the metallic ion-driven DNA/peptide conformation changes regulating the biomimetic ion channels reported by Jiang's group,^{50,77} Siwy *et al.* discovered that Ca^{2+} -induced voltage gating in a single conical PET nanochannel, and the channel produced voltage-dependent ionic current fluctuations in the presence of sub-millimolar concentrations of Ca^{2+} .^{78,79} Millimolar concentrations of Ca^{2+} reverse the rectification, and introduce a negative incremental resistance of this nanochannel. Fig. 12a shows I - V curves before and after adding Ca^{2+} . Adding Ca^{2+} induced a nonlinear behavior in the I - V curve, and a negative incremental resistance occurred at negative voltages. Therefore, larger amplitudes of voltage induced smaller ionic fluxes. The addition of small amounts of divalent cations to a buffered monovalent ionic solution results in an oscillating ionic current through an asymmetric nanochannel. This new phenomenon is caused by the transient formation and redissolution of nanoprecipitates, which temporarily block the ionic current through

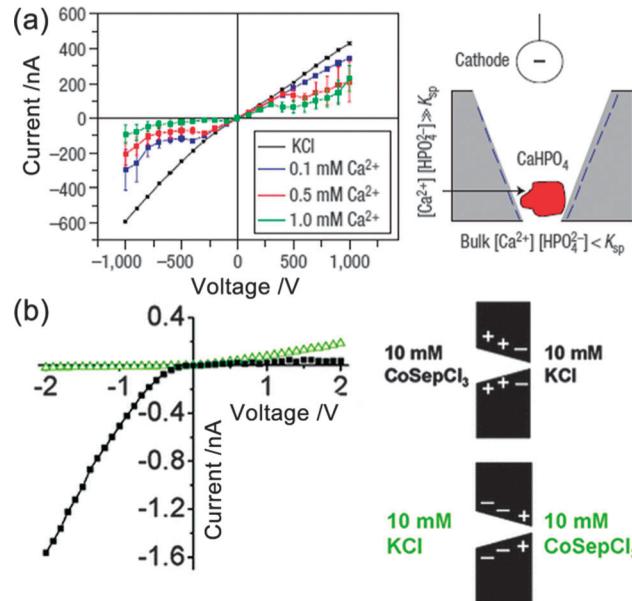


Fig. 12 Asymmetric ion-responsive single-gate nanochannels. (a) Calcium induced voltage gating in a single conical nanochannel. I - V curves were recorded in 0.1 M KCl with 2 mM PBS buffer alone (black trace) and with varying calcium concentrations. The cartoon shows the activities of Ca^{2+} and HPO_4^{2-} ions inside the nanochannel with negative surface charges then rise above the solubility product K_{sp} of CaHPO_4 , allowing nanoprecipitation to occur.⁷⁸ Copyright 2008 Nature Publishing Group. (b) I - V curves recorded with 10 mM CoSepCl₃ placed on one side of the membrane and 10 mM KCl on the other side of the membrane. The side with CoSep underwent charge inversion and the surface charge became effectively positively charged. The colors of the cartoons correspond to the colors for the recordings.⁸⁰ Copyright 2010 American Chemical Society.

the channel. The frequency and character of ionic current instabilities are regulated by the potential across the membrane and the chemistry of the precipitate.

Siwy *et al.* further show that a uniformly charged conical nanopore can have much more functional asymmetric ionic current gating properties by changing the ion species (K^+ , polyvalent cations like Ca^{2+} , and the trivalent cobalt sepulchrate (CoSep)) and their concentrations on each side of the membrane.⁸⁰ In order to check the performance of the asymmetric gating that are formed when charge inversion or neutralization occurs on one side of conical channels, the channels were placed between solutions of 10 mM CoSep and 10 mM KCl (Fig. 12b). In both cases with CoSep and Ca^{2+} , very strong current rectification was observed, providing evidence that diode junctions were indeed obtained in these systems. Cartoons in Fig. 12b illustrate the effective surface charge distributions formed on the channel walls. Recently, an asymmetric pH/ Ca^{2+} -responsive nanochannel has been reported by Ali *et al.* based on pH-dependent Ca^{2+} binding to a phosphonic acid modified channel wall.⁸¹

2.2.3. Molecule-responsive single-gate nanochannels. Azzaroni, Ali *et al.* reported a new approach to incorporate biosensing elements into conical nanochannels by using electrostatic self-assembly.⁵⁹ A facile strategy based on the use of bifunctional macromolecular ligands to electrostatically assemble biorecognition sites into the nanochannel wall, which can then be used as recognition elements for constructing a nanobiosensor. Fig. 13a describes the changes in the I - V plots upon putting into contact

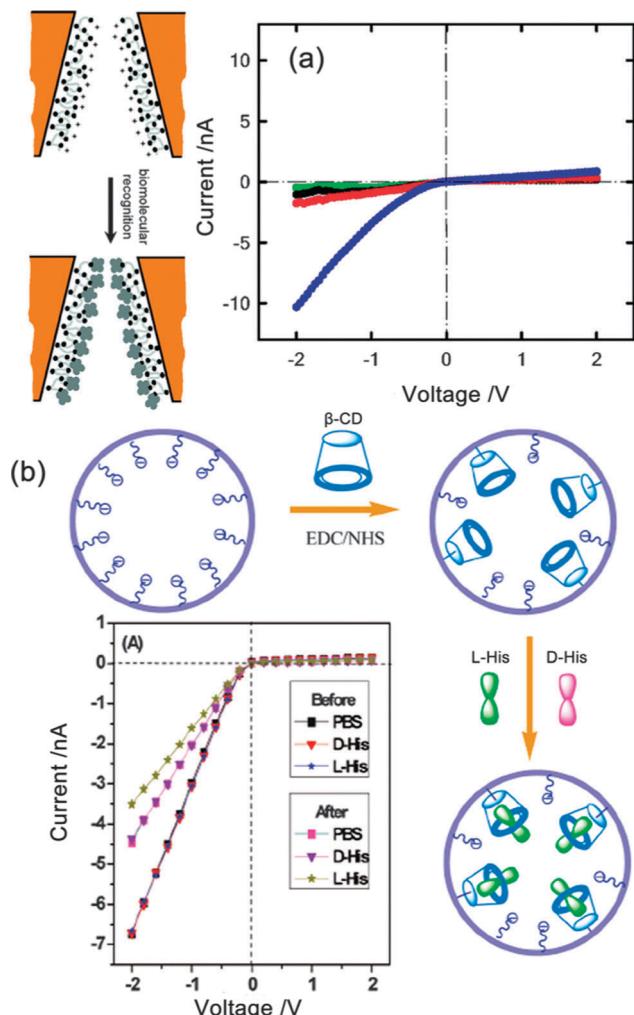


Fig. 13 Molecule-responsive asymmetric single-gate nanochannels. (a) I - V characteristics of a b-PAH-modified single conical nanopore in 0.1 M KCl in the presence of different concentrations of SAv: (dark blue) no SAv; (red) 1 pM; (black) 10 pM; (green) 100 pM. The carboxylate-terminated nanopore is used as a platform for the electrostatic immobilization of the bifunctional macromolecular ligand, b-PAH.⁵⁹ Copyright 2008 American Chemical Society. (b) I - V curves for the single conical nanochannel before and after β -CD modification in 50 mM PBS (pH 7.2) without or with the addition of 1 mM L-His or D-His, as labeled. The modified nanochannel works as a chiral receptor for His, as selective binding of L-His to the inner wall of the nanochannel disturbs the channel surface, resulting in a significant change in the transmembrane ionic current.⁸² Copyright 2011 American Chemical Society.

the biotin-modified nanochannel with streptavidin solutions of different concentrations. As expected, the presence of streptavidin, even at very low concentrations, led to a drastic change in the rectified current. The permselective transport of ions across the biotinylated poly(allylamine) (b-PAH) modified nanochannel, measured at -2 V, was -10.3 nA. The presence of 1 pM streptavidin (SAv) led to a rectified current of -1.7 nA; this means that the blockage of the nanochannel due to the formation of the bioconjugate decreased the ionic flux across the nanochannel by $\sim 85\%$. This effect was even more pronounced when working with more concentrated SAv solutions. The presence of 100 pM SAv promoted a $\sim 96\%$ decrease of the rectified current observed in the nonbioconjugated nanochannel.

These experimental results provide clear evidence that the electrostatic assembly enables the anchoring of ligands which are able to biorecognize receptors inside the nanochannel, and this biorecognition can be transduced in an electronic signal provided by the ionic flux through the channel.

Recently, Li *et al.* reported a simple enantioselective sensing device based on a single artificial β -cyclodextrin (β -CD)-modified single conical nanochannel system.⁸² It shows highly selective recognition of histidine enantiomers through the monitoring of ionic current signatures. Fig. 13b shows the fabrication and operating principle of the chiral-responsive system, and I - V curves of the single nanochannel before and after β -CD modification in the presence of 1 mM L- or D-His. It is obvious that the β -CD-modified nanochannel displayed His-specific chiral discrimination. The functionalized nanochannel exhibited a good chiral recognition capability toward L-His, which was manifested *via* the changes in the ionic current flowing through the nanochannel. Upon exposure of the β -CD-modified nanochannel to a solution of L-His, selective binding of L-His to the channel wall occurred inside the confined geometry. This effect induced a decrease in the transmembrane ionic current. In contrast, no significant changes in the ionic current were found when the modified channel was exposed to solutions of D-His or other aromatic amino acids.

2.2.4. Voltage-responsive single-gate nanochannels. A transmembrane potential is a particularly useful stimulus as it is non-invasive, tunable, and can act over a short time scale.⁸³ Electric potential-responsive materials in this review exclude the original asymmetric polymer nanochannels that show voltage-dependent ionic current fluctuations with opening and closing kinetics similar to voltage-gated ion channels⁷⁰ and biological nanochannels. It is clear that the ionic current rectification in ion channels is more complicated and involves the physical movement of an ionically charged portion of the channel in response to a change in the transmembrane potential.⁴⁷

With the inspiration of examples from nature, Martin, Siwy *et al.* created artificial ion channels that were designed to rectify the ionic current flowing through them *via* this “electromechanical” mechanism.⁴⁷ These artificial channels are based on conical gold single nanochannels with the critical electromechanical response provided by single-stranded DNA molecules attached to the nanochannel walls. Before DNA modification, the gold nanochannel does not rectify, even though there is adsorbed Cl on the nanochannel walls (Fig. 14a). The DNA-containing nanochannels rectify the ionic current, and it shows an on-state at negative transmembrane potentials (anode facing the mouth of the nanochannel) and an off-state at positive potentials. It was supposed that the ionic rectification in these nanochannels entailed electrophoretic insertion of the DNA chains into (off-state) and out of (on-state) the nanochannel mouth. The off-state is obtained because, when inserted into the mouth, the chains partially occlude the pathway for ion transport, yielding a higher ionic resistance for the nanochannel. This hypothesis can be supported from I - V curves as the magnitudes of the on-state currents in Fig. 14a decrease with increasing DNA chain length. This is because even in the on-state, the DNA chains partially occlude the mouth of the nanochannel and increase the nanochannel resistance.

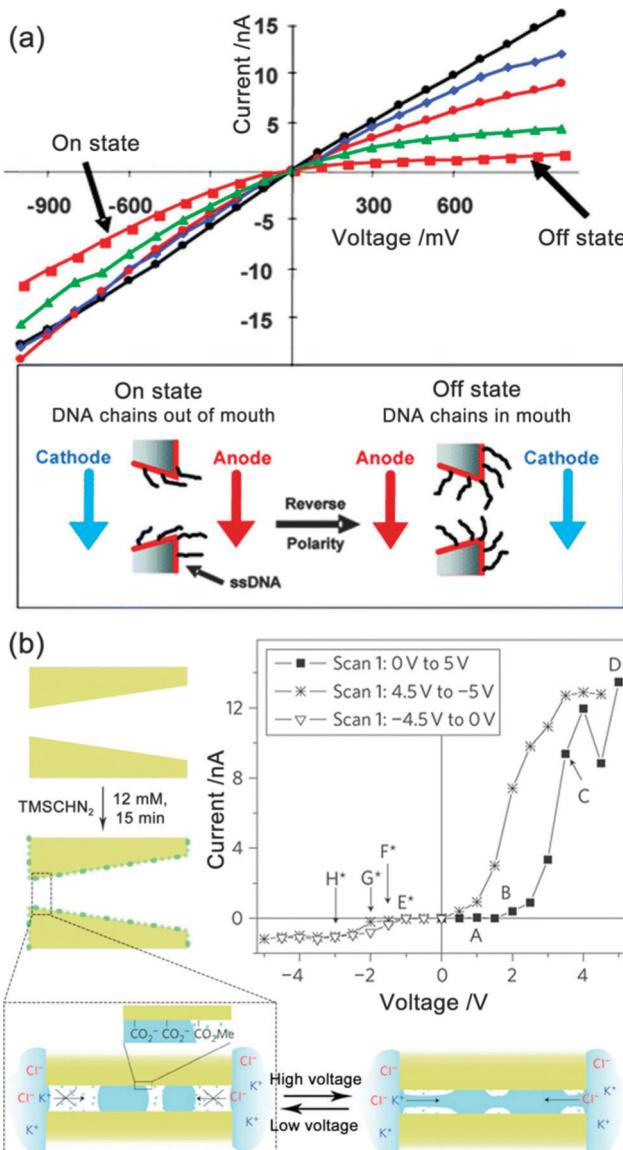


Fig. 14 Voltage-responsive single-gate nanochannels. (a) I - V curves for the DNA-modified single gold-polymer nanochannel containing no DNA (black) and an attached 12-mer (blue), 15-mer (red), 30-mer (green), and 45-mer (orange) DNAs. Schematics show electrode polarity and DNA chain positions for on and off states.⁴⁷ Copyright 2004 American Chemical Society. (b) I - V characteristic of a conical nanochannel with less hydrophobic surfaces characterized by contact angles less than 90°. It was proposed that local hydrophobic clusters are created, which induce the formation of local vapour pockets. An electric field applied across the membrane favours filling the pore with water and therefore ionic transport. A small fragment of a polymer nanochannel is presented and its shape is approximated by a cylinder.⁸⁴ Copyright 2011 Macmillan Publishers Limited.

Sawy *et al.* further developed a single hydrophobic nanochannel that can undergo reversible wetting and dewetting due to condensation and evaporation of water inside the channels.⁸⁴ The reversible process is observed as fluctuations between conducting and non-conducting ionic states and can be regulated by a transmembrane electric potential. Averaging the time series resulted in current–voltage curves that allowed for a quick assessment of the voltage sensitivity of the channels (Fig. 14b). Fig. 14b shows the ion current through a nanochannel with a

narrow opening (diameter, 16 nm) that was modified with 12 mM (trimethylsilyl) diazomethane for 15 min. For voltages below 1 V, the channel was mostly closed and no current was recorded. At 2 V the channel opened, and bursts of large-amplitude current signals of several nanoamperes could be observed. The bursts became more frequent at higher voltages and eventually, at 5 V, the channel remained in the open state.

2.2.5. pH/light dual responsive single-gate nanochannels.

Among the known addressable external stimuli, light-responsive molecular switches have opened a particularly challenging research area for applications in the development of light gating channels for externally modulating ionic transport due to a light response that can be regulated to achieve a response for a precise region. By using structure-based design, Trauner's group have successfully developed a novel chemical gate that confers light sensitivity to an ion channel.⁸⁵ Various relevant approaches for the active control of ion or molecule transport across nanoporous membranes have been investigated, such as light-induced variation of nanochannel diameter,⁸⁶ light-induced control of the hydrophobicity of a biological nanochannel,⁸⁷ and light control of nanochannel wetting.⁸⁸

Different from single stimulus-responsive nanochannel materials, several dual (*i.e.*, pH/light, pH/temperature, and pH/molecule) responsive nanochannels have been reported. Most recently, Jiang's group have reported many pH and light dual responsive single-gate nanochannels, in which the asymmetric ionic current gating was controlled by the pH/light dual responsive molecules-induced changes of the channel surface charge and wettability.^{89–91} As shown in Fig. 15, I - V curves of a spiropyran-modified conical nanochannel under and without UV light irradiation at pH 7 and pH 3 illustrate the asymmetric pH/light dual gating properties.⁸⁹ When the UV light is off, the nanochannel is in the closed state regardless of the polarity of the voltage. After irradiation, the ionic transport properties become asymmetric and depend on pH. At pH 7 the channel is negatively charged, hence, the high conductance state is obtained when the cations are driven from the tip to the base by electrophoresis. Conversely, at pH 3 the channel is positively charged, hence, the high conductance state is obtained when anions are driven from the tip to the base by electrophoresis.

2.2.6. pH/thermo dual responsive single-gate nanochannels.

Ulbricht *et al.* developed symmetric multiple nanochannels responding to pH and temperature stimuli *via* modification of dual responsive copolymer brushes.^{92,93} Most recently, Wang, Jiang *et al.* presented an integrated ionic gate and rectifier within an asymmetric single nanochannel *via* modifying pH and temperature dual responsive copolymer brushes (Fig. 16a).⁹⁴ The thermal gating ratios of this nanochannel remain approximately the same in the pH range from 3.6 to 9.4, but the ionic current rectification ratios increase with pH, which show a trend to saturation at high pH (Fig. 16b). Moreover, the temperature-controlled ionic gate works properly in the pH range from 3.6 to 9.4 and the pH-controlled ionic rectifier works equally well at both low (25 °C) and high temperatures (40 °C).

2.2.7. pH/molecule dual responsive single-gate nanochannels.

A pH and molecular dual responsive single nanochannel was created by Siwy *et al.* for biosensors.⁶⁴ Firstly, the original single

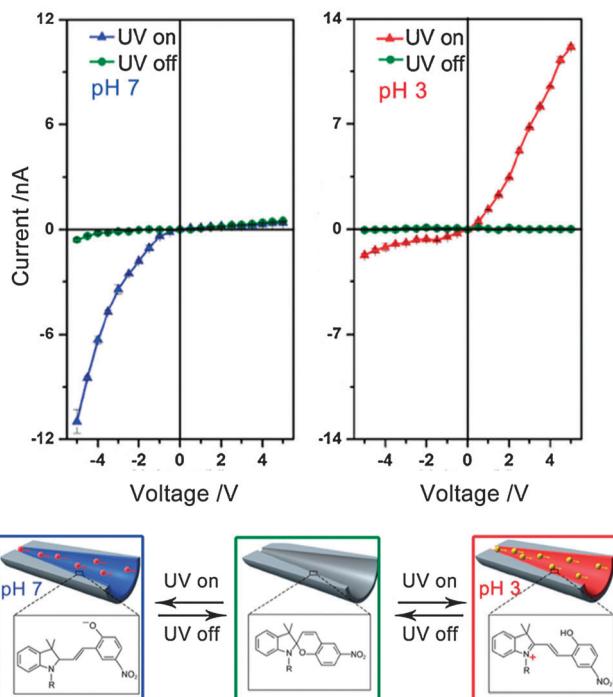


Fig. 15 pH/light dual responsive asymmetric single-gate nanochannels. *I–V* curves of a spirobifluorene-modified conical nanochannel under and without UV light irradiation at pH 7 and pH 3.⁸⁹ Copyright 2010 Wiley-VCH Verlag GmbH & Co. KGaA.

conically shaped polymer nanochannel was modified by a recognition agent only at the narrow opening using the method of surface patterning mentioned before.⁶³ As the next step, the tip of this single conical nanochannel was modified with a monoclonal antibody (mAb) for the capsular poly- γ -glutamic acid (γ DPGA). The resulting nanochannel showed a very strong dependence of its *I–V* behavior on pH (Fig. 17a and c).⁶⁴ At pH 8, the rectification direction was the same as for an unmodified channel. Placing this channel in an acidic pH resulted in a reversed rectification and in a significant increase of the rectification degree, providing evidence for the formation of a bipolar diode junction. After the channel was incubated with the bacterial γ DPGA, it showed that this channel rectified ionic current only in one direction for all examined pH conditions (Fig. 17b and d). However, pH values change the magnitude of ionic currents especially for negative voltages. Obviously, the influence of the surface charge on the tip of the conical nanochannel is the key factor for regulating ionic transport properties. In a similar vein, Ali *et al.* also reported a functionalized single asymmetric polymer nanochannel for biosensing.¹⁰⁴

3. Much more functional asymmetric double-gate nanochannels

Stimuli-responsive single-gate nanochannels have been well developed, however, how to endow these channels with more intelligence and building bio-inspired ion pumps are still challenging tasks. As already noted, the chemical properties and shape of the nanochannels are two key factors to control

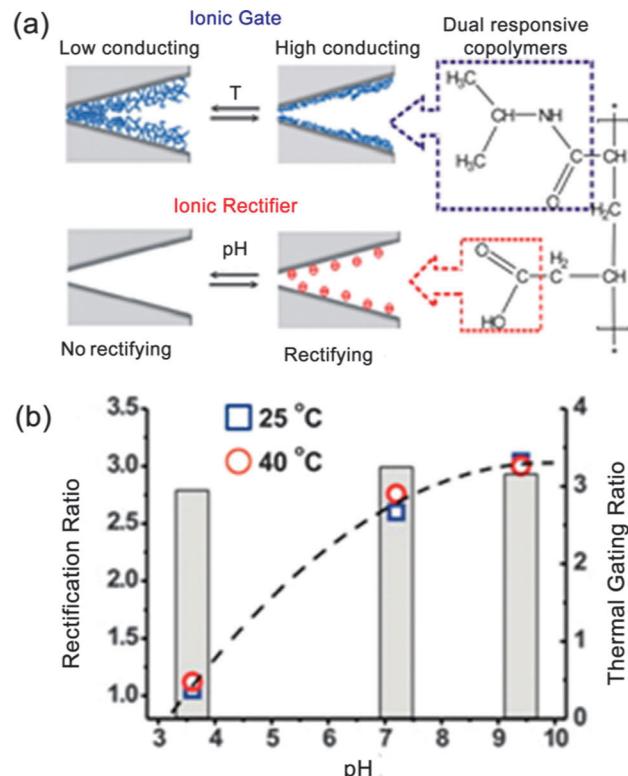


Fig. 16 pH/thermo dual responsive asymmetric single-gate nanochannels. (a) Schematic illustration of the chemical modification of the single cone-shaped PI nanochannels with poly(N-isopropyl acrylamide-co-acrylic acid) copolymer brushes.⁹⁴ (b) Ionic current rectification ratio and the thermal gating ratio measured in electrolytes of different pH.⁹⁴ Copyright 2010 Wiley-VCH Verlag GmbH & Co. KGaA.

ionic transport properties inside the nanochannels. Inspired by the biological ion pumps, preparing various symmetric and asymmetric shaped nanochannels for different chemical modification approaches to functionalize diverse specific local areas precisely with different functional molecules is essential to building a bio-inspired double-gate nanochannel and then to develop artificial single ion pumps. The first strategy focuses on asymmetrically grafting two different stimuli-responsive functional molecules on the inner surfaces of the nanochannel. The second one is to functionalize diverse specific local areas precisely with two opposite responsive molecules. Some examples are mentioned in the following section.

3.1. pH/thermo dual asymmetric responsive double-gate nanochannel

Based on the first strategy, a biomimetic asymmetric dual responsive double-gate nanochannel that displays the advanced feature of providing control over pH and temperature cooperation and tunable asymmetric ionic transport property was created by using an asymmetric chemical modification approach inside the single nanochannels (Fig. 18a).³⁶ In this dual responsive double-gate nanochannel, there is a negative correlation between the ionic current rectification ratio and the temperature with various pH (Fig. 18b), while the ratio of the nanochannel before modification stayed at nearly 1 with different temperature and pH.

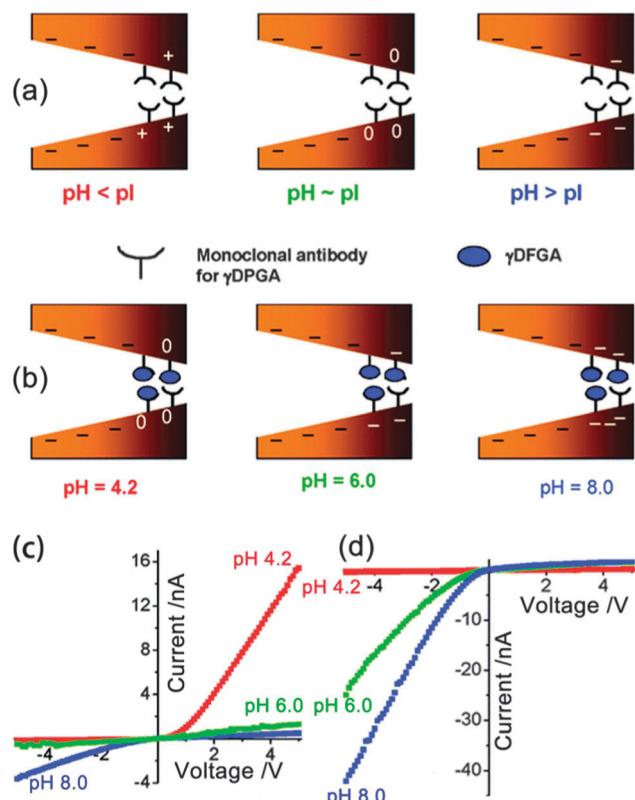


Fig. 17 A pH/molecule dual responsive single-gate nanochannel. Schematic representations describing the surface charge of the nanochannel before (a) and after (b) binding γ DPGA, in response to pH. (c) I - V curves were recorded for a conical nanochannel whose tip had been modified with a monoclonal antibody to the bacterial γ DPGA.⁶⁴ The measurements were performed in 10 mM KCl and at various pH values. (d) A nanochannel with mAb was incubated with a solution of γ DPGA for 3 h, and the measurements were performed in 10 mM KCl and at various pH values.⁶⁴ Copyright 2009 American Chemical Society.

3.2. Bio-inspired single ion pump based on a cooperative pH-responsive double-gate nanochannel

Jiang *et al.* further show a unique bio-inspired single ion pump based on a cooperative pH response double-gate nanochannel.³⁹ Two opposite pH-responsive polyelectrolytes, PVP and PAA, were separately grafted onto the left and right tip sides of the cigar-shaped nanochannel by a well-developed asymmetric modification method (Fig. 19a). PVP could undergo pH-responsive conformational changes from the swollen, positively charged, and hydrophilic state (open state) when the pH is below the pK_a of 5.2, to the collapsed, neutral, and hydrophobic state (closed state) when the pH is above the pK_a (Fig. 19a, left and up). However, PAA assumed a pH-responsive conformation of the collapsed, neutral, and hydrophobic state (closed state) when the pH is below the pK_a of 4.7 and of the swollen, negatively charged, and hydrophilic state (open state) when the pH was above the pK_a (Fig. 19a, right and up). Therefore the two polymer gates could be opened and closed alternately/simultaneously under external symmetric-asymmetric pH stimuli. Stimulating the double-gate nanochannel by continuous switching of the symmetric-asymmetric pH stimuli, the bio-inspired system systematically realized three key ionic transport features of biological ion pumps, including alternating gates ion pumping process under

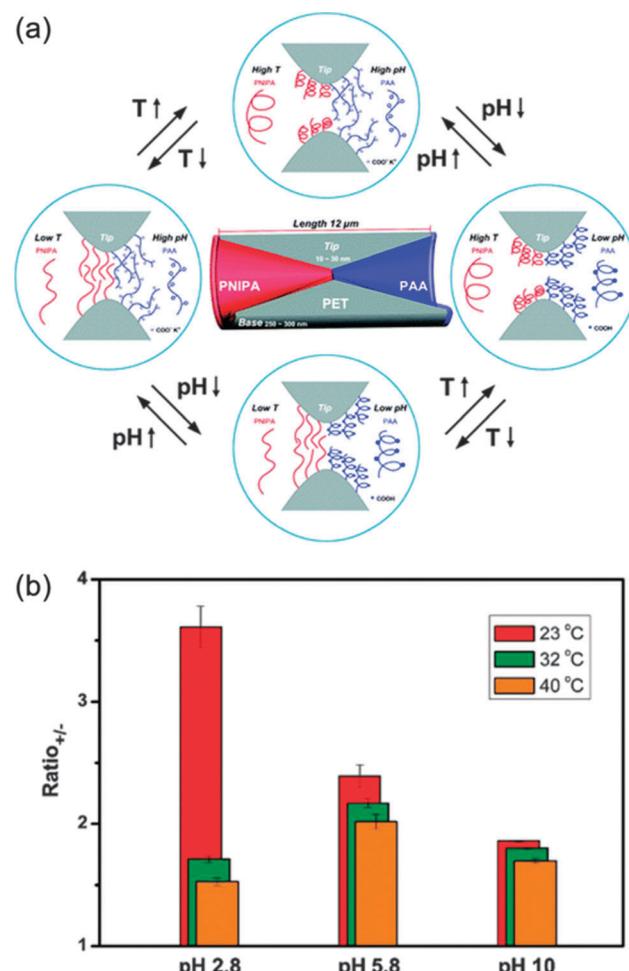


Fig. 18 A pH/thermo dual responsive double-gate nanochannel. (a) A biomimetic asymmetric dual responsive single nanochannel system.³⁶ (b) Ionic current rectification of the single nanochannel after asymmetric chemical modification at 2 V.³⁶ Copyright 2010 American Chemical Society.

symmetric pH stimuli, transformation of the ion pump into an ion channel under asymmetric pH stimuli, and fail-safe ion pumping feature under both symmetric and asymmetric pH stimuli (Fig. 19b). The ion pumping processes could be well reproduced under a concentration gradient. With the extraordinary ionic transport functions of biological ion pumps, the bio-inspired ion pump should find widespread applicability in active transportation controlling smart nanofluidic devices, efficient energy conversions and sea water desalination, and open the way to design and develop novel bio-inspired intelligent artificial nanochannel materials.

4. Potential application of nanochannel membranes

The term “application” in the context of bio-inspired smart single nanochannel materials does not indicate commercial products available on the market, and it is assumed that it can only be envisioned in the long-term. At present, developing smart nanochannel materials is still an emerging scientific

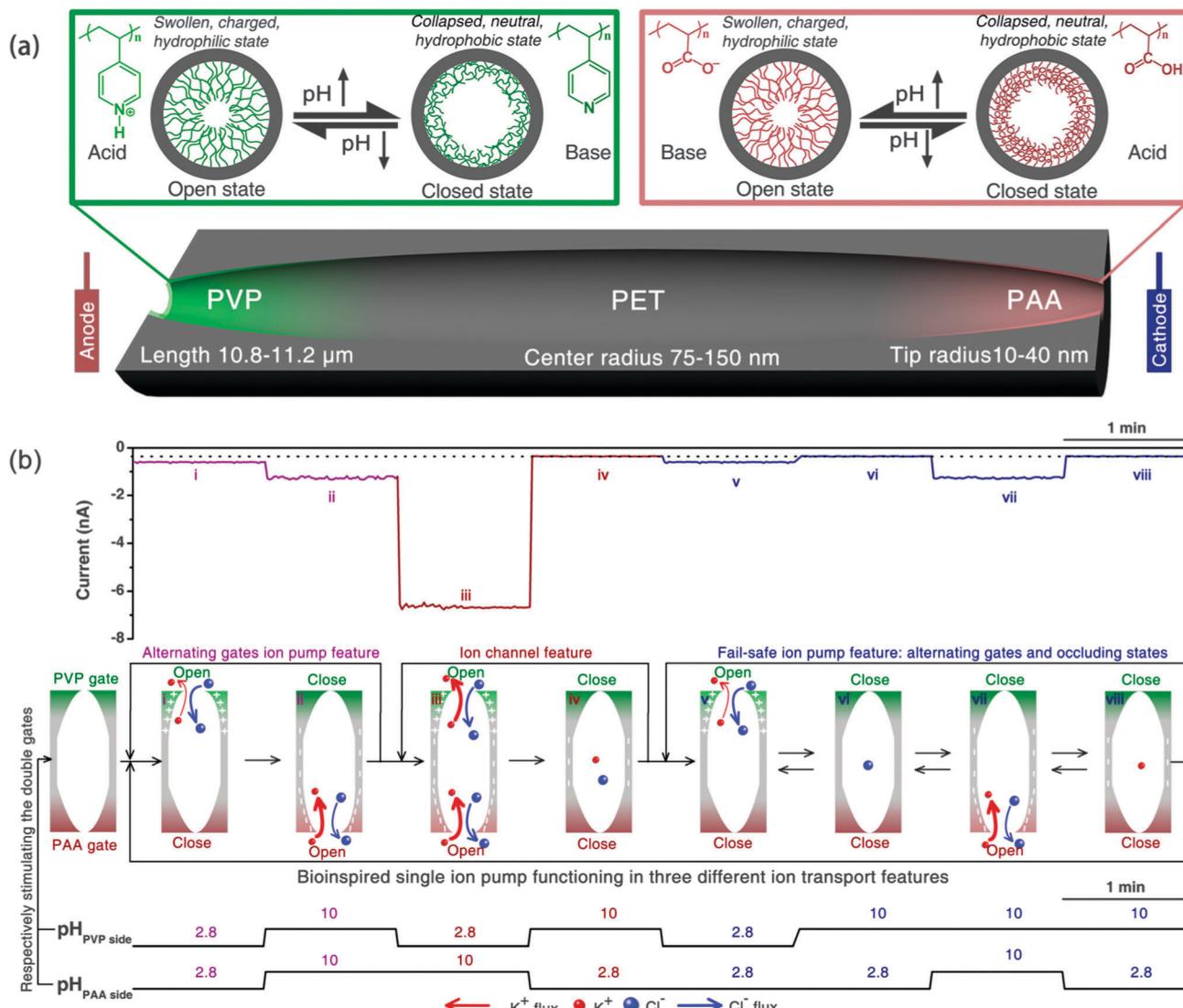


Fig. 19 A cooperative pH-responsive double-gate nanochannel. (a) Schematic representation of cross section of the artificial cooperative pH-responsive double-gate nanochannel for which the acid-driven PVP gate and base-driven PAA gate were respectively immobilized on the inner surface of the left and right tip sides of the nanochannel. During the pH changes within a certain range on the PVP side, PVP underwent pH-responsive conformation changes from the open state (acid condition) to the closed state (base condition) (left and up). At the same time, PAA underwent a pH-responsive conformation transition between the closed state (acid condition) and the open state (base condition) (right and up). (b) Bio-inspired artificial functional single ion pump based on the double-gate nanochannel characterizes in three different ion transport features. Ion current states (upper) and corresponding schematic representations of the ion transport processes (middle) of the three ion transport features resulting from respectively stimulating the double gates of the nanochannel by manually continuous pH stimuli switching (lower) at -2 V . Alternating gates form an ion pump under symmetric pH stimuli (left, violet), in which PVP and PAA gates opened and closed alternately to enable the exchange of K^+ for Cl^- ions across the nanochannel (i and ii). Ion channel-like function under asymmetric pH stimuli (center, red) that both PVP and PAA gates were simultaneously opened/closed to directly transport/block ions from one side to the other side (iii and iv). The fail-safe ion pump function (right, blue) consists of alternating gates (v and vii) and occluding states (vi and viii) under both symmetric and asymmetric pH stimuli.³⁹ Copyright 2013 American Chemical Society.

challenge with appealing applications in biosensors, nano-fluidic and energy conversion devices, molecular filtration, and many other areas.

Biosensors with functional nanochannels are expected to have a major impact on bioanalysis and the fundamental understanding of nanoscale chemical interactions down to the single molecule level, due to the major advantage of nanochannels that can offer the prospect of examining the analytes in the nanoscale by their nanometer diameter.⁹⁵ There are three major approaches to realizing biosensing inside the nanochannel, including biomolecule translocation through a nanochannel,

stimuli-responsive biomolecules immobilized on the nanochannel inner wall, and the nanochannel inner wall decorated with specific binding sites for biomolecule recognition. It is worth mentioning that the grafting of biomolecules on the inner walls of the nanochannel can mimic *in vivo* conditions, such as DNA and peptide-functionalized channels for metallic ion sensing.⁵⁰ And by modification of the nanochannel with various specific binding sites, the nanochannels show great capacities in ligand,^{27,48,59,64} enantioselective,⁸² and ion sensing.^{50,51,77} For sensing with nanochannels, there are several existing challenges, which limit their stability, sensitivity,

reliability, and practicability. Composite metal-polymer compounds provide a potential way to increase the robustness of nanochannels.⁶¹

Nanofluidic and energy conversion devices represent a new regime in the study of ion transport in the extremely small three dimensions.⁹⁶ There is increasing interest in measuring and investigating transport and electrochemical phenomena in nanochannel materials. Various kinds of unipolar and bipolar ionic diodes^{42,56,63,64,75} and ionic transistors³⁴ have been reported. Based on artificial nanofluidics, new generation energy conversion devices have also been developed. Dekker, Wang *et al.* reported power generation by the pressure-driven transport of ions in nanofluidic channels.^{97,98} Inspired by the light-driven cross-membrane proton pump of biological systems, a photoelectric conversion system based on a smart gating proton-driven nanochannel has been constructed.^{91,99} Another example is inspired by the electric eel who has the inherent skill to generate considerable bioelectricity from the salt content in their body fluid with highly selective ion channels and ion pumps in their cell membrane;¹⁰⁰ a fully abiotic single channel nanofluidic energy harvesting system that efficiently converts Gibbs free energy in the form of a salinity gradient into electricity has also been created.¹⁰¹

Nanochannel materials are also highly interesting for separation processes as molecular filters. The recognition of small organic molecules and large biomolecules is of great importance in pharmaceutical as well as biological applications. Recognition inside nanoporous membranes is particularly attractive because of the advantages associated with ligand–receptor interactions in confined spaces. Classical nanoporous membrane-based separations simply use the difference in size of the analytes comparable to the nanochannel diameter in the membrane.¹⁵ The density, the shapes, and the surface chemistry of the nanochannels are the key factors that determine substance transport and separation capabilities.¹⁰² For the purpose of selectivity beyond size, it is necessary to chemically modify the channel walls. Thayumanavan *et al.* reported a simple approach to functionalize the nanochannels using self-assembling and non-self-assembling polymers, and these modified nanochannels separated small molecules which could be differentially transported through the nanochannels based on their size and/or electrostatics.¹⁵

5. Conclusion and outlook

The increase in relevant publications in this field clearly indicates that the design and development of artificial functional nanochannels offer a flexible venue to create various bio-inspired intelligent nanomaterials. It is an emerging field that in many respects is still in its infancy. With the inspiration of examples from nature, our scientific community has started to build up diverse bio-inspired smart nanochannels from bio-inspired single-gate ion channels to double-gate ion pumps. The ability to symmetrically and asymmetrically tune the shape and the surface chemical properties of the nanochannel materials affords a flexible venue to address a host of questions and problems at the challenge forefront of nanotechnology and materials science.

In order to pursue “smart” materials, further multi-responsive materials and asymmetric modification methods need to be taken into account. In addition, making smart nanochannels stable, reversible and durable will remain essential for the successful implementation of the expected practical applications. A number of exciting developments in the near future may be anticipated from the design, preparation process and experimental results reported in this Feature Article. For future progress it will be important to further improve the fabrication for various shaped nanochannels and, more importantly, to maximize efforts to asymmetrically functionalize nanochannels with different, much more functional, molecules.

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