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Stimuli-responsive smart gating membranes

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Abstract

Membranes are playing paramount roles for sustainable development in myriad aspects such as energy, environments, resources and human health. However, the unalterable pore size and surface property of traditional porous membranes restrict their efficient applications. The performances of traditional membranes will be weakened upon the unavoidable membrane fouling, and they cannot be applied to the cases where self-regulated permeability and selectivity are required. Inspired by the natural cell membranes with stimuli-responsive channels, artificial stimuli-responsive smart gating membranes are developed by chemically/physically incorporating stimuli-responsive materials as functional gates into traditional porous membranes to provide advanced functions and enhanced performances for breaking the bottlenecks of traditional membrane technology. The smart gating membranes, integrating the advantages of traditional porous membrane substrates and smart functional gates, can self-regulate their permeability and selectivity via flexible adjustment of pore sizes and surface properties based on the "open/close" switch of the smart gates in response to environmental stimuli. This tutorial

review summarizes the recent development of stimuli-responsive smart gating membranes, including the design strategies and the fabrication strategies that based on introduction of the stimuli-responsive gates *after* or *during* membrane formation, the *positively* and *negatively* responsive gating models of versatile stimuli-responsive smart gating membranes, as well as the advanced applications of smart gating membranes for regulating substance concentration in reactors, controlling release rate of drugs, separating actives based on size or affinity, and self-cleaning of membrane surfaces. With self-regulated membrane performances, the smart gating membranes show great power for global sustainable development.

Key learning points

(1) Combination of traditional porous membranes and smart polymeric gating materials creating stimuli-responsive smart gating membranes.

(2) Chemical science of strategies for creating smart gates in membranes and the stimuli-responsive conformational switch and mechanism of functional gates in molecular level.

(3) Self-adjustment of the pore sizes and/or the surface properties with functional gates for manipulating the permeability and selectivity of membranes.

(4) Chemical technologies of stimuli-responsive smart gating membranes for wide applications in not only the traditional, but also the extended or even brand new fields.

(5) Potential self-cleaning functions of the new-generation membranes based on the stimuli-responsive pore sizes and surface properties.

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1. Introduction

Membranes are selective barriers that can separate components with different physical/chemical properties. Usually, mass transfer and separation based on membranes show fantastic features, because of many advantages such as no phase change, no additives and low energy consumption in the membrane processes, as well as the compacted structure and small space-occupancy of the membrane equipment.[1] Therefore, membrane technologies show great importance for global sustainable development in myriad fields such as conservation and regeneration of energy,[2] reduction of pollutant emissions,[3] highly-effective utilization of resources,[4] and hemodialysis.[5] Typically, the performance of membranes is determined by the permeability and selectivity.[1] The permeability is characterized by trans-membrane flux that evaluates the productivity of membrane process; while, the selectivity is featured by the ability of membrane for rejection/permeation of specific substance, which implies the efficiency of membrane separation. Both permeability and selectivity depend on the pore size and surface property of the membrane. Generally, increased pore size enables enhanced permeability, and the pore size also decides the membrane selectivity for size-based separation. Meanwhile, the membrane selectivity also depends on the affinity between the pore surface and the substances. However, the pore size and surface property usually remain unalterable for traditional porous membranes due to their unchangeable physical/chemical structures. Thus, their performances will be weakened upon the unavoidable membrane fouling, since the fouling depositing on the pore surface can reduce the pore size and hinder the interaction between the substances and membranes.[6] Moreover, such unalterable pore size and surface property may restrict the wide and efficient applications of traditional membranes for extended fields. For example, the membrane-based ethanol fermentation usually requires constant ethanol concentration in the reactor for efficient

continuous fermentation.[7] Therefore, with increased ethanol concentration during the fermentation, increased membrane permeability is needed to instantaneously remove the additional ethanol for concentration maintaining. For size-based membrane separation, tunable pore sizes are fantastic for single membrane to achieve adjustable selectivity for efficiently separating versatile substances with different sizes. However, these requirements remain challenging for traditional membranes, although traditional membranes have already played paramount roles in myriad fields. Development of smart membranes with self-regulated permeability and selectivity can create new opportunities for membrane applications.

Inspired by the cell membranes with stimuli-responsive channels for self-regulating permeability and selectivity in response to environmental signals,[8] artificial smart gating membranes have been created by chemically/physically incorporating stimuli-responsive materials into porous membrane substrates as functional gates.[9-11] In response to environmental stimuli, such as changes of temperature, pH, specific ions/molecules, light, magnetic field, and redox, their functional gates enable conformational switch for adjusting the pore sizes and/or the surface properties of membranes and thus for manipulating the permeability and selectivity. Such gating membranes combine the advantages of the porous substrates and the smart gates for advanced performances and enhanced applications. For example, for membrane fouling, such as those induced by silt, protein, and bacteria, the permeability of gating membranes can be increased by "opening" the gates to enlarge pore size for flux enhancement. Meanwhile, the membrane surface property can also be adjusted by changing the wettability of the gates; thus, the affinity between the fouling components and membrane surface can be weakened for reducing or even eliminating the fouling.[3] The self-regulated permeability also benefits the concentration maintenance of ethanol in reactors for fermentation,[12] controlled release of actives

from capsule membranes for drug delivery,[13] and simple separation of substances with different sizes by a single membrane for size-based separation.[14] Moreover, the stimuli-responsive affinity adjustment can also be applied for controlling the interaction between proteins and the pore surfaces that grafted with stimuli-responsive polymers such as poly(*N*-isopropylacrylamide) (PNIPAM) for protein separation.[15] Therefore, such gating membranes with self-regulated permeability and selectivity enable enhanced and advanced performances for wide applications in not only the traditional, but also the extended or even brand new fields such as detection of harmful pollutants for environment protection[16] and stimuli-responsive controlled release of drugs for biomedical application[17].

In this tutorial review, we highlight the recent development of stimuli-responsive smart gating membranes, including the fabrication strategies and techniques, responsive properties, gating models, and advanced applications. This is introduced by starting with the design strategies of the gating membranes, and following with the fabrication strategies and techniques. Then, versatile smart gating membranes with *positively*- or *negatively*-responsive gating model in response to various stimuli are described. Finally, the applications of smart gating membranes for chemical valves, separations, controlled release, and self-cleaning are discussed.

2. Strategies for creating smart gates in membranes

2.1 Design strategy

The cell membrane provides fantastic inspirations for scientists to develop artificial smart gating membranes. The cell membrane contains channels with stimuli-responsive "smart gates" that can selectively open or close for specific substances to transfer across, so as to maintain desired intracellular and extracellular concentrations for ensuring life activities.[8] Such natural models

inspire great efforts for creating artificial membranes with smart gates for achieving advanced performances. Artificial smart gating membranes can be designed and fabricated with various styles (Fig. 1). Typically, the membrane type can be flat (Fig. 1A1),[15] fiber (Fig. 1A2)[18] or capsule (Fig. 1A3),[19] which can be skillfully employed for versatile applications such as stimuli-responsive separation, water treatment, and controlled release.[15,18,19] The functional gates in membrane pores usually can be linear polymer chains (Fig. 1B1),[20] crosslinked hydrogel networks (Fig. 1B2),[21] or microspheres (Fig. 1B3),[18] which enables stimuli-responsive swelling/shrinking switches for adjusting effective pore size and surface property. The gate materials can be incorporated into membrane pores in pore-filling form (Fig. 1C1) for robust gating performance,[22] or in pore-covering form (Fig. 1C2) for rapid response.[23] Based on the versatility of stimuli-responsive materials, versatile smart gating membranes can be developed by incorporating these materials as functional gates. The fabrication techniques for smart gating membranes can be classified into two categories base on whether the gate materials are introduced *after* or *during* the membrane formation.

2.2 Stimuli-responsive gates introduced *after* membrane formation

The strategy that introduces the gates *after* membrane formation usually incorporates the gate materials on existing porous membrane substrates by "grafting" techniques, which can be divided into the "grafting-from" and "grafting-to" methods. Both methods allow fabrication of gating membranes with steady gating structures and highly efficient gating performances.

For the "grafting-from" method, gating membranes are fabricated by first inducing active sites on the pore surface, and then polymerizing functional monomers from the active sites to constitute linear polymers or crosslinked networks in the pores as the smart gates (Fig. 2A).[21,22]

With grafting techniques such as chemical grafting,[24] UV-induced grafting,[25] and plasma-induced grafting,[15-17] various functional gates can be incorporated into a wide range of membrane substrates for creating smart gating membranes.

For the "grafting-to" method, gating membranes are fabricated by chemically/physically incorporating pre-formed functional gates, usually in the form of polymer chains or microspheres, onto the pore surfaces with pre-treated active sites (Fig. 2B,2C).[18,20] Comparing with the bonding between the gates and pore surface by physical interactions such as Van der Waals' force,[18] the bonding based on chemical covalent bonds is more robust for application.[20] Moreover, since the polymer chains or microspheres with well-controlled length or size can be pre-synthesized by well-established methods, the "grafting-to" method offers improved controllability and flexibility for the gate microstructures.

2.3 Stimuli-responsive gates introduced *during* the membrane formation

The strategy that introduces the gates *during* the membrane formation allows concurrent one-step formation of both membranes and stimuli-responsive gates, showing great potential for easy scale-up. This strategy enables development of gating membranes by utilizing polymers with stimuli-responsive side chains, or blending them with their pristine ones for membrane formation (Fig. 2D).[26] Alternatively, stimuli-responsive block copolymers (Fig. 2E)[27] or microspheres (Fig. 2F)[28] can also be introduced as functional gates by blending them with the membrane-forming polymers *during* membrane formation. These approaches that combine the gate incorporation with the membrane formation, provide an efficient and promising strategy for industrial manufacture of smart gating membranes with currently existing equipment.

3. Stimuli-responsive gating

Generally, development of gating membranes with various gating functions is necessary for meeting the versatility requirements of myriad applications. Typically, the gating can be divided into two models, *i.e.*, *positively*- or *negatively*-responsive gating. The *positively*-responsive gating allows increased membrane permeability when the stimulus appears or increases (Fig. 3A), while the *negatively*-responsive gating just show reversed property (Fig. 4A). The gating functions are achieved by the shrinking/swelling transitions of stimuli-responsive gates, which can open/close the membrane pores for increasing/decreasing permeability. Besides, the hydrophobic/hydrophilic changes associated with the shrinking/swelling transitions of certain gates can adjust the surface property of pores. Numerous stimuli, which are important for industrial production or biological activity, can be employed as triggers for achieving the responsive gating, due to the versatility of stimuli-responsive materials. The information on the researchers who pioneered to develop each stimuli-responsive smart material as well as gating membrane has been summarized in Tables S1 and S2 in the *Supplementary Material*. For example, temperature and pH are the most common parameters that may vary in biological/chemical reactions, and organs and tissues.[29] Ions such as potassium ions (K^+) are essential for biological metabolism,[30] while heavy metal ions such as lead ions (Pb^{2+}) are seriously harmful for living organism.[31] Specific molecule such as glucose, the concentration of which in blood is an important indicator for diabetes and hypoglycemia.[32] Light and magnetic field are usually clean stimuli that can be used for remote control.[33,34]

3.1 *Positively* responsive gating

3.1.1 Thermo-responsive gating. Thermo-responsive polymers such as *N*-substituted polyamides, polyethers, poly(2-oxazoline)s, poly(vinyl caprolactone) and poly(methyl vinyl ether),[34] usually present a low critical solution temperature (LCST) that is critical for the *positively* responsive gating function. For example, PNIPAM, with LCST (~32 °C) close to human body temperature, is widely used as *positively* thermo-responsive gates (Fig. 3B).[14] At temperatures below the LCST, PNIPAM chains are swollen and hydrophilic due to the hydrogen bonding between the amide groups and water molecules, thus the membrane pores "close". While increasing temperature above the LCST, the PNIPAM chains become shrunken and hydrophobic due to the hydrogen bonding cleavage, thus the membrane pores "open". Since the LCST can be tuned by incorporating hydrophilic or hydrophobic groups into the PNIPAM chains, gating membranes with tunable triggering temperatures for gating can be achieved for more flexible applications.[36]

3.1.2 pH-responsive gating. Typically, polymers containing weak alkaline groups, which can be protonated or deprotonated for configuration change, can be used as *positively* pH-responsive gates. For example, poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDM) can swell in acidic environment due to the electrostatic repulsion between protonated -$N(CH_3)_2$ groups; by contrast, in basic environment, the PDM can shrink due to the deprotonation of the amine groups (Fig. 3C).[26]

3.1.3 Ion-responsive gating. Copolymers based on PNIPAM and crown ether are typical examples of ion-responsive gates, which employ the crown ethers as ion receptors and PNIPAM units as actuators. Typically, for the *positively* K^+-responsive gates based on PNIPAM and 15-crown-5, once the K^+ ions appear, the 15-crown-5 moieties capture the ions and form stable 2:1 “sandwich” complexes. Such host-guest complexations break the hydrogen bonding between the

crown ether and water molecules, leading to contraction of the copolymer chains to achieve a "close" to "open" pore switch; as a result, the pore size changes from *ca.* 43 nm to *ca.* 118 nm. (Fig. 3D).[37]

3.1.4 Molecule-responsive gating. The *positively* molecule-responsive gates are usually designed by integrating the molecular recognition ability of beta-cyclodextrin (*β*-CD) and the thermo-responsivity of PNIPAM for separating or detecting specific molecule (Fig. 3E).[38] These gates can be isothermally opened by recognizing guest molecules with a hydrophobic side group (*e.g.*, 8-anilino-1-naphthalenesulfonic acid ammonium salt (ANS)) at a certain temperature, due to copolymer shrinking induced by the *β*-CD/ANS complexation.

3.1.5 UV-light-responsive gating. The *positively* UV-light-responsive gates usually utilize azobenzene-based materials, which can undergo a *trans-cis* isomerization transition in response to UV light (Fig. 3F).[39] Upon UV irradiation, the azobenzene groups can change their planar configuration into a non-planar one, with a drastic decrease in the distance between the *para* carbon atoms from 9.0 Å to 5.5 Å. Such configuration changes of azobenzene groups effectively control the membrane pore size.

3.1.6 Glucose-responsive gating. Typically, *positively* glucose-responsive gates can be developed by combining glucose oxidase (GOD) and pH-responsive polymers with weak acid groups such as carboxylic acids groups.[17] For example, when poly(acrylic acid) (PAAc) chains immobilized with GOD are used as gates, the carboxyl groups are dissociated at neutral pH in absence of glucose; thus the gates "close" due to the PAAc chain extension caused by the electrostatic repulsion between their negatively-charged carboxyl groups. When glucose concentration increases, the GOD catalyzes glucose into gluconic acid, leading to lower pH and

protonation of the carboxylate group; thus the gates "open" because of the reduced electrostatic repulsion between the carboxylate groups (Fig. 3G).

3.1.7 Magnetic-responsive gating. Magnetic-responsive property can be incorporated into the gates by doping magnetic nanoparticles such as iron oxides with thermo-responsive polymers. Usually, superparamagnetic Fe_3O_4 nanoparticles are used to obtain *positively* magnetic-responsive gates by incorporating with temperature-responsive PNIPAM polymers because of the advantages of Fe_3O_4 nanoparticles such as easy-to-gain and high heating efficiency (Fig. 3H).[40] Since the nanoparticles can generate heat under alternating high frequency magnetic field, such gates can be remotely opened or closed by turning "on/off" the magnetic field.

3.2 *Negatively* responsive gating

3.2.1 Thermo-responsive gating. Polymers with interpenetrating networks (IPNs) composed of poly(acrylamide) (PAAm) and PAAc can be used as *negatively* thermo-responsive gates (Fig. 4B). The polymeric gates can shrink due to the formation of PAAm/PAAc complex via hydrogen bonds at temperatures below the upper critical solution temperature (UCST) of IPNs, resulted in pore "open". While at temperatures above the UCST, the IPNs can swell due to their dissociation by breakage of hydrogen bonds, leading to pore "close". Thus, the membrane pores can switch from "open" to "close" state once the temperature increases across the UCST.[21]

3.2.2 pH-responsive gating. The *negatively* pH-responsive gates usually possess weak acidic groups that can gain or lose protons in response to pH changes. For examples, the polymer chains of *negatively* pH-responsive PAAc gates can shrink due to the formation of intermolecular hydrogen bonding between their carboxylic groups at low pH (Fig. 4C).[27] In

basic environment, the PAAc chains can extensively swell due to the electrostatic repulsion between the protonated carboxylic groups.

3.2.3 Ion-responsive gating. As a typical example, *negatively* ion-responsive gates can be fabricated by incorporating PNIPAM with 18-crown-6 groups.[16] The 18-crown-6 moiety can selectively recognize certain ion such as Pb^{2+} to form stable 1:1 host-guest complex. When Pb^{2+} ions appear, the opened pores can close due to the ion-responsive isothermal swelling of the gates, causing the change of pore size from 159 nm to 94 nm (Fig. 4D).

3.2.4 Molecule-responsive gating. Copolymers with cyclodextrin and PNIPAM can also be used as *negatively* molecule-responsive gates, because they can isothermally change from shrinking to swelling by recognizing guest molecules with a hydrophilic side group or without side groups (*e.g.* 2-naphthalenesulfonic acid) at a certain temperature.[38] Thus, membrane pores can change from "open" to "close" state due to molecule-responsive volume transition of the gates (Fig. 4E).

3.2.5 UV-light-responsive gating. The *negatively* UV-light-responsive gates are usually spiropyran-containing polymers.[41] The nonpolar form of the spiropyran groups under visible-light is hydrophobic and shrunken in solution. When exposed to UV, the spiropyran groups can be isomerized into polar merocyanine forms with charges, which are hydrophilic and swollen (Fig. 4F). This allows the membrane pores close triggered by UV light.

3.2.6 Ion-strength-responsive gating. Zwitterionic polymers such as poly(*N,N*'-dimethyl(methylmethacryloyl ethyl) ammonium propane sulfonate) (PDMAPS) are usually used as *negatively* ion-strength-responsive gates due to the concurrent presence of positive and negative charges on their structures. Such zwitterionic polymers can exhibit configuration changes depending on ion strength of ions such as sodium chloride (NaCl).[42] For example, at

low ion strength of NaCl, the electrostatic attraction between the cations and anions forces the PDMAPS polymers into a coiled conformation (Fig. 4G. While at high ion strength, the Na^+ and Cl^- ions disrupt these electrostatic interactions by forming ion pairs with the anions and cations of the PDMAPS polymers, resulting in an increase of net charge and a more stretched conformation of the PDMAPS chains.[42] So, the "open" and "close" of the membrane pore can be effectively controlled by changing the ion strength.

3.2.7 Redox-responsive gating. The *negatively* oxidation-responsive gates usually consist of polymers that can be easily oxidized, such as poly(3-carbamoyl-1-(*p*-vinylbenzyl)pyridinum chloride) (PCVPC) (Fig. 4H). The PCVPC polymers are water-soluble in their oxidized state, but water-insoluble in their reduced state. In the reduced state, the polymers are deionized; thus they shrink and "open" the pores. By contrast, in the oxidized state, the PCVPC polymers are ionized due to the charges formed via oxidation; thus they swell and "close" the pores.[43]

4. Applications of smart gating membranes

The *positively*- and *negatively*-responsive gating functions in response to various stimuli enable precise control of the pore size and surface properties of smart gating membranes, as well as the permeability and selectivity. The versatilities of smart gating membranes and their flexible gating models provide flexible strategies to meet the demands of specific applications for myriad fields.

4.1 Stimuli-responsive permeations

4.1.1 Self-adjustment of hydraulic permeability. With self-regulated hydraulic permeability, which is defined as the convective flow of solvents driven by pressure difference,

smart gating membranes are promising as chemical valves for maintaining concentrations in reactors or sensing specific components in solutions. For example, gating membranes with ethanol-responsive gates,[12] provide opportunities for regulating the ethanol concentration (C_E) at relatively stable level in reactors for more efficient fermentation (Fig. 5A). The gates that swell at C_E below a certain value (C_{E1}) (Fig. 5B), can shrink when C_E increases across C_{E1} during the fermentation, causing increased permeability to remove the excess ethanol for concentration maintenance. Although further increasing C_E above another certain value (C_{E2}) leads to the swelling of gates, such a high value of C_{E2} is difficult to achieve since the maximum C_E in ethanol fermentation is usually lower than C_{E2}. Both the values of C_{E1} and C_{E2} vary with changing the operation temperature. For example, at 22 °C, 25 °C and 28 °C, the corresponding C_{E1} values are respectively 16.8 vol.%, 12.3 vol.% and 10.8 vol.%, and the corresponding C_{E2} values are 35.0 vol.%, 32.0 vol.% and 28.3 vol.%, respectively (Fig. 5C).[12] Thus, we can infer that, the membrane permeability could be flexibly regulated depending on the C_E at certain temperature for maintaining concentrations for efficient fermentation. Such concentration-dependent self-regulated hydraulic permeability can also be used for sensing special metal ions and/or degrading toxic organics. For example, *positively* K^+-responsive gating membranes enable "open/close" switch of their pores for regulating their permeability in response to K^+ concentration specifically (Fig. 6A).[37] Such membranes can achieve high permeability in 0.1 M K^+ solution while low permeability in pure water (Fig. 6B). Similarly, *negatively* Pb^{2+}-responsive gating membranes can reduce their permeability in response to trace Pb^{2+} of $1.3\sim10\times10^{-6}$ mol/L in solution (Fig. 6C).[16] Both ion-responsive gating membranes can be applied as sensors for specific ion detection in water via measuring the flux change. Moreover, the Pb^{2+}-responsive gating membranes are promising for Pb^{2+} removal based on the

complexation between Pb^{2+} and the crown ether on the gates.[16] Besides, by combining bioactive membrane with pH-responsive gating membrane, water purification systems can be developed for degrading toxic organics (Fig. 6D).[44] The pores of top membrane contain polycation and polyanion immobilize with GOD for catalytically producing hydrogen peroxide from glucose. The bottom membrane contains pH-responsive PAAc hydrogel gates with doped iron species, which can decompose the hydrogen peroxide into free radical oxidants for degrading toxic organics such as trichlorophenol, into alkali ions for increasing pH for pore closing. Thus, this leads to reduced flux of toxic organics, and allows longer time for their efficient degradation.[44]

4.1.2 Self-adjustment of diffusional permeability. Smart gating membranes with self-regulated diffusional permeability, which is defined as molecular diffusion driven by concentration gradient, are promising for regulating the mass transfer of actives across the membrane for controlled release. Particularly, capsule membranes are important for controlled drug release due to their enclosed internals for encapsulation. For example, *positively* glucose-concentration-responsive gating membranes enable controllable insulin release for diabetes therapy (Fig. 7A).[45] When glucose concentration changes from 0 to 0.2 mol/L *in vitro*, the insulin release rate increases 9.4 times, and the diffusion coefficient elevates form 0.79 cm^2/s to 7.4 cm^2/s (Fig. 7B).[17] Moreover, such membranes can reversibly increase/decrease their release rate of insulin by repeatedly changing the glucose concentrations between 100 and 400 mg/dL (Fig. 7C).[46] The gating membrane can also be incorporated into enclosed systems for improved controlled release (Fig. 7D).[47] The gating membrane with *positively* pH-responsive gates serves as a functional valve for controlling the substance release from such a system, while the *negatively* pH-responsive hydrogel inside the system works as a pump for pumping the substances out. Upon request, the membrane pores open and the hydrogel swells; thus the

encapsulated substances can be pumped out through the open pores to achieve an enhanced release rate, beyond the limit of concentration-driven diffusion.

4.2 Stimuli-responsive separations

4.2.1 Size-effect-based sieving. With stimuli-responsive self-regulation of pore size, gating membranes can be applied for graded sieving separation. Generally, only smaller molecules/particles can permeate across the membrane with closed pores, while both smaller and larger molecules/particles can permeate when the pores open (Fig. 8A). Thus, separation of substances with different sizes can be achieved by using single gating membrane, with the pore size regulated by designed stimuli. For example, pH-responsive gating membranes can selectively reject dextran molecules with proper molecular weight from their mixtures with different molecular weights of 10, 40 and 70 kDa, depending on the environmental pH (Fig. 8B).[27] Temperature-responsive gating membranes enable fast permeation of small molecules such as NaCl (hydrodynamic radius ~0.1 nm), showing large diffusional coefficients at both 25 ^{o}C and 40 ^{o}C (Fig. 8C); while large molecules such as VB12 (hydrodynamic radius ~2 nm) can only permeate through the membrane with opened pores at 40 ^{o}C.[14] Similarly, Ba^{2+}-responsive gating membranes can sieve molecules with different sizes such as dextran molecules with radius of 2~30 nm (Fig. 8D).[48]

4.2.2 Affinity-based adsorption/desorption. With self-regulated surface property for controlling the affinity between pore surface and substances, smart gating membranes offer ingenious tools for stimuli-responsive separation or purification of substances such as proteins and chiral molecules. For example, gating membranes with gates that allow thermo-induced switch between hydrophilic and hydrophobic states can be used for separating hydrophobic

substances such as bovine serum albumin (BSA) based on hydrophobic adsorption (Fig. 9A). The BSA can be adsorbed when the gates are hydrophobic, and desorbed when the gates become hydrophilic. This can be simply controlled by varying the operation temperature (Fig. 9B).[15] As another example, by combining PNIPAM with functional *β*-CD, which can act as host molecule or chiral selector, gating membranes for chiral resolution are achieved (Fig. 9C).[22] At temperatures below the LCST of PNIPAM, the PNIPAM/*β*-CD gates are swollen and hydrophilic. During the solution permeation, one of the enantiomers can be selectively captured by the *β*-CD groups based on their stronger association. When increasing the temperature above the LCST, the PNIPAM/*β*-CD gates become shrunken and hydrophobic, leading to decomplexation of the *β*-CD and captured enantiomer due to the weakened association constant; thus the enantiomer can be separated. Therefore, the smart membranes with functional gates for enantioseparation allow simple membrane regeneration by changing temperature, and high efficiency for selective chiral resolution.[22]

4.3 Self-cleaning of membranes

Membrane fouling, which usually leads to weakened membrane performance such as permeability loss, is an unavoidable problem for membrane-involved processes. Generally, polymers used for porous membrane manufacture are usually hydrophobic in nature; as a result, the organic foulants in water are highly susceptible to deposit on the membrane surface due to the hydrophobic interaction between the membrane and foulants.[3] Thus, hydrophilic polymers grafted on membrane surface can provide steric-osmotic barriers against the fouling adsorption for reduced membrane fouling; however, the grafted polymers also reduce the intrinsic permeability owing to the partial blocking of the membrane pores.[3] Smart gating membranes

with tunable surface properties create opportunities to achieve self-cleaning functions for reducing membrane fouling while remaining the permeability. Upon adding stimulus, the shrunken and hydrophobic gates become swollen and hydrophilic; such transitions weaken the interactions between the fouling and membrane surface for fouling detachment (Fig. 10A). Thus, the fouling could be easily cleaned by water washing. After that, the gates can be recovered to shrunken state to preserve the permeability (Fig. 10A). Recently, thermo-responsive surfaces are shown to reversibly capture and release targeted Michigan Cancer Foundation-7 cells by changing temperatures between 37 ^{o}C and 20 ^{o}C (Fig. 10B).[49] This offers opportunities for the gating membranes as smart substrates with self-cleaning function for cell culture. Moreover, the *negatively* K^+-responsive gating membranes can self-clean the dead A549 lung carcinoma cells on their surface during the cell culture, due to the swelling of polymer bush in response to K^+ ions from the dead cells, or in response to temperature change from 37 ^{o}C to 10 ^{o}C for dead cell detachment (Fig. 10C).[50] Such gating membranes with stimuli-induced self-cleaning functions could be a new-generation of membranes.

5. Summary and outlook

This paper reviews recent progresses on stimuli-responsive smart gating membranes, including the design strategies, fabrication approaches, stimuli-responsive properties and gating models, and the emerging applications. Inspired by the intelligent channels across cell membranes, smart gating membranes are fabricated by chemically/physically tailoring the membranes with stimuli-responsive gates *after* or *during* membrane formation. The gating membranes allow self-regulation of the pore size and surface property, as well as the permeability and selectivity, in response to various stimuli. Such smart features enable not only enhanced performances for

wide applications in traditional fields, but also advanced performances for exploiting new applications in extended fields. However, challenges still remain for further applying the smart gating membranes to industrial manufacturing and/or biomedical applications. For example, the mechanisms for mass transfer in the pores of gating membranes are still not clear enough, and the long-term stability of gating membranes in the large-scale industrial applications still needs to be tested. Up to now, the greatest technical challenge for applying gating membranes in large-scale industrial applications is the lack of facile and controllable methods to achieve industrial-scale production of desired gating membranes. For biomedical purpose, the biocompatibility of gating membranes is also an important and crucial issue needs to be verified before practical applications. The future efforts should focus on the exploitation of novel materials for fabricating new smart gating membranes, investigation of the synergistic effect between the chemical/physical structures and the responsiveness of gates for designing novel gating functions, as well as the mechanisms for mass transfer and separation, development of facile membrane formation processes for industrial-scale production, and enhancement of sensitivity and response rate for process intensification. We believe these researches would benefit the development of novel smart gating membranes for industrial productions and/or biomedical applications.

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Figures

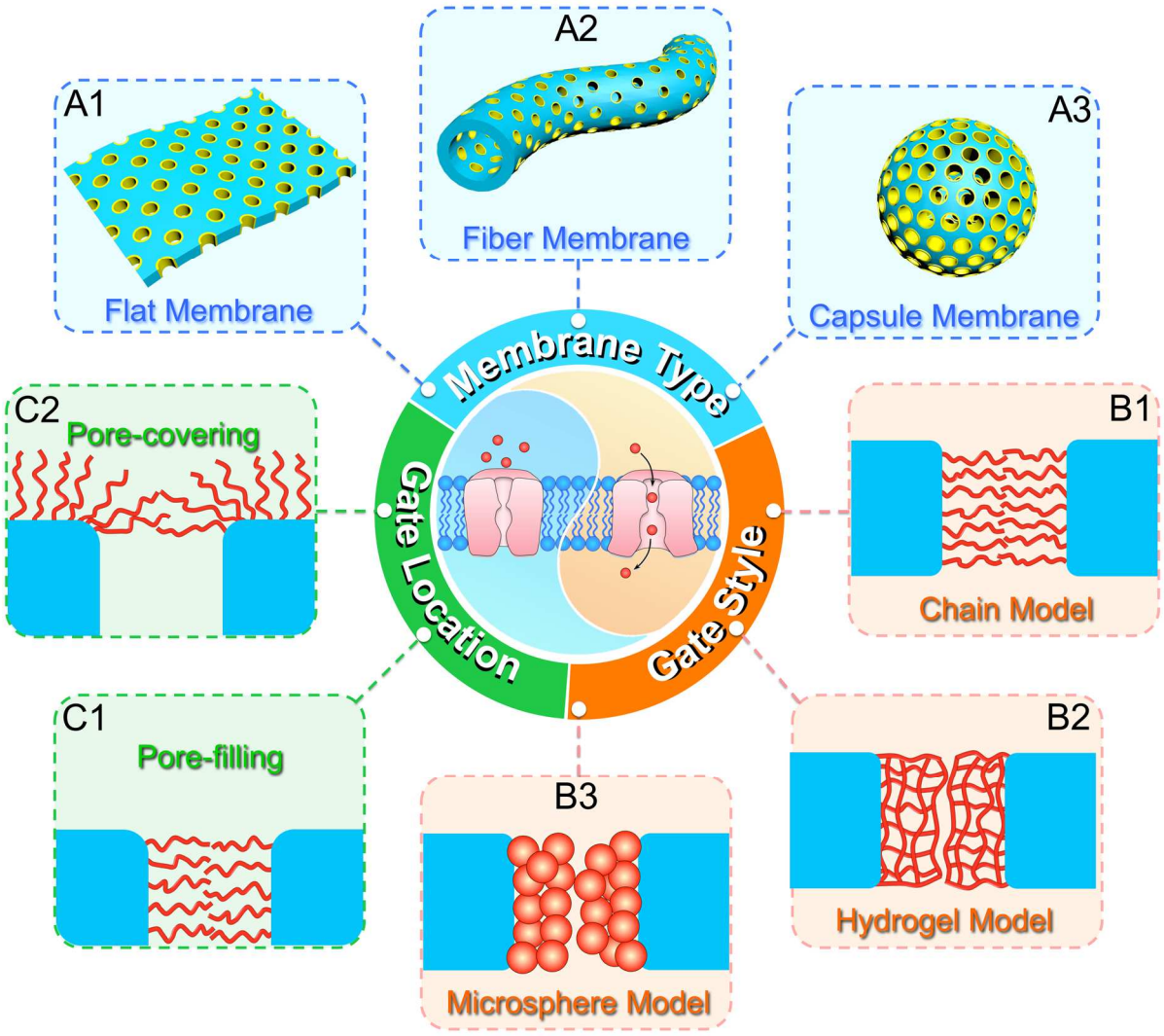

Fig. 1 Smart gating membranes, which are inspired by cell membranes with ion channels (central images), can be designed and fabricated with various styles. The membrane type can be flat membrane (A1), fiber membrane (A2) or capsule membrane (A3), the gate style can be linear polymer chains (B1), crosslinked hydrogel networks (B2) or microspheres (B3), and the gate location in the membrane pore can be pore-filling (C1) or pore-covering (C2).

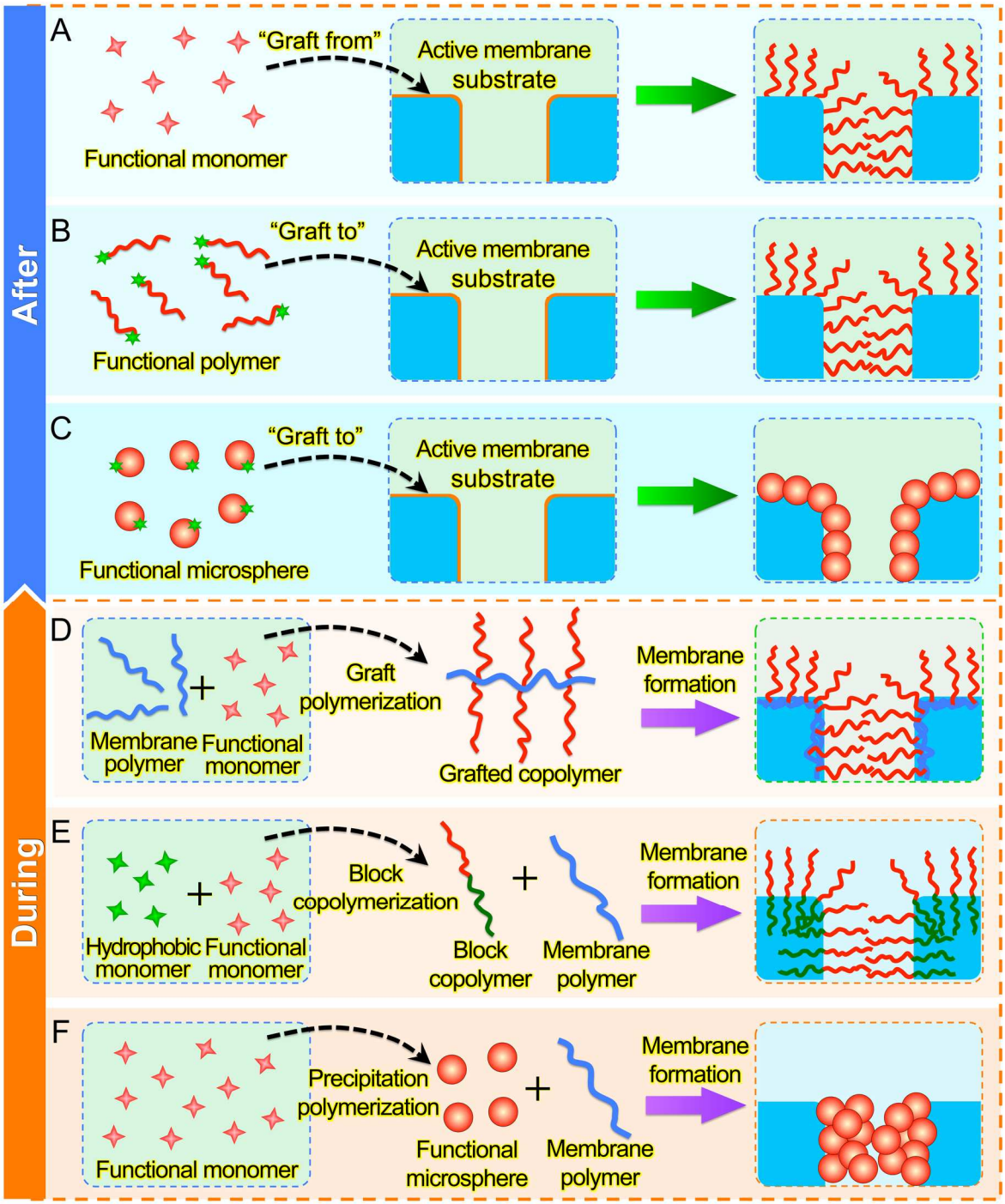

Fig. 2 Strategies for fabricating smart gating membranes by introducing stimuli-responsive domains into membranes *after* (A-C) or *during* (D-F) the membrane formation. (A) Gates are fabricated on the membrane substrate by grafting from functional monomers. (B, C) Gates are fabricated by grafting functional polymers (B) or microspheres (C) onto the membrane substrate. (D-F) Gates are fabricated by blending functional grafted (D) or block (E) copolymers, or microspheres (F) with membrane-forming materials *during* the membrane formation.

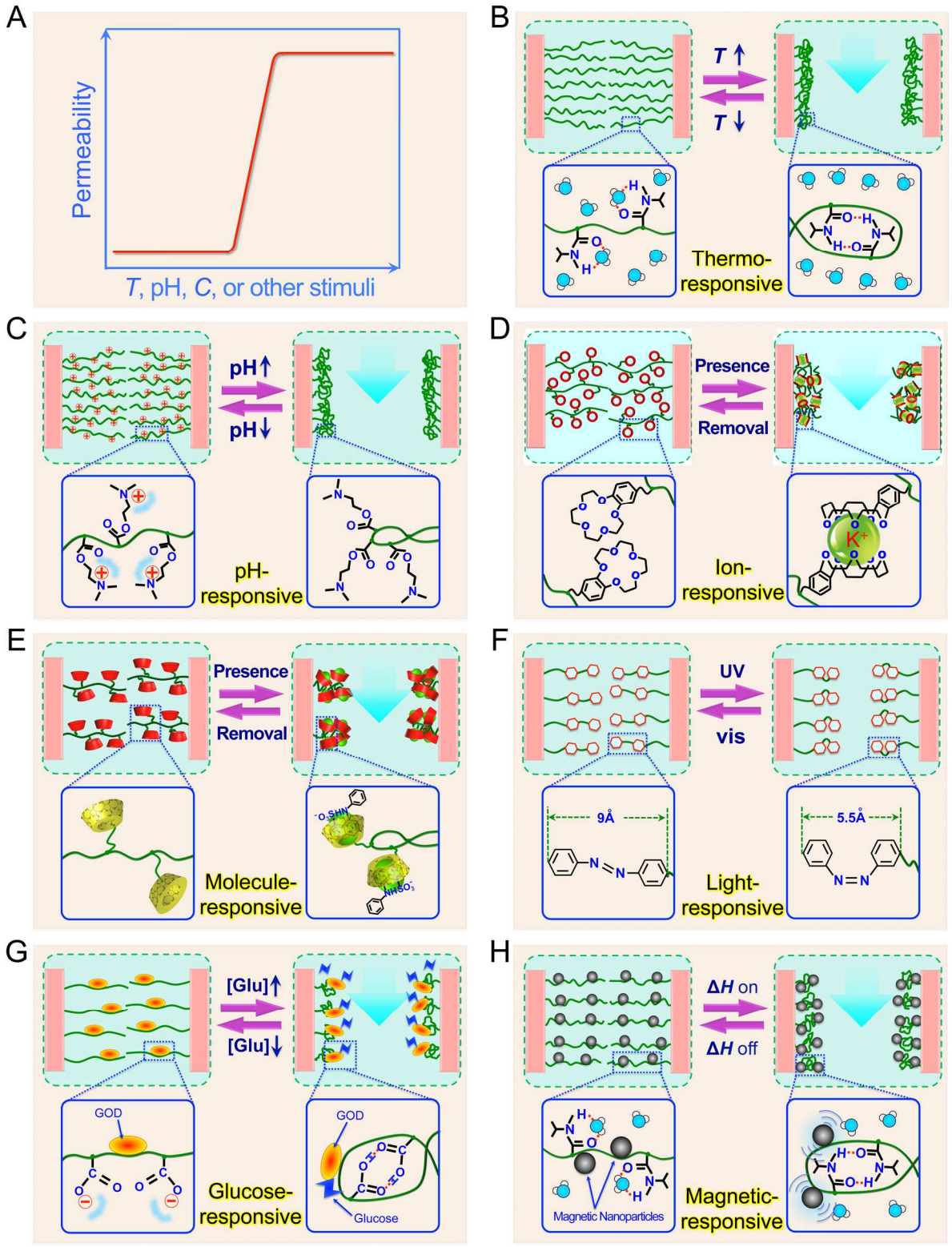

Fig. 3 Smart gating membranes with *positively*-responsive gating model. The membrane permeability increases dramatically with opening membrane pores in response to increase or presence of stimulus (A), such as temperature (B), pH (C), specific ion (D) or molecule (E), UV light (F), glucose concentration (G), or magnetic field (H).

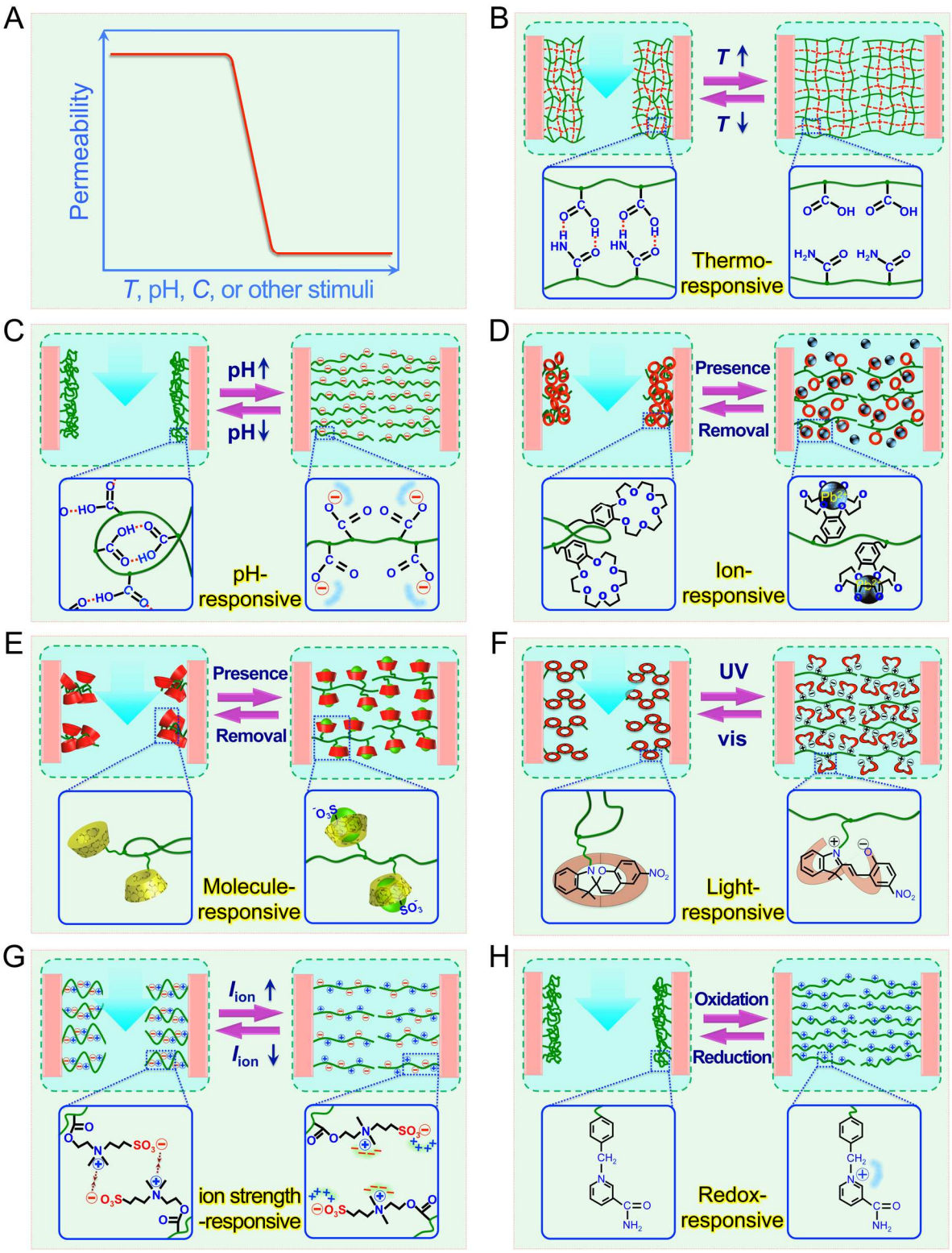

Fig. 4 Smart gating membranes with *negatively*-responsive gating model. The membrane permeability decreases dramatically with closing membrane pores in response to increase or presence of stimulus (A), such as temperature (B), pH (C), specific ion (D) or molecule (E), UV light (F), ion strength (G), or oxidation (H).

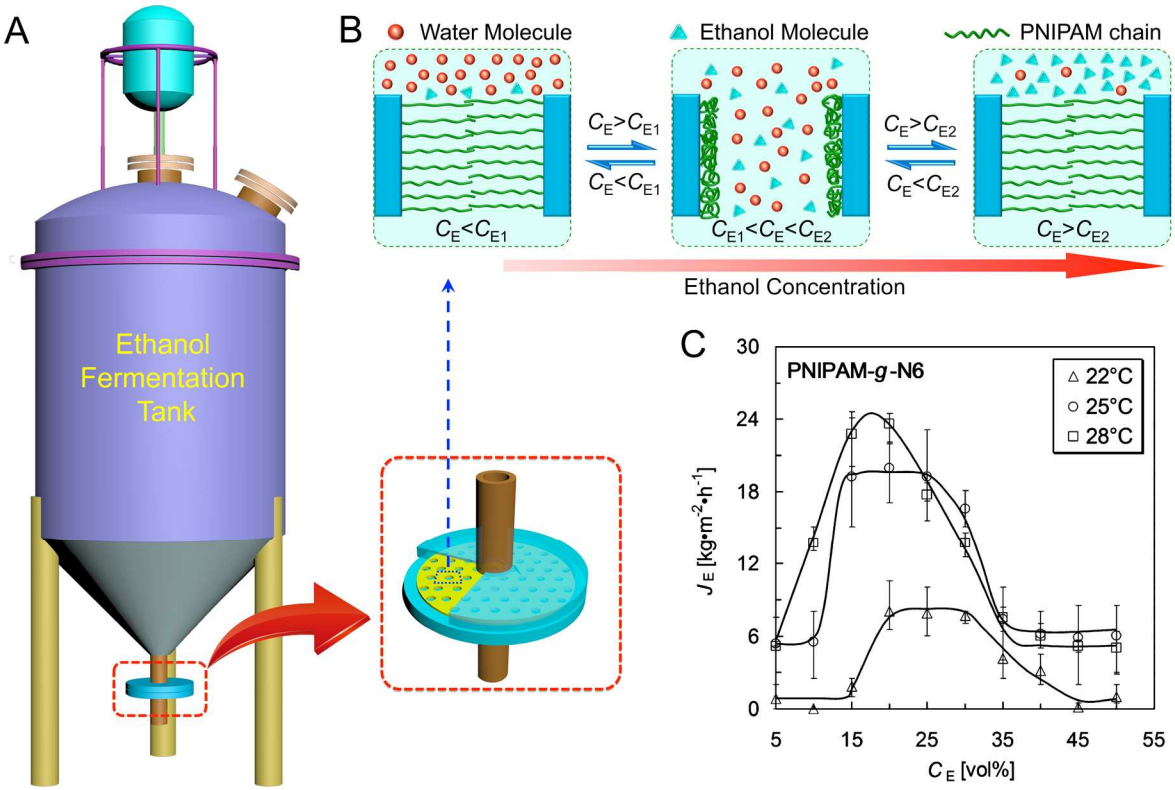

Fig. 5 Smart gating membranes for regulating ethanol concentration in fermentation. (A) Schematic illustration of a fermentation reactor equipped with ethanol-concentration-responsive gating membranes for maintaining the inside ethanol concentration (C_E). (B) Membranes with PNIPAM gates for ethanol-responsive gating, in which C_{E1} and C_{E2} are two critical response concentrations of the PNIPAM gates. (C) Isothermal regulation of membrane permeability with varying the C_E value. (B) and (C) are reproduced with permission from ref. 12, Copyright 2012 American Chemical Society.

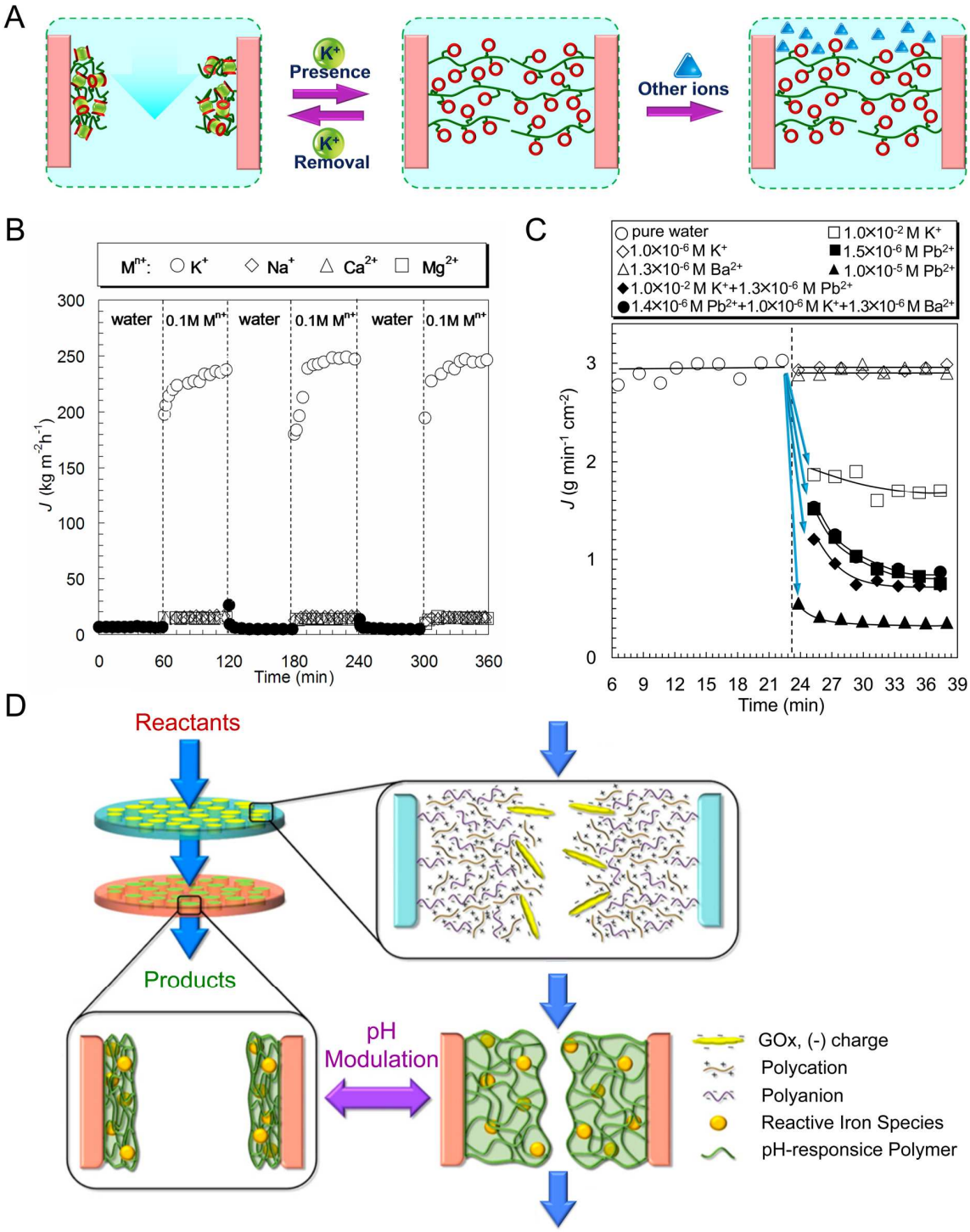

Fig. 6 Smart gating membranes for sensing ions and treating toxics. (A, B) K^+-responsive gating membrane (A) and the K^+-responsive permeability (B). Reproduced with permission from ref. 37, Copyright 2012 Wiley-VCH. (C) Gating membranes with Pb^{2+}-responsive self-regulated permeability. Reprinted with permission from ref. 16, Copyright 2013 The Royal Society of Chemistry. (D) Integrated membrane system for degrading toxic organics for water purification. Reproduced with permission from ref. 44, Copyright 2011 National Academy of Sciences, U.S.A..

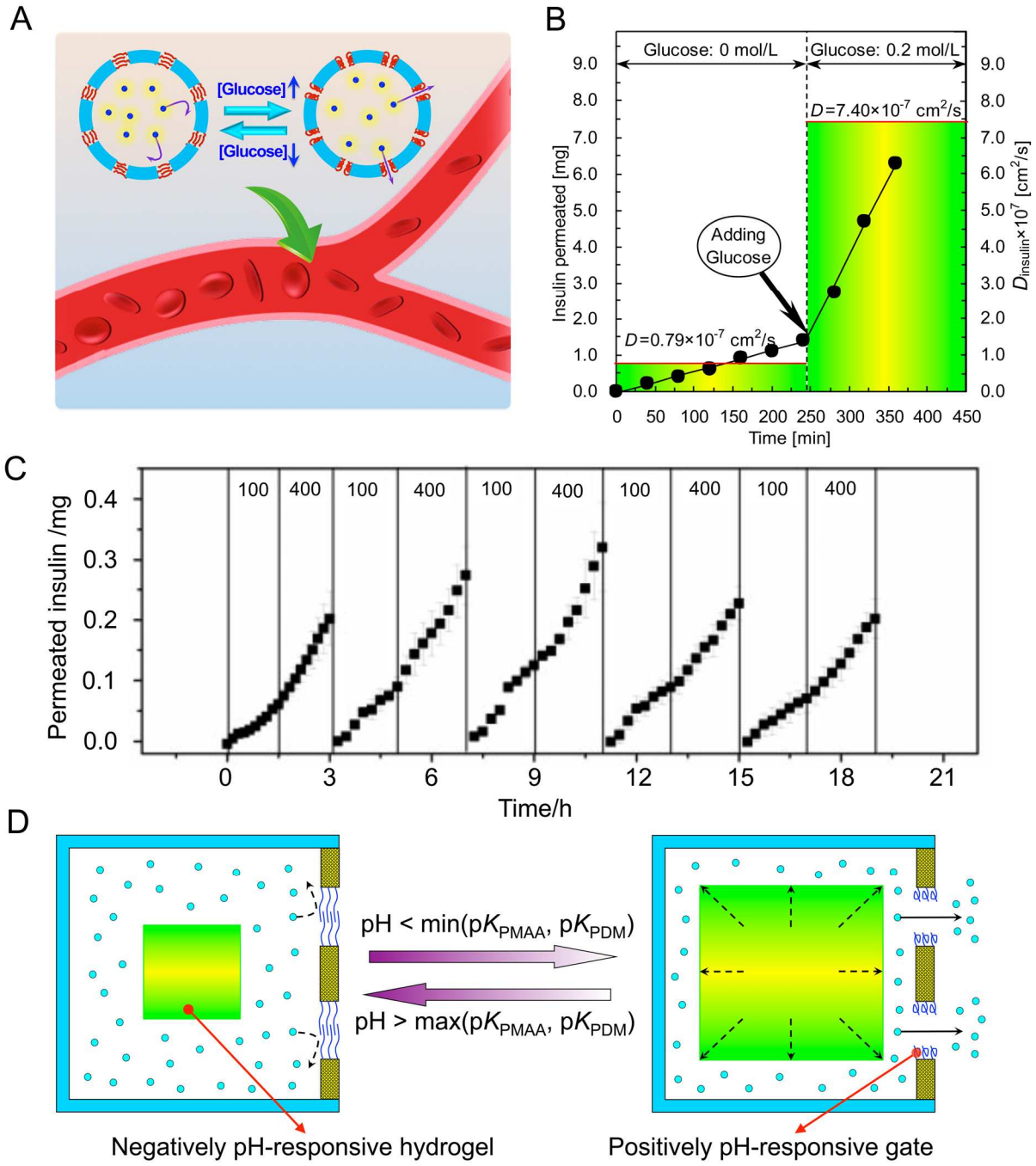

Fig. 7 Smart gating membranes for controlled release. (A) Smart microcapsule membrane with glucose-responsive gates for controlled release. Reproduced with permission from ref. 45, Copyright 2004 Elsevier. (B, C) Glucose-responsive release of insulin from the glucose-responsive gating membrane. (B) is reprinted with permission from ref. 17, Copyright 2004 Elsevier; (C) is reproduced with permission from ref. 46, Copyright 2010 Wiley-VCH. (D) Pumping systems with gating membranes containing pH-responsive gates for enhanced controlled release. Reproduced with permission from ref. 47, Copyright 2006 Wiley-VCH.

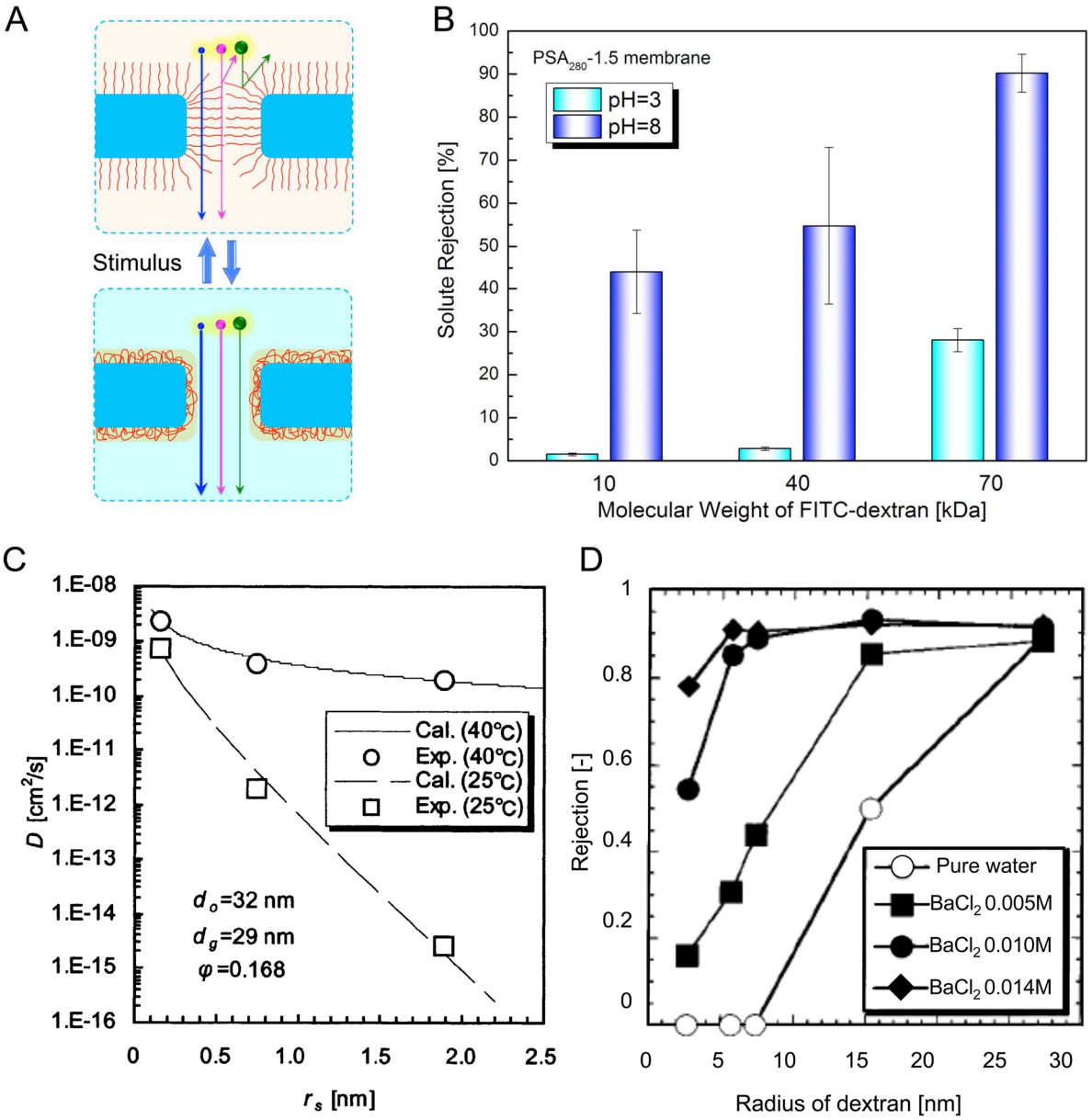

Fig. 8 Smart gating membranes for size-sieving-based separation. (A) Schematic illustration of the stimuli-responsive size-sieving-based separation. (B-D) Graded size-sieving-based separations by pH-responsive (B), thermo-responsive (C), and ion-responsive (D) gating membranes. (B) is reprinted with permission from ref. 27, Copyright 2014 Elsevier; (C) is reprinted with permission from ref. 14, Copyright 2003 American Institute of Chemical Engineers (AIChE); (D) is reprinted with permission from ref. 48, Copyright 2002 American Chemical Society.

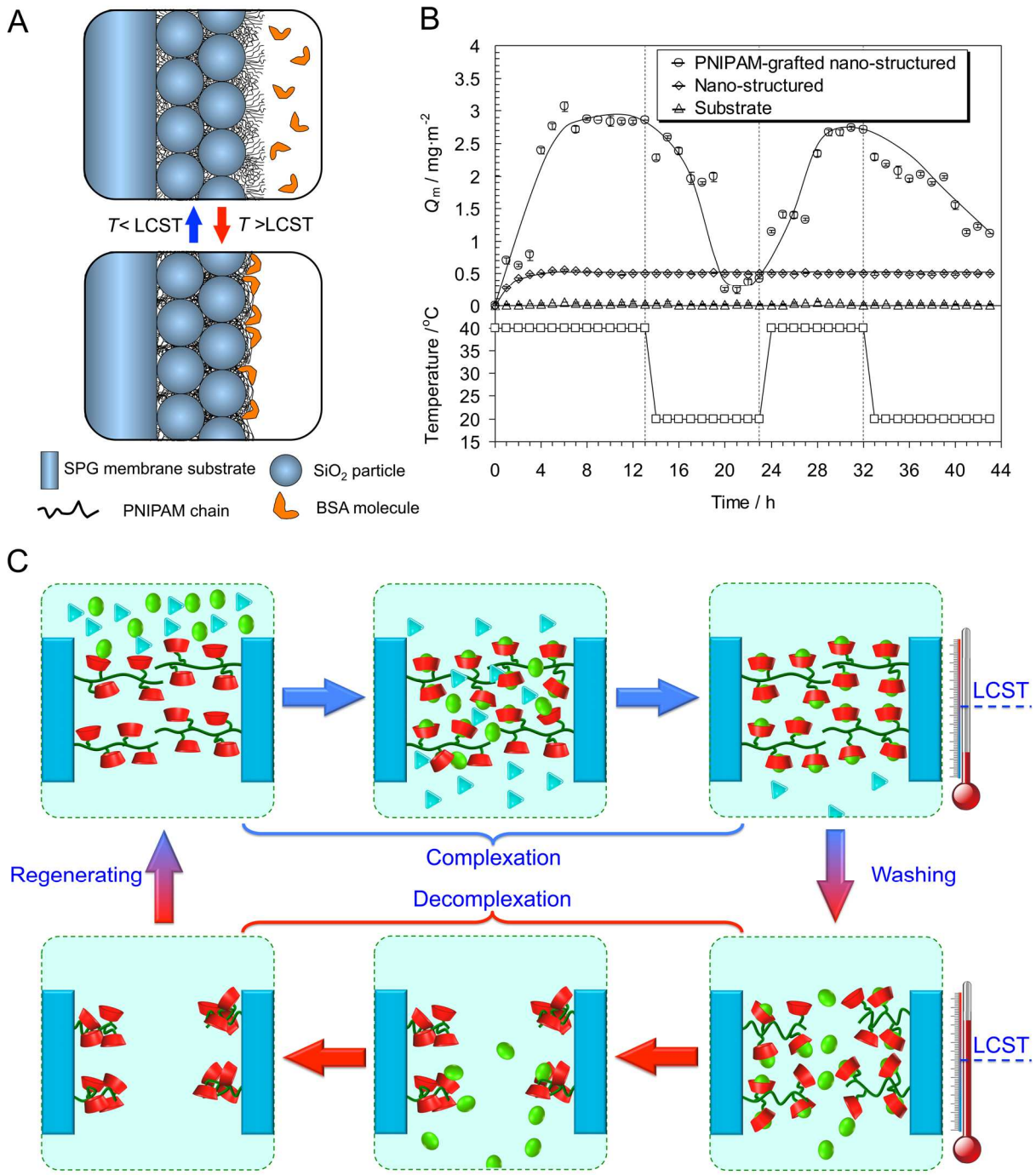

Fig. 9 Smart gating membranes for affinity-based separation. (A, B) Schematic illustration (A) and experimental data (B) showing membranes with PNIPAM-based gates for thermo-induced adsorption/desorption of BSA molecules. Reproduced with permission from ref. 15, Copyright 2010 Elsevier. (C) Membranes containing thermo-responsive PNIPAM chains with appended *β*-CD moieties as functional gates for chiral resolution. Reproduced with permission from ref. 22, Copyright 2008 Wiley-VCH.

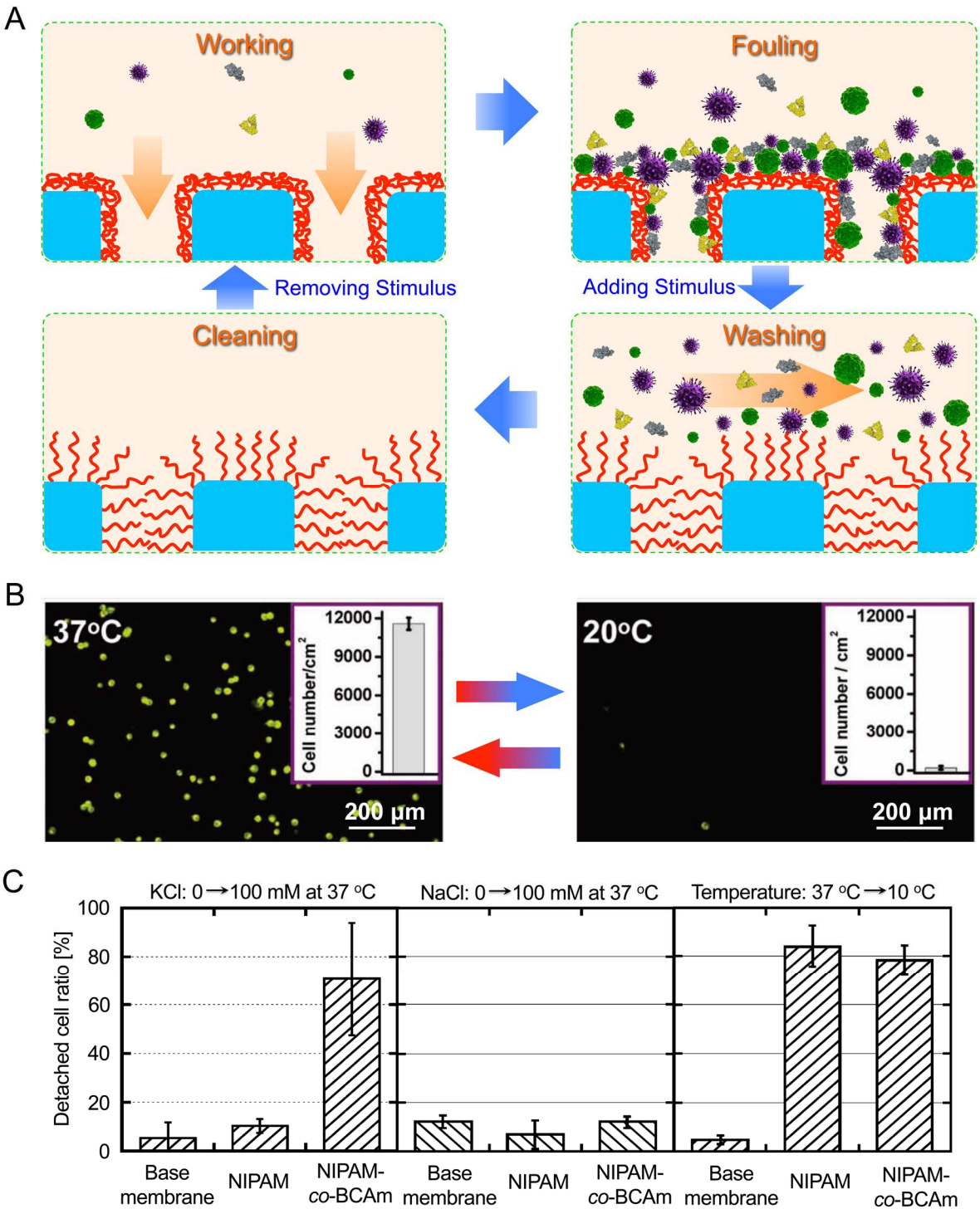

Fig. 10 Smart gating membranes for self-cleaning. (A) Schematic illustration of the self-cleaning principle with smart gating membrane by easily adding/removing simple environmental stimulus, *e.g.*, temperature decrease for PNIPAM gates. (B) Thermo-induced self-cleaning of cells on smart gating membrane surface. Reproduced with permission from ref. 49, Copyright 2013 Wiley-VCH. (C) Detached cell ratios of the smart gating membrane in response to various signals. Reproduced with permission from ref. 50, Copyright 2005 American Chemical Society.

Graphic Abstract for Table of Content (TOC)

This review highlights recent developments of stimuli-responsive smart gating membranes, including the design and fabrication strategies, versatile stimuli-responsive gating models and advanced applications.