



Review

Responsive polymers for analytical applications: A review

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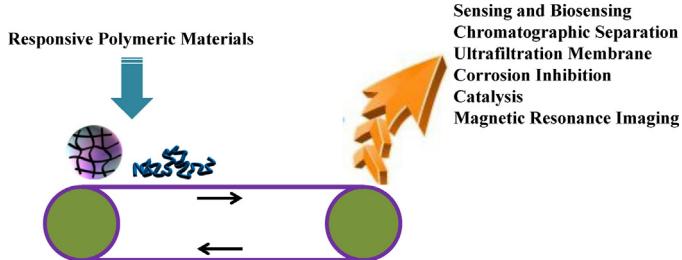
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HIGHLIGHTS

- Stimuli-responsive polymers can respond to various environmental changes.
- The response can lead to a change in the polymer's chemical or physical properties.
- The polymer response can be used for a variety of analytical applications, e.g., chromatography, sensing/biosensing.

GRAPHICAL ABSTRACT



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ABSTRACT

Stimuli-responsive polymers are capable of translating changes in their local environment to changes in their chemical and/or physical properties. This ability allows stimuli-responsive polymers to be used for a wide range of applications. In this review, we highlight the analytical applications of stimuli-responsive polymers that have been published over the past few years with a focus on their applications in sensing/biosensing and separations. From this review, we hope to make clear that while the history of using stimuli-responsive polymers for analytical applications is rich, there are still a number of directions to explore and exciting advancements to be made in this flourishing field of research.

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1. Introduction

Polymers, or more colloquially referred to as “plastics”, have seemingly found their way into every part of our lives. From the smart phones in our pockets, and the cars we drive, to artificial heart valves that are necessary to keep some alive—polymers are ubiquitous. If that wasn't enough, polymers are also responsible for who we are; DNA, the carrier of all genetic information for individuals, is also a polymer. While polymers seem to be everywhere, they weren't always so openly accepted. Specifically, in the early-to-mid 20th century, there was much debate about the mere existence of such high molecular weight single molecules or “macromolecules”. In fact, only after much research and debate, and a Nobel Prize (Staudinger, 1953 Nobel Prize in Chemistry) was the idea of the polymer finally accepted. The acceptance of polymers paved the way for the remarkable work of Paul J. Flory (1974 Nobel Prize in Chemistry), Jean-Marie Lehn (1987 Nobel Prize in Chemistry), and Pierre-Gilles de Gennes (1991 Nobel Prize in Physics), which really shaped our understanding of polymers to allow for advances in modern areas such as energy and computing [1–6].

While polymers in general are an interesting class of matter, this review will focus on a specific set of polymers termed “stimuli-responsive polymers” or also referred to as smart polymers/materials. These polymers have the ability to respond physically and/or chemically in response to environmental changes [7–13]. As seen schematically in Scheme 1, a polymer chain can undergo a conformational change from extended to collapsed in response to a stimulus. Stimuli-responsive polymers can also make up a portion of a block copolymer, and thus, only a portion of the whole polymer will undergo a change in response to a stimulus [14,15]. The environmental changes (or stimulus) can be pH, temperature, ionic strength, light, electric or magnetic field [16–20]. While polymer-based systems can be engineered to respond to a single stimulus, they can also be made to respond to multiple stimuli, e.g., temperature and pH [21–23]. That is, by polymerizing multiple monomers together that themselves yield polymers



Scheme 1. (Top), A stimuli-responsive polymer showing a conformational change in response to a stimulus and (bottom), a cross-linked stimuli responsive polymer-based material showing reversible swelling and deswelling due to the application of a stimulus.

with various responses; one can achieve a system that changes in response to the application of a variety of stimuli. For most applications, the polymer's response to the stimulus should be reversible upon the removal of the stimulus. That is, in the example in **Scheme 1**, the polymer should re-extend when the stimulus is removed. Furthermore, cross-linked responsive polymer networks have been constructed, as well as responsive gels, self-assembled structures and composites [24–29]. Regardless of the form, these materials have enormous potential in a wide range of modern industries, and have already been used in chromatography [30–37], optoelectronics [1,38–43], drug delivery and biosensors [44–54].

While there are a number of polymers that respond to a variety of stimuli [55–75], the thermoresponsive polymer poly (*N*-isopropylacrylamide) (abbreviated as PNIPA, PNIPAAm, PNIPAA, IPAAm or pNIPAm) has received the most attention. PNIPAm was first synthesized in the 1950s [76], but its temperature responsiveness, i.e., thermoresponsivity, was discovered later by Heskins and Guillet [77]. They established that the lower critical solution temperature (LCST) for pNIPAm is 32 °C. Contrary to the behavior of most polymers in (aqueous) solutions, polymers that exhibit LCST behavior become less soluble in a given solvent at elevated temperatures. The conformational changes primarily result from dehydration of the isopropyl groups of pNIPAm [78,79]. Cross-linked pNIPAm-based materials, known as hydrogels, can also be synthesized and exhibit LCST behavior. These materials, being chemically cross-linked, are very stable dimensionally and chemically. The behavior of these materials has been extensively studied, and is very well understood, thanks to the pioneering work of Tanaka [80–84]. Colloidally stable hydrogel particles, known as microgels or nanogels are well known as well. PNIPAm-based temperature sensitive microgels were first discovered in 1978 by Robert Pelton and have been studied extensively since [85–91]. Core–shell microgels have also been synthesized [92–96], and have found numerous analytical and biological applications [97–100]. Finally, a number of different methods to synthesize responsive polymers and gels with various architectures and functionalities have been introduced [101–110].

There are number of reviews [111–119] highlighting the development and success of responsive polymers and responsive polymer-based materials. In this submission, we focus on the *analytical applications* of various responsive polymers and polymer-based materials reported primarily over the last 3 years.

2. Applications of responsive polymers

2.1. Conformationally responsive polymers

As mentioned above, conformationally responsive polymers “react” to the application of a stimulus by changing their conformation. The most common conformationally responsive polymers are those that respond to temperature (thermoresponsive), pH and ionic strength [120–134,33,135–141]. Among them, pNIPAm-based polymers, hydrogels, and microgels are the most extensively studied and exploited.

PNIPAm-based microgels and their assemblies have found numerous applications in our laboratory over the last few years [120–124]. For example, we demonstrated that pNIPAm-co-acrylic acid (AAc) microgels and their aggregates are capable of removing large amounts of organic molecules from water, which depends on the AAc content of the microgels, as well as their concentration in solution. We also found that the extent of removal depends on temperature, e.g., the extent of removal increases if the temperature of the microgel solution is cycled from low–high–low temperature [120,121,125,126]. Furthermore, we have shown that visually colored materials can be fabricated by depositing, via a “painting

protocol”, a layer of pNIPAm-based microgels on a Au coated glass substrate, followed by the deposition of a subsequent Au layer on top [127–130]. A schematic of this device can be seen in Fig. 1(a). These devices show visual color and distinct, multiplex reflectance spectra, as seen in Fig. 1(b–f). It has also been found that etalons can be fabricated using metal layers other than Au [131]. From Fig. 1, it is also apparent that the color of the devices, and the number of peaks in the reflectance spectra (peak order), can be rationally tuned by simply changing the diameter of the microgels between the two Au layers. We have also shown that the color of the devices could be tuned with temperature, pH, and glucose concentration and thus the device can be used for sensing solution temperature, pH [122] and glucose concentration [123]. We also investigated the deswelling kinetics of the devices to understand what controls the deswelling time for the assemblies. We determined that the thickness of the Au layer covering the microgel layer greatly influenced the deswelling and solvent exchange kinetics with thinner layers giving faster responses than etalons coated with thicker Au layers [130,132]. We recently found that the molecular weight (MW) of polyelectrolyte can be detected by pNIPAm-co-AAc microgel-based etalon by varying the thickness of the Au overlayer [124] as shown in Fig. 2. We showed that when the pNIPAm-co-AAc-based etalons are at pH > 4.25 (pK_a for AAc) the microgels become multiply negatively charged. When they are exposed to a solution containing positively charged polymer (polycation) the etalon's microgel layer deswells due to intermolecular cross-linking of the charges in the microgels; they are unresponsive to the presence of the like charged polyelectrolyte. We also found that the etalon's response depended on the thickness of the Au overlayer. Low molecular weight (MW) polyelectrolyte could penetrate the various Au overlayer thicknesses, while high MW polyelectrolytes could only penetrate the etalons fabricated from thin Au overlayers. We hypothesized that this is due to a decrease in the Au pore size with increasing thickness [130,132], which excludes the high MW polyelectrolytes from penetrating the microgel-based layer. These devices show promise as MW selective sensors and biosensors.

Working on the same polymeric system based on pNIPAm, Kumashiro et al. [133] investigated temperature-modulated adsorption of ferritin-modified pNIPAm (pNIPAm-ferritin) on a solid substrate. They found that pNIPAm-ferritin adsorbed onto hydrophobic surfaces with surfactants at 37 °C, while pNIPAm-ferritin did not effectively adsorb onto these hydrophobic surfaces at 25 °C. From these studies, the authors concluded that grafted pNIPAm underwent a phase transition at $T > 32$ °C, subsequently increasing hydrophobicity of the polymer, which in turn promoted polymer binding to the hydrophobic surfaces. Similarly, at $T < 32$ °C, modified pNIPAm becomes more hydrophilic in nature and reduced the efficacy of polymeric binding to hydrophobic surfaces. PNIPAm-ferritin polymers may serve as adaptive biosensors in the detection of disease conditions within biological organs, via thermally induced differential binding of polymers to hydrophobic surfaces.

Using 1-alkyl[2-(acryloyloxy)ethyl]dimethylammonium bromides with hexyl or cetyl groups and 2-hydroxyethylacrylate (HEA) or N-isopropylacrylamide (NIPAM), four block copolymers were synthesized by Budgin et al. and employed for functionalization of monodisperse iron oxide nanoparticles (NPs) [134]. The authors claimed that these block copolymer NPs could be used as magnetic stoppers in biorelated membrane separations. They also incorporated Pd species in submicrometer particles making them promising candidates for catalytic applications as magnetically recoverable catalysts with a high magnetic response. In another effort for protein purification, Poly(*N*-isopropylacrylamide-co-*N,N'*-dimethylaminopropylacrylamide-co-*N*-tert-butylacrylamide), P(NIPAm-co-DMAPAm-co-tBAAm) brush-grafted silica-beads

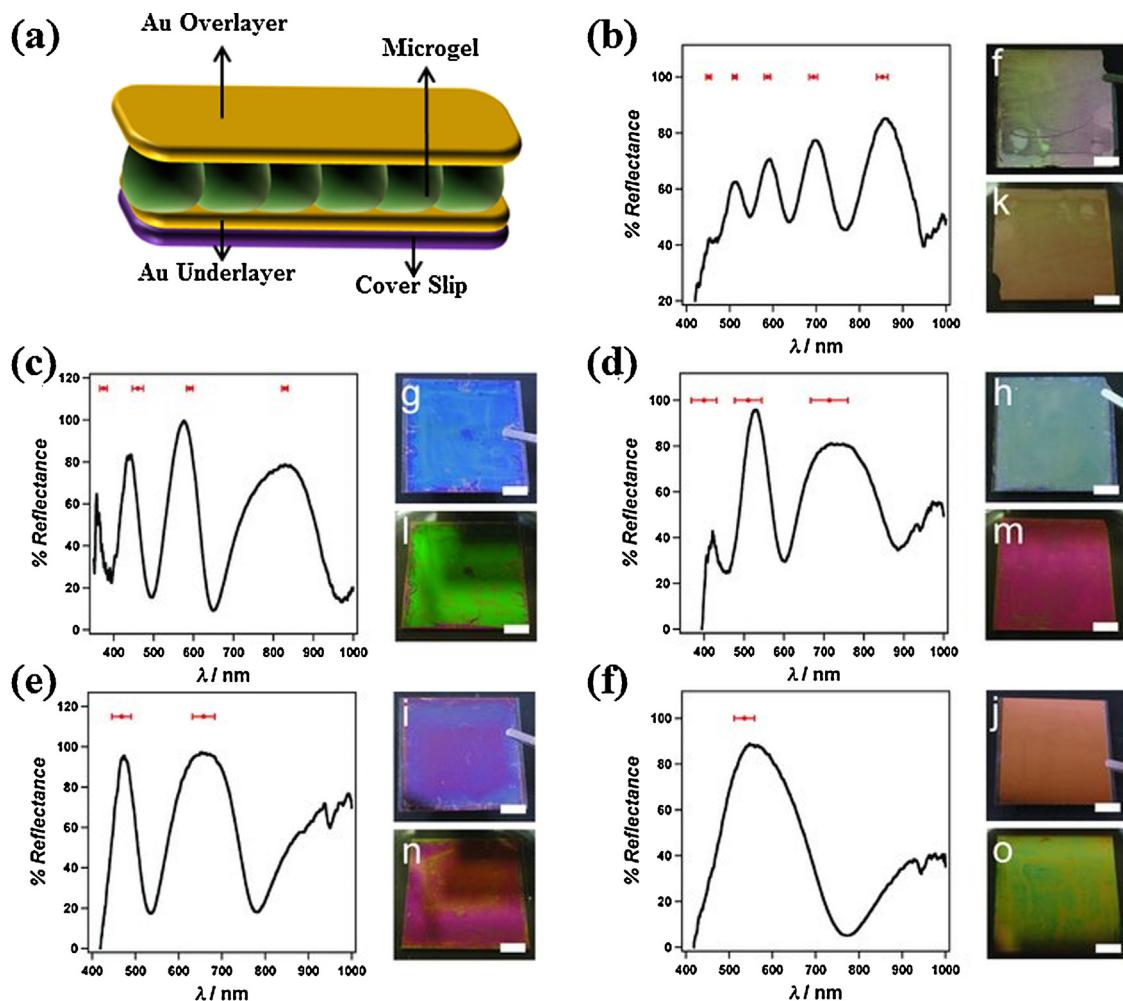


Fig. 1. (a) Schematic illustrating the structure of a poly(*N*-isopropylacrylamide) microgel-based etalon (b–f). Representative spectra for etalons composed of b) large diameter poly(*N*-isopropylacrylamide)-co-acrylic acid (pNIPAm-co-AAc) microgels (hydrodynamic diameter (D_H) = $1548 \pm 69 \text{ nm}$) c) poly(*N*-isopropylacrylamide)-coacrylamide (pNIPAm-co-AAm) ($D_H = 653 \pm 10 \text{ nm}$) d) medium diameter poly(*N*-isopropylacrylamide)-co-acrylic acid (pNIPAm-co-AAc) microgels ($D_H = 653 \pm 10 \text{ nm}$) e) poly(*N*-isopropylacrylamide)-co-vinyl acrylic acid (pNIPAm-co-VAA) ($D_H = 603 \pm 17 \text{ nm}$), and f) small diameter poly(*N*-isopropylacrylamide)-co-acrylic acid (pNIPAm-co-AAc) microgels ($D_H = 229 \pm 10 \text{ nm}$), all obtained in pH 3 formate buffer. The average peak position (\pm one standard deviation) from six spectra is shown in red above each spectrum. f–j) Photographs for the etalons (b–f) in the dry state, respectively. k–o) Photographs of the etalons (b–f) hydrated in pH 3 formate buffer. Scale bars in the photographs are 5 mm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Figure b–f are reproduced with permission from reference [129].

were prepared through a surface-initiated atom transfer radical polymerization (ATRP). It was reported that the copolymer brush-grafted silica-beads adsorbed negatively charged proteins both through electrostatic and hydrophobic

interactions by the modulation of column temperature [33].

PNIPAm hydrogel-modified silica-beads were prepared by a radical polymerization through modified 4,4'-azobis

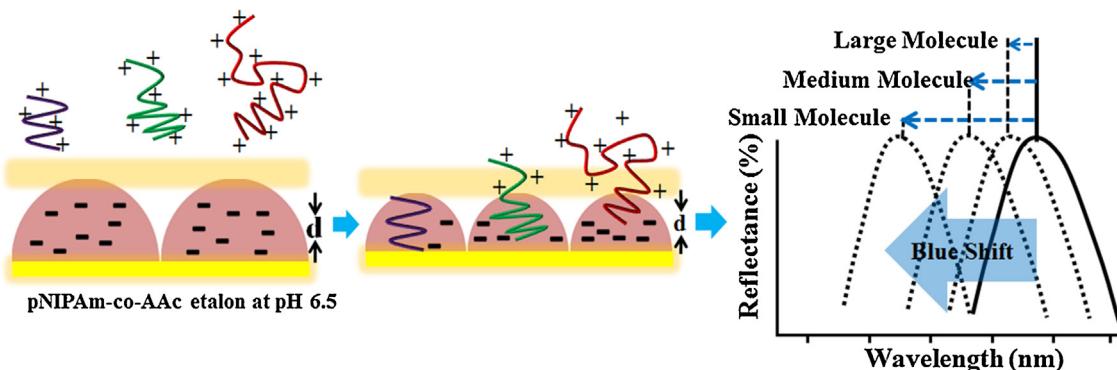


Fig. 2. Polyelectrolyte penetration through the porous Au overlayer of an etalon.

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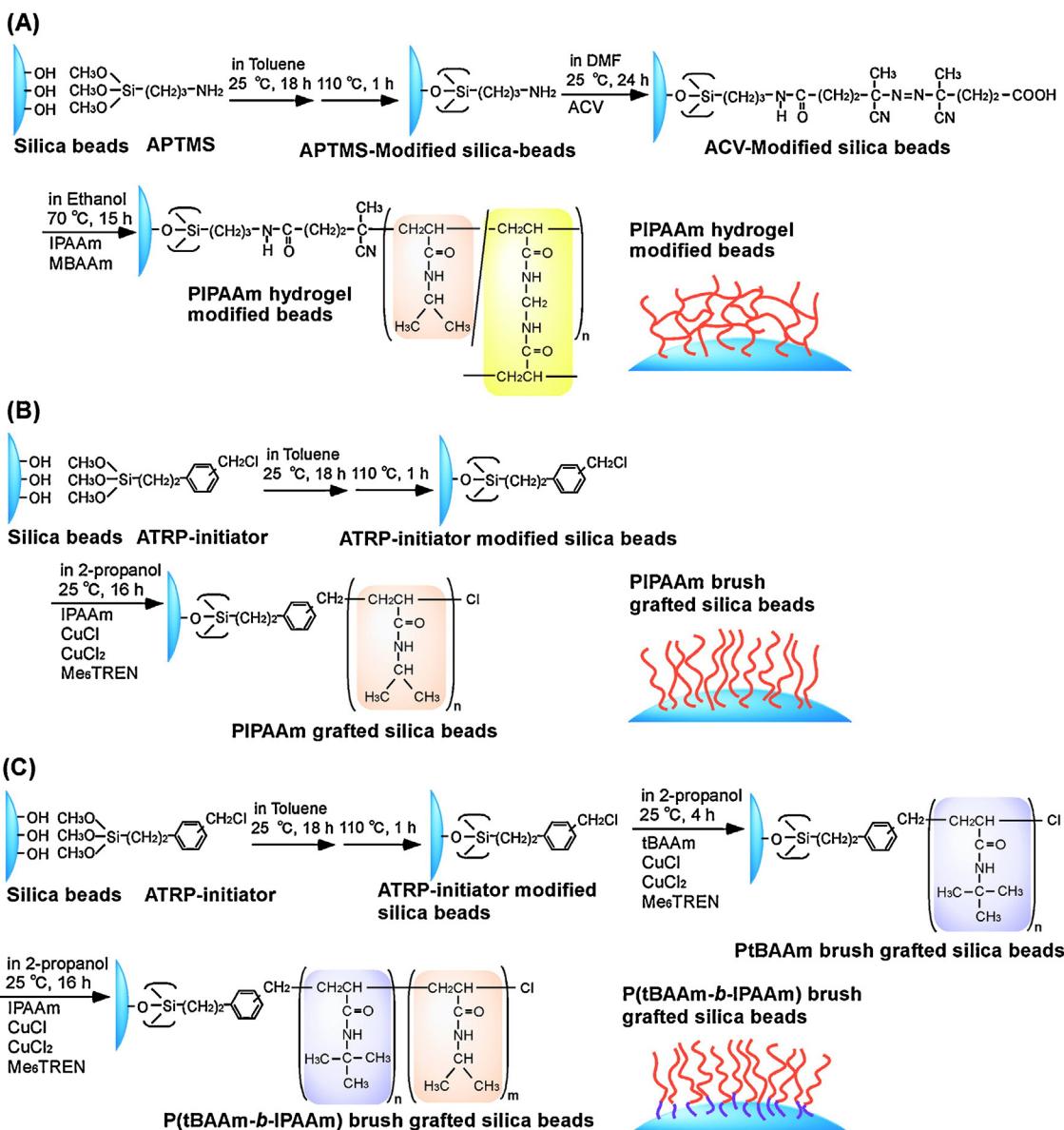


Fig. 3. Schematic showing the preparation of thermoresponsive polymer-grafted silica-beads using a surface-initiated atom transfer radical polymerization (ATRP); (A) pNIPAm hydrogel-modified beads and (B) pNIPAm brush-grafted surface, and (C) poly(*tert*-butylacrylamide-*b*-N-isopropylacrylamide (tBAAm)-*b*-IPAAm). Reproduced with permission from reference [136].

(4-cyanovaleric acid) and N,N'-methylenebisacrylamide with chromatography matrices with different architectures and found that prepared beads with a dense polymer brush structure maintained a stable separation efficiency due to strong hydrophobicity arising from dehydrated copolymer at elevated temperature. The retention times of different hydrophobic steroids suggest stronger hydrophobicity of the beads. Thus, precisely modulating graft configuration of thermo responsive polymers on interfaces provided chromatography matrices with a high separation efficiency and stability for continuous use, resulting in extending the longevity of chromatographic column [135].

In a related effort for the separation of biomolecules utilizing pNIPAm and copolymer of N-isopropylacrylamide and N,N'-dimethylaminopropylacrylamide (DMAPAAm), Nagase et al. performed temperature responsive chromatography with an aqueous mobile phase without using an organic solvent [136]. They prepared thermoresponsive polymer-grafted silica-beads pNIPAm hydrogel-modified beads, pNIPAm brush-grafted surface,

and poly(*tert*-butylacrylamide-*b*-N-isopropylacrylamide (tBAAm)-*b*-IPAAm) (Fig. 3). They used temperature to change surface properties without changing the mobile-phase composition. The separation of the biomolecules, such as nucleotides and proteins were achieved by this dual temperature- and pH-responsive chromatography system with a very high resolution (Fig. 4). The same group reported other cationic, bio-responsive and hydrophobic brushes for the separation of biomolecules [137–139].

A thin mixed polymer brush has been grafted onto a Si wafer consisting of highly hydrophilic PAA and hydrophobic PS, which were synthesized using a “grafting to” approach. It was found that the wetting properties of the surfaces can be switched between advancing and receding water contact angles [140]. The locking and unlocking of the hydrophobic brush in a specific solvent was demonstrated and proposed that this system could find applications in smart textiles and microfluidic devices [140]. The same group reported that poly (2-vinylpyridine) polymer brushes immobilized on glass substrates exhibited pH responsivity. It was

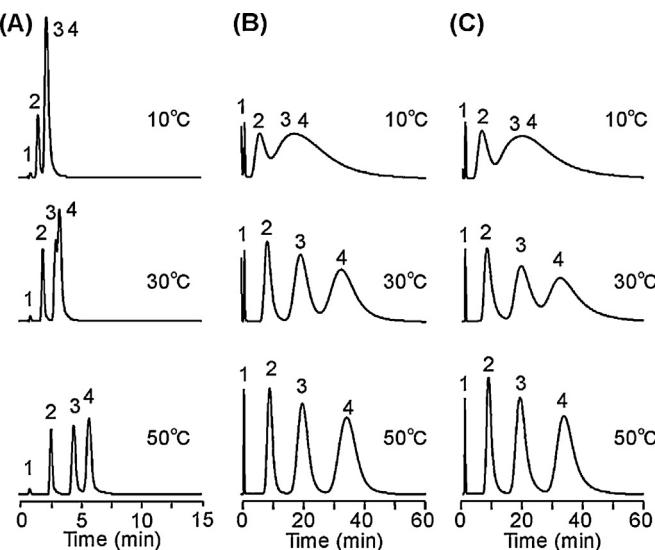


Fig. 4. HPLC chromatograms of steroids separated using pNIPAm-grafted silica-beads as the packing materials at various temperatures: (A) PIPAAm hydrogel-modified silica-bead-packed column, (B) PIPAAm-brush-grafted silica-bead column (IP-B), and (C) poly(tert-butylacrylamide (tBAAm)-*b*-IPAAm) brush-grafted silica-bead column (tBIP-B). Mobile phase was Milli-Q water. The peak 1 represents adenosine; peak 2, hydrocortisone; peak 3, dexamethasone; peak 4, hydrocortisone acetate.

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reported that the spacing between two kinds of nanoparticles—gold nanoislands immobilized on a transparent support and gold colloidal particles adsorbed on the brush surface can be tuned by varying the pH of the solution and detected by surface plasmon resonance [141]. The authors claimed that highly sensitive nanosensors could be made out of that system.

Wang et al., synthesized a dual-stimuli-responsive Poly (2-(2-methoxyethoxy) ethyl methacrylate-*b*-oligo (ethylene glycol) methacrylate-*b*-acrylic acid) (PMOA) hydrogel system through a free-radical polymerization reaction with thermo responsive comonomers, oligo (ethylene glycol) methacrylate (OEGMA) and 2-(2-methoxy-ethoxy)ethyl methacrylate (MEO2MA), and pH-responsive acrylic acid (AAc) comonomer. They concluded that temperature and pH induced hydrogel deswelling is characterized by a first-order kinetics equation, and that deswelling kinetics is faster from 18 to 55 °C [142] which will find application in drug delivery and biosensors.

In a recent effort, a novel thermoresponsive statistical block copolymer has been designed from dialkyl vinylphosphonates by rare earth metal-mediated group transfer polymerization using tris-(cyclopentadienyl)ytterbium [143]. The obtained copolymers of diethyl vinylphosphonate (DEVP) and dimethyl or di-n-propyl vinylphosphonate (DPVP), Poly(dimethyl vinylphosphonate-co-diethyl vinylphosphonate) (P(DMVP-co-DEVP)) shows thermoresponsive properties with tunable lower critical solution temperature (5–92 °C). This copolymer is sensitive to the concentration and to the presence of additives and proposed to be a promising candidate for controlled cell growth and release.

2.1.1. pH and ionic strength responsive polymer

pH-responsive polymers contain weak electrolyte groups on the polymer chains, such as a carboxylic acid group, or an amino group, which can accept or donate protons in response to a change in the environmental pH. Around the pK_a of the weak electrolyte groups the degree of ionization is dramatically altered. A change in the net charge of pendant groups causes a change of the hydrodynamic volume of the polymer chains, which ensues from changes

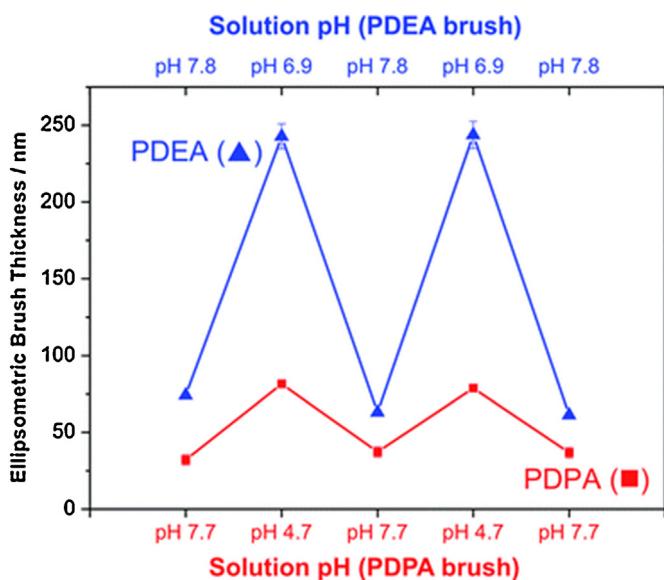


Fig. 5. Aqueous in situ ellipsometric thickness against pH for a PDPA (■) and a PDEA (▲) brush grown from anionic macro-initiator on aminated silicon wafers. The samples were immersed in buffer solutions with alternating pH and allowed to reach equilibrium. Dilute phosphate buffer solutions (0.01 M) were used to perform the experiment.

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in the osmotic pressure exerted by mobile counter ions neutralizing the polymer charges as well as charge-charge (Coulombic) repulsion. Furthermore, pH-responsive polymers are also responsive to changes in ionic strength, where screening of repulsive electrostatic interactions increase with increasing ionic strength resulting in polymer chains collapse.

Two weak polybases Poly [2-(diethylamino) ethyl methacrylate] (PDEA) and poly[2-(diisopropylamino) ethyl methacrylate] (PDPA) brushes were grown by surface-initiated atom transfer radical polymerization [144]. Using in situ ellipsometry an acid-induced swelling transition was observed at pH 7.4 for PDEA and pH 6.5 for PDPA, similar to the pK_a values reported for the corresponding free polymer chains as shown in Fig. 5. On exposure to humid HCl vapor, PDPA brushes become hydrophilic, resulting in water uptake and swelling, producing a visible change in the thin film. This film can be used as chemical sensor.

Bousquet et al. reported nanostructured adaptive polymer surfaces by diffusion of amphiphilic polystyrene-block-poly(acrylic acid) (PS-*b*-PAA) toward the interface [145]. The PAA segments placed at the interface respond to pH and can switch from an extended hydrophilic state at pH values above 6.0 to a collapsed hydrophobic state at pH 3.0. Accordingly, the surface morphology changed from swollen micelles to nanometer size holes. Ampholytic hydrogels through chemical cross-linking were synthesized from two cellulose-based polyelectrolytes quaternized cellulose (QC) and carboxymethyl cellulose (CMC) [146]. The hydrogels exhibited excellent pH sensitivity in the range of pH from 1 to 13 and shrunk significantly at pH 12 on the whole. The hydrogels displayed smart swelling behavior in NaCl, CaCl₂, and FeCl₃ aqueous solutions. The results revealed that CMC mainly contributed to increasing the swelling as a result of strong water adsorption, whereas QC played a role in controlling the charges in the QC/CMC system, leading to the pH sensitivity. An environmentally responsive ultrafiltration membrane was created on a commercial microporous Polyvinylidene fluoride (PVDF) membrane support with a cross-linked poly-N-vinylacetamide hydrogel [147]. The membrane permeability increased significantly with increase in salt concentration due to the collapse of the hydrogel onto the surface

of the supporting PVDF membrane. The transmission behavior of model proteins in response to change in salt concentration was demonstrated by parameter scanning ultrafiltration experiments.

pH-responsive polymer brushes facilitate efficient transduction mechanisms, which make them suitable for use in sensor applications. For example, Tokareva et al. demonstrated the tuning of the plasmon-resonance coupling between gold nanoparticles and a gold substrate mediated by a 20-nm-thick swellable P2VP brush layer [148]. The film can be used as a highly sensitive pH-responsive nanosensor with short response times by minimizing the diffusion of the analyte to the sensor. The authors demonstrated a large (50 nm) shift in the plasmon-resonance position as a result of changing pH values (within $\text{pH } 3.8 \pm 0.5$) caused by shrinking of the brush thickness from 22 to 7 nm. Li and Lotsch fabricated 2D inverse opal monolayers out of a swellable P2VP polyelectrolyte gel for pH sensing [149]. The photonic membrane shows a fast response to pH and can be readily read out from either its optical spectra or visible colors (Fig. 6).

Electrostatic layer-by-layer (LbL) assembly has been introduced for the facile fabrication of responsive polyelectrolyte films. The mechanism of response of LbL assemblies was analyzed by Rubner and co-workers [150] for poly (allylamine hydrochloride)/polystyrene sulfonate (PAH/PSS) systems, who attributed the dramatic variation in the degree of swelling (up to 400%) at high pH (pH 9.5) to changes in the degree of ionization of the weak polyelectrolytes. The authors claimed that hydrophobic association can increase the local density of amine groups of the weak polyelectrolyte (PAH) and/or decrease the local dielectric constant experienced by this weak functional group. As a result, weak functional groups become more difficult to ionize. A sharp swelling and deswelling transition detected for LbL films at $\text{pH} > 8.5$ manifested itself in reversible pH-controlled variations of swelling percentage, surface roughness and refractive index. The PAH swelling was associated with the variation in ionization of its free amine groups, and a hysteresis loop was related to the chain dynamics within swollen LbL films.

Different LbL films with embedded biomolecules and nanoparticles have been exploited as soft organized matrices for uploading nanoparticles to fabricate pH-responsive and biosensitive polymeric nanomaterials based on the surface plasmon-resonance (SPR) phenomena [151]. Various metal nanoparticles were embedded within polymeric systems to use them as sensors for various applications [148,152,153]. Specifically, gold nanorods were embedded in cross-linked poly(methacrylic acid)-poly(allylaminehydrochloride) and poly (methylacrylicacid)-poly(N-vinylpyrrolidone) LbL films to act as pH-responsive plasmonic sensors. Swelling and deswelling of these gels at pH 8 and pH 5, respectively, resulted in reversible, large shifts of a strong, easily detectable longitudinal plasmon resonance located in the near-infrared region ($\approx 700 \text{ nm}$) owing to variable side-by-side nanorod interactions. A novel fiber-optic pH sensor was fabricated by coating LbL films of negatively charged polyelectrolyte complex nanoparticles and positively charged poly(diallyldimethylammonium chloride) (PDDA) on the surface of a thin-core fiber modal interferometer (TCFMI) [154]. The fabricated TCFMI pH sensor has different transmission dip wavelengths under different pH values and shows high sensitivities of 0.6 and -0.85 nm/pH unit for acidic and alkaline solutions, respectively, and short response time of 30–50 s.

2.1.2. Bio-responsive polymers

Recently, thermoresponsive microgels have attracted attention to develop sensors for various biomolecules, such as saccharides, protein, and DNA etc. Hoare and Pelton [155] were focused on the use of phenylboronic acid (PBA) functional groups in the design of glucose-sensitive polymers. They synthesized pNIPAm-based

PBA-functionalized microgels, which possess well-defined glucose swelling or deswelling responses under a range of environmental conditions. When the microgels are used to detect glucose, the anionic charge density within the gel increases as the glucose concentration is increased, driving a swelling response via both Donnan equilibrium and direct charge-charge repulsion effects. Using the same concept, Sorrell and Serpe [123] described an APBA-functionalized microgel-based etalon device to detect glucose concentration by the shift in the peaks of the device's reflectance spectra. Here APBA-functionalized microgels were sandwiched between two gold layers (Fig. 7). When glucose interacts with boronic acid modified microgels, they swell, resulting in an increase in the distance between the etalon's Au mirrors, which leads to the red shift of the reflectance peaks.

Using pNIPAm-co-AAc microgel-based etalons, Islam and Serpe recently reported a method to detect the concentration of streptavidin in solution [156]. In this method the authors exploited the phenomenon of penetration of positively charged polyelectrolyte PAH and biotinylated-PAH through the etalon's Au overlayer to interact with the microgel in the etalon, which were at a pH that rendered them negatively charged. The PAH and PAH-biotin is capable of cross-linking the microgels, causing them to collapse, resulting in a blue shift in the peaks in the etalon's reflectance spectrum. The extent of the shift in the reflectance peaks is related to the concentration of PAH-biotin and hence was used to determine the concentration of streptavidin in solution as shown in Fig. 8.

Lyon et al. developed a new approach to biosensing using microlenses derived from dual thermo- and pH-responsive NIPAm and acrylic acid (AAc) microgels [157–159]. They designed microlenses that would display a change in refractive index and particle diameter upon binding with protein for use in sensing applications [159–163]. They designed microlenses for two different sensing pathways: a direct binding-induced response and a displacement-induced response. To illustrate each method; a small vitamin biotin was conjugated to the acrylic acid groups on the microgels. For the binding-induced method, avidin or anti-biotin (antibody) was added to the solution around the microlens, resulting in binding of the protein to the microlens surface. Since both avidin (four binding sites) and anti-biotin (two binding sites) are able to bind multiple equivalents of biotin, the protein-binding events increase the surface cross-linking of the microlens and hence changes the refractive index. A displacement-induced method can be achieved by designing a reversible antibody–antigen cross-linking construct. In this case, a photoaffinity approach is used to couple a bound antibody to the antigen-laden microlens. When the free biotin disrupts the cross-links via displacement, the microlens swells and the focal length increases accordingly. A biotin-free buffer wash removes the free biotin, allowing for re-cross-linking of the gel and regeneration of the sensor. Using microgels as microlenses is attractive because of the ability to use many different solution-based bioconjugation methods and the ease of assembly with simple electrostatic adsorption [164,98].

Miyata et al. [165,166] have reported antigen-responsive hydrogels using antigen–antibody binding. They synthesized acrylamide-based hydrogels using a co-monomer (N,N-succinimidyl acrylate, NSA) which is covalently attached with antigen and antibody. When free antigens are present in the analyte solution, the hydrogel swells due to the disruption of cross-links between the polymerized antigen and antibody. Another example of biomolecule recognition in a hydrogel is the lectin–glycoprotein interaction. Maeda et al. [167] detected saccharide–protein interaction capitalizing on the gel-modified field effect. This lectin-sensitive polymer gel changes volume in response to the formation of molecular interactions between carbohydrate and the lectin concanavalin A and this polymer gel has the ability to transduce volume changes into electrical signals for the field effect transistor. Kuroki et al. [168] presented

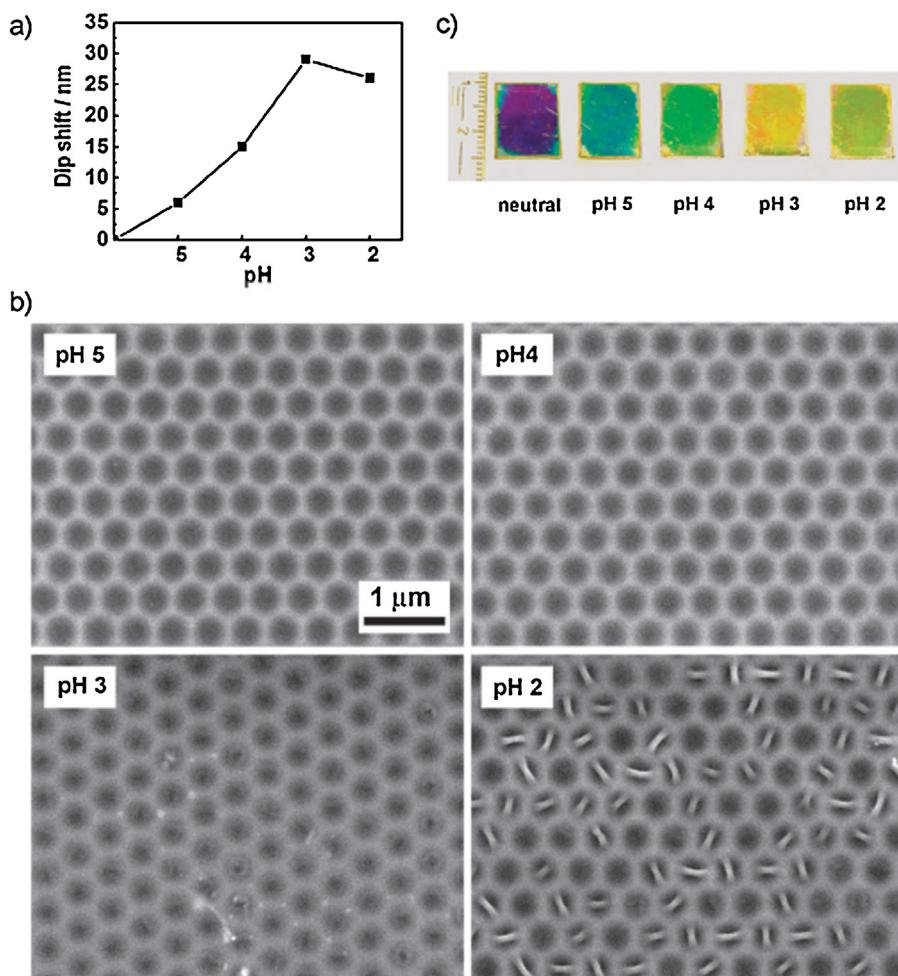


Fig. 6. Transmission dip shift (a), morphological changes (b) and interference colors (c) of 2DPC-PGs in response to different pH conditions. The 2DPC-PGs were prepared with 470 nm opal monolayers and a spin-coating speed of 2000 rpm on glass (a) and silicon wafer (b, c), respectively.

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for the first time that a biomolecule-recognition gating system responding to small signals of biomolecules by the cooperation of biorecognition cross-linking and polymer phase transition in nano-sized pores (Fig. 9). They used pNIPAm as the stimuli-responsive polymer and biotin as a biomolecule-specific receptor for avidin. The pore states can be distinguished by a volume phase change of biotin grafted polymers.

Feng et al. [169] synthesized a new fluorescent polyelectrolyte microgel for detecting DNA and enzymes. The covalent linking of a conjugated polyelectrolyte moiety into the microgel prevents leakage of fluorophore and retains its fluorescent property. The microgel can be used to detect DNA and enzyme in homogeneous solution and in gel phase the microgel is reusable after washing with high ionic strength aqueous solution. Zhao et al. [170] made a novel hydrogel suspension array, which is capable of label-free, multiplex detection of DNA. To accomplish this they designed acrylamide-based hydrogel beads with 5'- and 3'-acryloyl-modified ssDNA as crosslinkers. In the presence of complementary ssDNA, these hydrogel beads swell due to the coiling of the dsDNA. This can be detected as a corresponding blue shift in the Bragg diffraction peak position of the beads that can be used for quantitatively estimating the amount of target DNA. Kivlehan et al. [171] have prepared and fabricated surface-attached PEG-diacylate hydrogel, by a photopolymerization process. Control of gel growth to micrometer size was achieved by controlling the light source. This hydrogel was used as a sensing platform in DNA hybridization assays with

a detection limit of 3.9 nM. They allow for the diffusion of fluorescently labeled target sequences into the hydrogel matrix to hybridize to probe oligos, which are attached to the polymer backbones.

2.1.3. Electric responsive polymer

Polymers that change conformation in response to the application of an electrical stimulus have also been synthesized and used for analytical applications. Ouyang et al. [172] investigated that polyelectrolyte brushes can be grafted on a nanofluidic channel to control flow. Under external electric fields, polyelectrolytes brushes undergo extension/collapse transition, which can be used to regulate the opening and thus the flow rate of the channel. With molecular dynamics simulation, they showed that the polymer brush modified nanochannel can be closed and opened by switching on and off external electric fields (Fig. 10), and the flow rate can also be adjusted. Moreover, as a nanoscale valve the dynamic response time is at the sub-microsecond level.

2.1.4. Pressure responsive polymers

There are various pressure responsive polymers such as N-isopropylacrylamide (NIPAm), polydimethylsiloxane (PDMS), polyethylmethacrylate (PEMA) reported so far which respond to a specific pressure stimulus by changing their conformation. In 2010, Lietor-Santos et al. [173] found that the particle size of pNIPAm decreases with hydrostatic pressure by small angle neutron

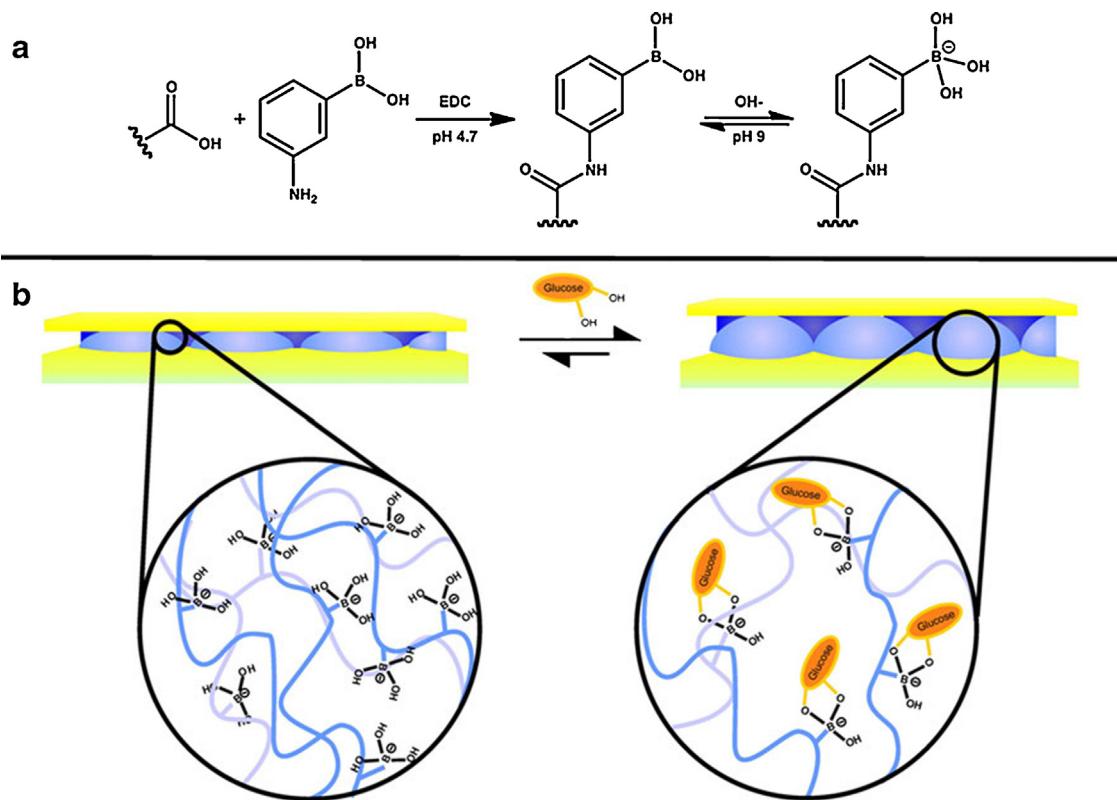


Fig. 7. Reaction scheme for (a) the functionalization of the acrylic acid moieties on the microgel with 3-aminophenylboronic acid (APBA) followed by the activation of the boronic acid with base and (b) a cartoon depiction of the glucose responsivity of an APBA-functionalized microgel etalon at pH 9. Reproduced with permission from reference [123].

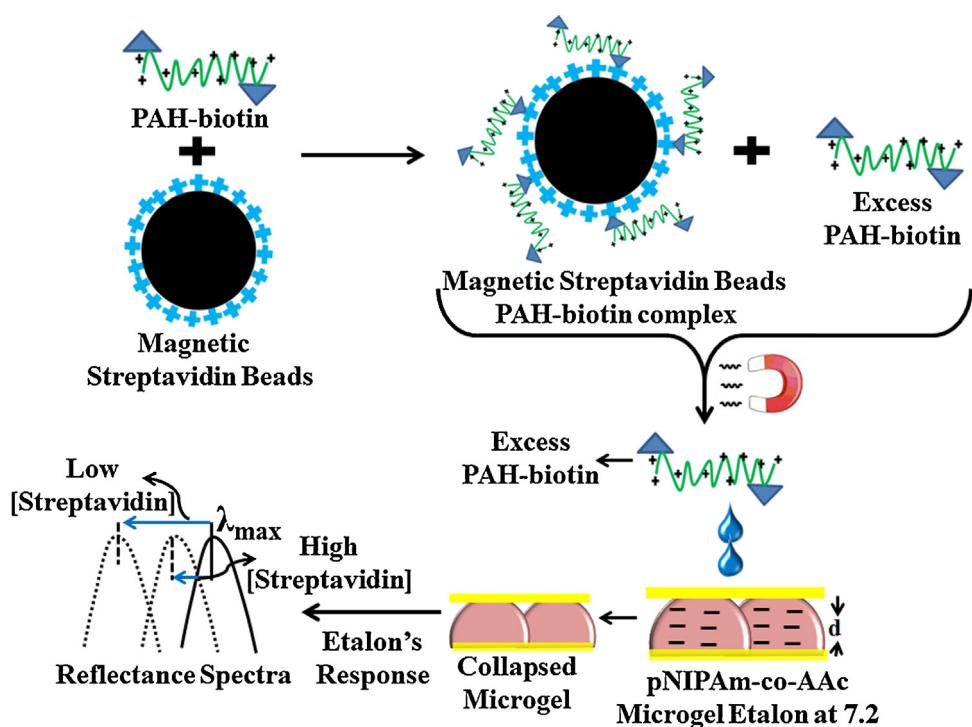


Fig. 8. The proposed mechanism of sensing highlighting the interaction of PAH-biotin with the streptavidin modified magnetic beads and the effect of addition of free PAH-biotin to the pNIPAm-co-AAc microgel-based etalon on its reflectance spectrum. Reproduced with permission from reference [156].

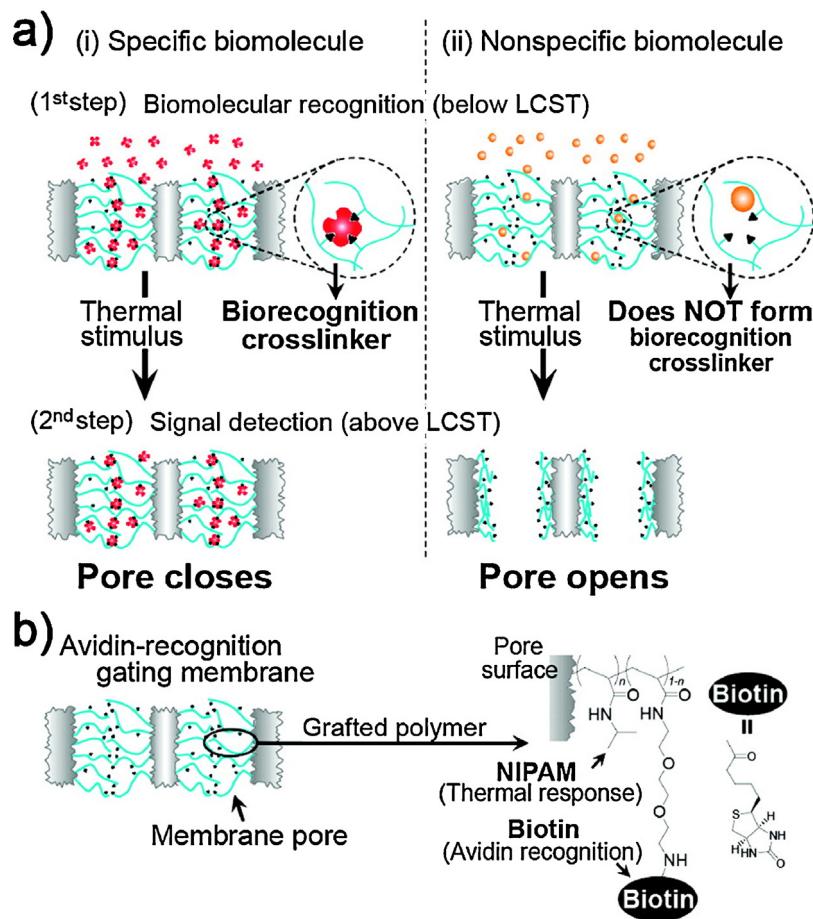


Fig. 9. (a) Schematic describing this study: (i) specific biomolecule and (ii) nonspecific biomolecule. (b) Illustration of an avidin-recognition gating membrane. Reproduced with permission from reference [168].

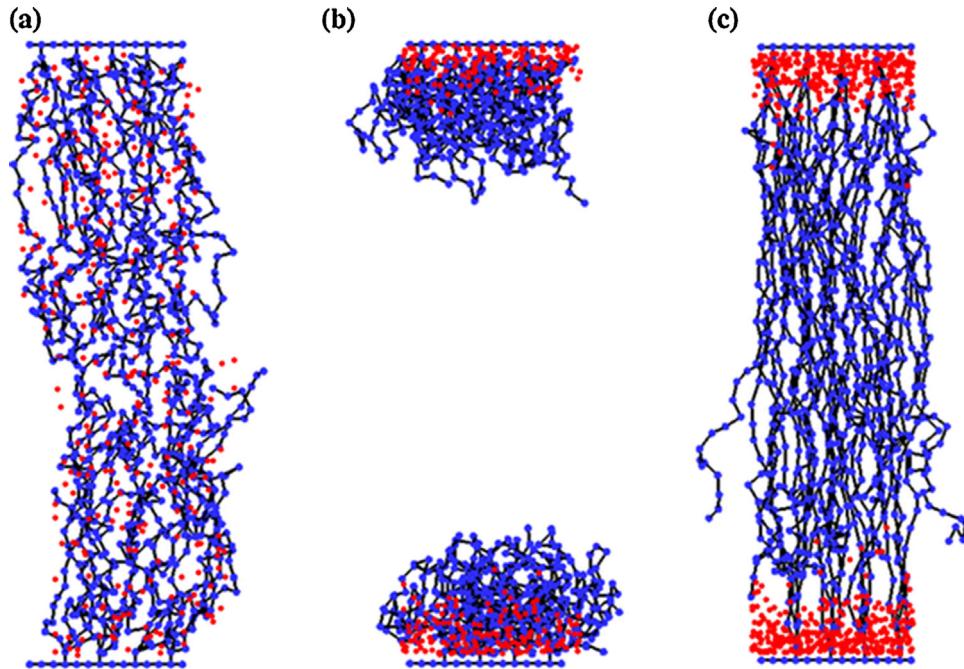


Fig. 10. Snapshots of hydrophilic polyelectrolyte brushes for zero pressure gradient ($F_x = 0$) at a) equilibrium state, $E=0$; b) open state, $E=-3$; c) close state, $E=3$. Here " E " stands for electric field strength. Blue beads on black curves represent polyelectrolyte monomers; blue beads on straight lines represent wall beads; red beads represent counterions. Water beads are not shown for simplicity.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Reproduced with permission from reference [172].

scattering and Puhse et al. [174] confirmed the result by FTIR-spectroscopy. Lietor-Santos et al. [175] published a study about the effect of hydrostatic pressure on the polymer solubility. In 2012, Chen et al. [176] demonstrated Belousov Zhabotinsky (BZ) oscillations in the matrix containing pNIPAm-co-Ru(bpy)₃ gels. Under the influence of a critical pressure, the BZ oscillations are initiated and the whole polymer system is developed into a medium with periodic color changes in the solution. Fan et al. [177] designed a self-powered pressure sensor device based on PDMS gel where a pyramid patterned arrays polydimethylsiloxane film was sandwiched between two ITO-coated PET membranes for measuring the amplitude of the pressure on the device by voltage. Hoe et al. [178] embedded the vertical-cavity surface-emitting laser (VCSEL) into the PDMS gel and then added a reflective phase on the top of gel to measure the pressure by self-mixing interferometry of the emitting light.

A polymer has been prepared by photopolymerization of a mixture of cholesterylacrylate and the eutectic mixture of cholesteryloleylcarbonate, cholesterylchloride and cholesterylnonanate with polyethyleneglycol diacrylate and Genocure LTM (photo initiator) at room temperature by Seebot et al. [179], which exhibits a pressure dependent reversible shift of the selective reflection wavelength over the entire visible range. The change of the selective reflection has its origin in a compressible helix structure. Thus, the pitch length is switched by pressure changes. The pressure controlled color changes can be detectable by the naked eye.

2.1.5. Magnetic responsive polymer

Magnetic responsive polymers have been widely investigated due to the unique properties of the magnetic responsive particles (MRPs). As such, the properties of the magnetic responsive polymers can be triggered by external magnetic field. These MRPs include iron [180–182] (e.g., Fe₂O₃, Fe₃O₄), nickel [183] as well as cobalt [184]. One of the most common approaches of making magnetic responsive polymers is cross-linking monomers in the presence of an aqueous solution of MNPs via a physical encapsulation [181,182,185–187]. The most common monomers are NIPAm and Oleic acid [185–187]. Covalently bound magnetic nanoparticles with polymers have been prepared [184,188–192]. Magnetic responsive gels have found various applications in drug delivery, [185,186] soft actuators, and separations [192]. There have been reports on sensing applications, e.g., detection of DNA [193], bovine serum albumin [194], as well as small molecules [187,195]. There has been some research on cellular tracking by magnetic responsive particle. Lee et al. [196] synthesized microgels doped with MNPs, which served to enhance contrast by magnetic resonance imaging. More importantly, these MNPs did not affect cellular function and phenotype.

2.1.6. Explosives and gas responsive polymer

Detection of explosive chemicals and gases is very important due to the threat to human health and security. It is very important to sense and monitor the presence of minute amounts of explosive chemicals and gases accurately and quickly. Among all of the high energy explosives, trinitrotoluene (TNT) is a widely used explosive that brings devastation to human lives and contaminates soil and water. Even though a large number of reports are available, a simple and quick approach to the detection of explosives at extremely low concentration still remains a challenge. Swager et al. reported conjugated organic polymer-based molecular wires for sensing chemicals. This strategy of molecular wires are capable of enhancing the chemosensory responses over many orders of magnitude and based on that principle a number of advanced sensors have been developed. Based on the chemoresistivity of molecular wires, Nomadics Inc. markets the Fido, which is able to detect very low

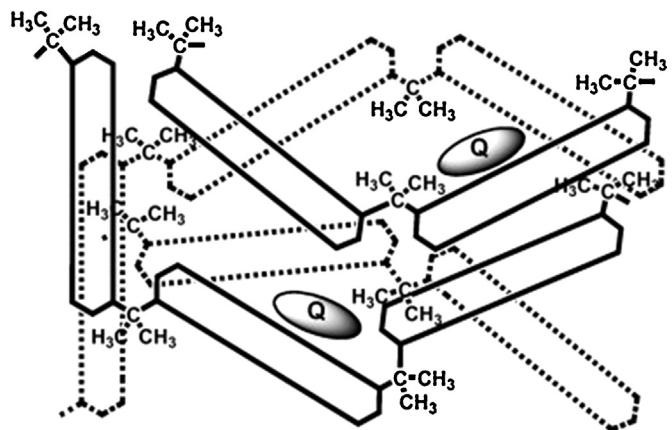


Fig. 11. Schematic illustration of how isopropylene spacers induce porosity in films. Reproduced with permission from reference [204].

levels of explosives [197–201]. The challenge can be overcome by translating molecular events to a detectable signal. Fluorescence-quenching based sensing has gained increasing interest in detection of explosives because of reproducibility, stability, high sensitivity, low cost, ease of use, and quick signal transmission and we will mention some recent works based on fluorescent quenching.

A coil-shaped twisted plastic optical fiber (POF) of different diameters coated with conjugated polymer poly(2-methoxy-(2-ethylhexloxy)-p-phenylene-vinylene) (MEH-PPV) was employed as sensor head to detect nitro aromatic explosives by Chu and Yang [202]. The most sensitive sensor head was the coil with diameter of 4 mm with sensitivity 5 ng mL⁻¹. By incorporating 2,2-isopropylene spacer to introduce a bend in the structure of a conjugated polymer composed of p-quaterphenylene segments tethered by their meta positions along the polymer main, an improved method of the sensing power of fluorescent polymer thin films has been reported [203].

The same group demonstrated that amorphous segmented conjugated polymers bearing relatively compact shape chromophores such as 2,7-diphenylfluorene chromophores tethered by isopropylidene connectors can be used as sensing materials with performances comparable to those presented by conjugated polymers with more elaborate structural design [204]. It has been reported that isopropylene increases the porosity and hence enhances the sensitivity (Fig. 11). Poly[2-methoxy-5-(30,70-dimethyloctyloxy)-1,4-phenylenevinylene] (MDMO-PPV) solution has been reported to show very fast response for detecting nitrated explosives such as 2,4,6-trinitrotoluene (TNT) by changing color from orange to brownish black [205].

In another report, the fluorescence-quenching properties of thin film of poly(phenylene ethynylene) containing the rigid pentptycene and large cholesteryl ester pendent groups in response to vapor of 2,4-dinitrotoluene (DNT) have been investigated by varying the film thickness and by applying an undercoating and blending with another polar polymer [206]. A widely available polymer, polyfluorene has been reported as an excellent sensor for low vapor pressure explosive detection of DNB at 9.8 ppb [207]. Conjugated microporous polymers (CMPs) achieved by condensation of a carbazole derivative has been shown to exhibit enhanced detection sensitivity of arenes upon exposure to their vapors [208]. There are several recent reports where conjugated polymer and silica hybrid materials were used to detect TNT in solution through electron transfer [209–211].

Dudhe et al. [212] reported that a combination of poly(3-hexylthiophene) (P3HT), Cu(II) (tetraphenylporphyrin) and a copolymer of diethynyl-pentptycene and dibenzyl-ProDOT

(substituted decyloxythiophene) is a good sensor for nitro-based explosives. It was found that graphene oxide-methyl cellulose composite is capable of detecting picric acid [213]. An optimized and highly sensitive piezoresistive SU-8 polymer nanocomposite microcantilever sensor has been reported [214] with dispersed carbon black for application in detection of explosives in the vapor phase at ppb levels. A nano-aggregate formed from addition of water into THF solution of a high molecule weight hyperbranched polysilole reported to be used as the fluorescent sensor [215] for nitro-based gas sensors.

Guan et al. [216] reported a facile and general methodology for the synthesis of various molecularly imprinted shells at the surface of polystyrene (PS) colloidal spheres to recognize nitro-based explosive compounds (Fig. 12). Molecularly imprinted microparticles (MIP) prepared using methacrylic acid as the functional monomer to detect high explosive compounds such as TNT has been reported as well [217]. Lee et al. [218] have demonstrated the first example of a selective chemosensor for the detection of chloride by conversion of a coordination gel.

The attachment of the sensing polymers onto a chromatographic support also allows for simultaneous separation of an explosive mixture, and component identification through the use of multiple sensing polymers. In this regard, Martinez et al. [219] reported that the luminescent organosilicon copolymers poly(silafluorenyldiethynylspirobifluorene) and poly(tetrasilolediethynylspirobifluorene) can be covalently linked to a silica gel thin layer chromatography (TLC) support through the use of a trimethoxysilyl end group. Surface functionalization of silica with the fluorescent sensing polymer allows enhanced detection sensitivity. A terthiophene (3T) derivative of 5-(1-pyrenyl)-2,2':5,2"-terthiophene (Py-3T) was chemically immobilized onto a glass wafer surface via a flexible spacer by employing a single-layer chemistry technique, which displays unprecedented photochemical stability at ambient conditions [220]. Fluorescence studies confirmed that the emission of the film as fabricated is significantly and selectively quenched by the presence of nitro aromatic compounds (NACs), both in the vapor phase and in aqueous solution. Thin films of thiophene-based polymers containing 1,2,3-triazole with appropriate alkyl side chains show enhanced fluorescence-quenching in the presence of nitro aromatic vapors [221]. A new nanoscale sensing concept was developed by Tenhaeff et al. [222] which consists of poly(4-vinylpyridine) (P4VP) layers deposited inside microfabricated trenches which on contact with nitro aromatic swell and close the electric circuit making it possible to detect ppb level explosive.

2.2. Chemically responsive polymers

Chemically responsive polymers respond to various stimuli by chemical bond formation or dissociation. Various degradable crosslinkers are used to make the polymeric systems chemically responsive. Winnik and co-workers reported a thermal and/or redox sensitive nanogel prepared via RAFT polymerization of NIPAM mediated by a polysaccharide (pullulan)-based chain transfer agent [223]. In the presence of an oxidant, pNIPAm-graft-polysaccharide with thiol end groups readily formed disulfides, which produced chemically cross-linked nanogels able to withstand changes in temperature (Fig. 13). Zou et al. grafted individual PFS polymer molecules to gold surfaces for force spectroscopy experiments on the single-molecule level [11,224]. Shi et al. have shown in single-molecule force spectroscopy studies that ex situ redox chemistry using FeCl_3 can be used to change the elastic properties of poly(ferrocenyldimethylsilane) (PFS) macromolecules [225]. Recently, significant efforts have been directed at redox-labeled nucleotides, especially ferrocene, towards the development of DNA biosensors, which are able to detect single

nucleotide mismatches under real-to-life conditions ideally without the need for PCR amplification of the analyte [226–228].

Recent interest in developing molecularly imprinted polymers (MIP) as biomimetic materials has been extended to realize a wide variety of applications due to the fact that MIPs can be synthesized to identify specific molecules and molecular events. Molecular imprinting is a process by which a specific functional monomer is allowed to self-assemble around a template molecule and is subsequently polymerized in the presence of a crosslinker. After the extraction of the template molecule, a cavity is left, which is capable of rebinding the template molecule [229]. MIP could selectively perform molecular recognition and hence it can be applied for the determination of several analytes represented by small molecules such as pharmaceuticals, pesticides, amino acids, sugars, and so forth. Herein, the most recent applications of preparing electrodes modified with MIPs are introduced for capacitive biosensing [230], potentiometric sensing [231–233] and other electrochemical sensing approaches [234]. Aghaei et al. [230] developed a capacitive biosensor by electropolymerization of 2-mercaptopbenzimidazole (2-MBI) on a gold electrode in the presence of cholesterol as a template. The sensor's linear response range was between 5 and $30 \mu\text{M}$, with a detection limit of $0.42 \mu\text{M}$. The proposed molecularly imprinted polymer capacitive (MIPC) sensor exhibited good selectivity for cholesterol. Alizadeh et al. [234] prepared an Hg^{2+} imprinted polymer based on cross-linked vinyl pyridine for a novel highly selective and sensitive electrochemical sensor. Compared to previously developed mercury selective sensors, the proposed electrochemical sensor was more selective, regarding the common potential interference. This sensor showed a linear response range of 2.5×10^{-9} to $5.0 \times 10^{-7} \text{ M}$ and lower detection limit of $5.2 \times 10^{-10} \text{ M}$ (SN^{-1}). Moreover, the sensor was successfully applied to the determination of mercury in real samples. Liang et al. [231] described a potentiometric sensor based on a polymeric membrane ion-selective electrode for determination of melamine. The membrane electrode shows near-Nernstian response (54 mV/decade) to the protonated melamine over the concentration range of 5.0×10^{-6} to $1.0 \times 10^{-2} \text{ mol L}^{-1}$. A potentiometric sensor is also fabricated for determination of 2-aminopyridine (2-AP) [232]. The membrane potential increases with 2-AP concentration over a wide range of concentration ($5 \mu\text{M}$ to 100 mM) with a near-Nernstian response of 54.1 mV/decade and detection limit of $2.0 \mu\text{M}$. The utility of the sensor was successfully tested by examining of 2-AP in piroxicam (PX) as a potential impurity.

Electrodes have also been modified with polymers other than MIP for voltammetric and amperometric sensing. Based on polyaniline composite with graphene, a voltammetric sensor of 4-aminophenol (4-AP) has been designed [235]. This sensor 4-AP exhibits enhanced voltammetric response at GR-PANI modified GCE. This electrochemical sensor shows a favorable analytical performance for 4-AP detection with a detection limit of $6.5 \times 10^{-8} \text{ M}$ and high sensitivity of $604.2 \mu\text{A mM}^{-1}$. Moreover, 4-AP and paracetamol can be detected simultaneously without interference of each other in a large dynamic range. A polymer electrogenerated from Fe(III)-5-amino-1,10-phenanthroline solution at a carbon nanotubes paste electrode (CNTPE) is investigated in amperometric response of hydrogen peroxide. The analytical application of the resulting electrode is demonstrated in connection with the design of a glucose biosensor based on the deposition of GO_x and diluted Nafion on the top of the polymer-modified CNTPE. The quantification of glucose in human serum samples showed a good correlation with the values obtained by the spectrophotometric technique.

Conductive electroactive polymers have been blended or cross-linked to form highly hydrated hydrogels, which is named electroconductive hydrogels (ECHs). An electroconductive hydrogel describes a polymer that combines the properties of hydrogels

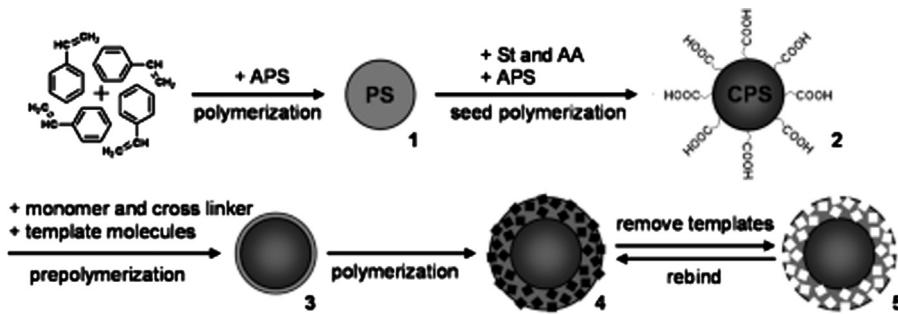


Fig. 12. Preparation of molecularly imprinted core–shell microspheres. PS seeds (1) were first prepared by polymerization of styrene (St), and then transferred to carboxylated PS (CPS) spheres (2) through the copolymerization of St and acrylic acid (AA) on PS seeds. When CPS spheres were suspended in the reaction solution, the imprinting precursors assembled on the surface of PS cores and pre-polymerized to form oligomer coated PS spheres (3). Subsequently, the oligomer layers directed the selective imprinting polymerization, leading to the core–shell microspheres (4). After removal of templates, molecularly imprinted core–shell microspheres (5) were obtained. Reproduced with permission from reference [216].

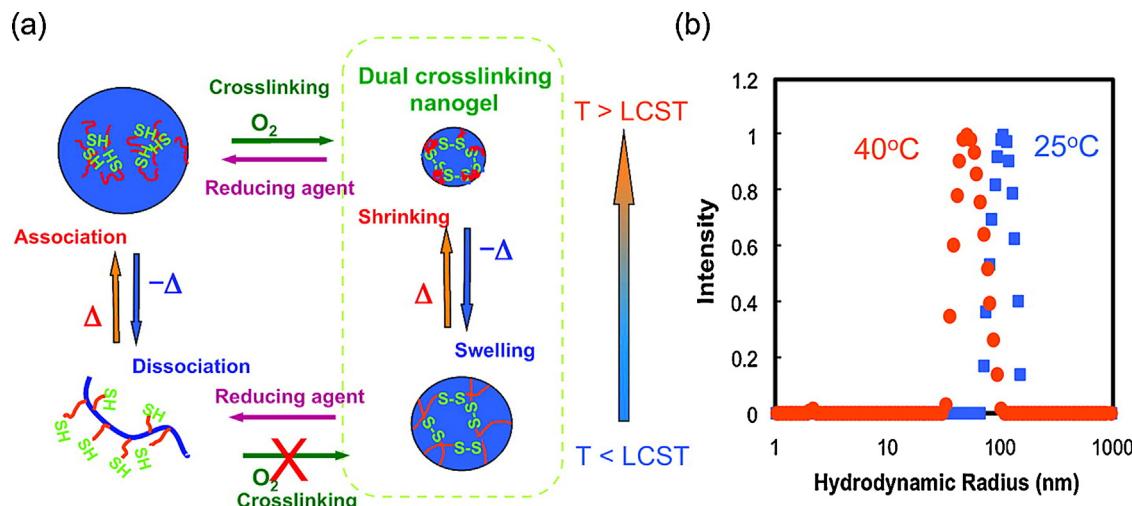


Fig. 13. (a) Schematic representation of temperature and redox responsive SS-N26gPul nanogels constructed by RAFT polymerization of NIPAm onto PulSTS. (b) Hydrodynamic radius of the dual responsive SS-N26gPul nanogels in water below and above LCST.

Reproduced with permission from reference [223].

and conductive systems and appears to have first originated with Gong et al. [236] who described a conductive charge transfer salt complex of 7,7,8,8-tetracyanoquinodimethane (TCNQ)-loaded hydrogel. In analytical fields, electroconductive hydrogels can be applied as a biorecognition membrane layer in a biosensor. Enzymes entrapped within polypyrrole (PPy) films and other electroconductive hydrogels have been commonly used to prepare electrodes. Kotanen et al. [237] reported a glucose responsive biotransducer which was prepared by potentiostatic electropolymerization of pyrrole at Poly(hydroxyethyl methacrylate)-based hydrogel-coated Pt micro-electrodes from aqueous solutions. A glucose bioelectrode [238] was coated with carboxylated carbon nanotubes, a biocatalytic hydrogel composed of a conductive redox polymer, glucose oxidase, and a crosslinker. The current density on oxidation of glucose is 16.6 mA cm^{-2} at 0.5 V (vs. Ag/AgCl) in oxygen-free glucose solution. Moreover, Guisseppi-Elie [239] developed a temporary, implantable, integrated glucose and lactate biosensor and communications biochip. The dual responsive, amperometric biotransducer was fabricated on a microdisc electrode array format upon which were separately immobilized glucose oxidase and lactate oxidase within biorecognition layers of 3 mol% tetraethyleneglycol diacrylate cross-linked p(HEMA-co-PEGMA-co-HMMA-co-SPA)-p(Py-co-PyBA) electroconductive hydrogels. The device was then coated with a bioactive hydrogel layer containing phosphoryl

choline and polyethylene glycol pendant moieties [p(HEMA-co-PEGMA-co-HMMA-co-MPC)] for indwelling biocompatibility. The glucose and lactate biotransducers exhibited linear dynamic ranges of 0.10–13.0 mM glucose and 1.0–7.0 mM and response times of 50 and 35–40 s, respectively. Operational stability gave 80% of the initial biosensor response after 5 days of continuous operation at 37 °C. The author reported that in vivo studies in a Sprague–Dawley hemorrhage model showed tissue lactate levels rise more rapidly than systematic lactate. The study shows the potential of an implantable biochip that supports telemetric reporting of intramuscular lactate and glucose levels allows the refinement of resuscitation approaches for civilian and combat trauma victims.

3. Conclusion

Researchers around the globe are constantly pursuing highly efficient responsive polymer-based materials and systems to translate the application of a stimulus (e.g., an analyte) into a response. A majority of the reports published to date describe temperature, pH, and ionic strength responsivity, although emerging systems are able to respond to mechanical forces, electrical and magnetic field, light, redox potential, and molecules/biomolecules etc. Along these lines, responsive polymers and systems have been developed that are capable of responding to the application of multiple stimuli. In this review, we pointed out representative examples of each, and

more. We would like to point out that while responsive polymers show great promise in the field of analytical chemistry, they have found many applications associated with health, energy and the environment. With so much chemical versatility, and a wide reaching array of applications, the future is bright for stimuli-responsive polymers.

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