Stimuli-Responsive Polymers: Fundamental Considerations and Applications

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Abstract: Stimuli-responsive polymers are capable of changing their chemical and/or physical properties in response to environmental stimuli. This unique feature has allowed stimuli-responsive polymers to be used in a variety of applications. In this review, we present a basic introduction to the theories that have been developed to describe polymer chains, brushes, and networks. We then detail numerous examples of how stimuli-responsive polymers can be used for sensing and biosensing, drug delivery, and as artificial muscles. While we focus the review on these particular areas, there are numerous other demonstrations of the applications of these fascinating materials, and we are certain that many applications have yet to be discovered.

Keywords: stimuli-responsive polymer, sensing and biosensing, drug delivery, artificial muscles and actuators

1. Introduction

1.1. Polymer history

Polymers are large molecules, or macromolecules, composed of many repeating subunits (monomers), and can either be natural (e.g., cellulose, rubber, silk) or synthetic (e.g., polystyrene, polyethylene and polypropylene). Their large molecular mass yields physical properties that are significantly different than small molecules. Furthermore, the properties of polymers and polymer-based materials (e.g., toughness, elasticity, viscosity) can be tuned to fit a particular application. While much is now known about polymers, the modern concept of polymers was met with much controversy. In 1920, Hermann Staudinger introduced the first description a polymer as a covalently bonded macromolecular structure,[1,2] and spent the next decade producing experimental evidence for this hypothesis.[1-3] In 1935, Wallace Carothers developed the first commercially successful synthetic thermoplastic polymer, Nylon. Whereas Staudinger focused his investigations on the analysis of natural polymers, Carothers synthesized polymers by reacting small organic molecules using well-known reactions. The research accomplishments of Staudinger and Carothers, along with those of their colleagues, during the 1920s and 1930s laid the foundation of modern polymer science and today's plastics, synthetic fiber, and rubber industries. Staudinger received the Nobel Prize in 1953 for his ground breaking work in this area, and many others have gone on to receive Nobel Prizes for their work with both natural and synthetic polymers.

The fact that polymers have a high molecular weight, and tunable chemistry accessible by using a variety of functional monomers, makes them distinct from other forms of matter.[4-6] In recent years, as a result of a better understanding of polymer structure–property relationships, introduction of new polymerization techniques, and availability of new and low-cost monomers, the concept of truly tailor-made polymers and materials is (and is becoming) a reality. Furthermore, polymers that exhibit "intelligence" by responding in defined ways to their environment can also be generated, as detailed in the next section.

1.2. Stimuli-responsive polymers

Although the technological and scientific importance of polymers with various functionalities has been well established over the last few decades, increasing attention has been focused on stimuli-responsive (or smart/intelligent) polymers.[7-9] Stimuli-responsive polymers have gained significant attention for myriad applications due to their ability to respond to internal and/or external chemical/physical stimuli that is often manifested by their large macroscopic response.[10,11,12] Many have turned to nature to gain inspiration for the design and development of stimuli-responsive polymers. For example, the human body is able to change its chemistry at both the molecular (e.g., insulin release and cell signalling/endocytosis)[15,16] and macroscopic level in response to changes in the environment. These examples have inspired scientists to generate ‘smart’ materials that respond a variety of stimuli, e.g., pH,[13] temperature,[14] mechanical stress,[15] the presence of various small molecules and biomolecules,[16] and electric/magnetic fields.[17-19] Due to the breadth of the responsivities that can be built into stimuli-responsive polymers and materials, they have found applications as sensors and biosensors,[20] for controlled and triggered drug delivery,[21] for environmental remediation,[22] and as chemomechanical actuators.[23-25]

Stimuli-responsive polymers can be synthesized by incorporating functional monomers into the polymer or copolymer backbone that yield the polymer response.[7] In many cases the polymer responsivity is dictated by the chemistry of the monomers, and their distribution/concentration in the polymer chain. Therefore, it is very important to prepare polymers with well-defined chemistry and architecture. To accomplish this, a variety of polymerization approaches have been developed, e.g., living anionic[26,27] and cationic polymerization,[28,29] controlled radical polymerizations[30-32] such as nitroxide mediated radical polymerization,[33,34] atom transfer radical polymerization,[35-37] and reversible addition fragmentation chain transfer polymerization.[38-40] While polymers that respond to many different stimuli have been generated,[41] temperature responsive (thermoresponsive) polymers have garnered the most attention. For example, some polymers exhibit a lower critical solution temperature (LCST),[42] which is the lowest temperature at which thermally induced demixing occurs. That is, below the LCST the polymer chains and solvent molecules are in one homogenous mixed phase, Above the LCST, a phase separation occurs via an entropically driven process. Poly (*N*-isopropylacrylamide) (pNIPAm)[14,43-45] is the most extensively studied polymer with an LCST; pNIPAm's LCST is at 32 ^{o}C. At this temperature, the pNIPAm chains transition from a random coil to a globular conformation. For individual polymer chains, the coil to globule transitions can be thermodynamically controlled by adjusting polymer composition,[46] e.g., the LCST shifts to higher or lower temperature by copolymerization with hydrophilic or hydrophobic monomer, respectively.[47,48] There are many different polymers with LCSTs, such as poly(*N*, N-dimethylaminoethyl methacrylate) (PDMAEMA),[49-51] poly(2-(*N*-morpholine)ethyl methacrylate) (PMEMA),[52] poly(*N, N*-diethylaminoethyl methacrylate) (PDEAEMA),[52] poly[*N*-[2-(diethylamino)ethyl acrylamide] (PDEAEAM),[53] poly(*N, N*-diethylacrylamide) (PDEAAM),[54,55] and poly[oligo(ethylene glycol) methacrylate].[56,57] Additionally, by incorporating different functional groups into temperature responsive polymers, systems with multiple responses could be achieved. For example, pH responsive compounds that have ionizable functional groups capable of donating or accepting protons upon environmental pH changes could be used. Some common examples are, acrylic acid (AAc)[13,58-60] and *N, N*-dimethylaminoethyl methacrylate (DMAEMA).[61-63] Light responsive monomers can also be used to generate materials that exhibit both a temperature and light response; a common example is azobenzene.[64-66] Biologically responsive systems, like glucose responsive polymers[67,68] and enzyme responsive polymers,[69-71] can also be generated, which have the ability to respond to stimuli that are inherently present in biological systems.[72] In all of these cases, considerable effort was put into the design of the smart materials and architectures, which relies on a firm understanding of fundamental polymer theories and behavior. Below, some of the fundamental aspects of single polymer chains, brushes, and networks are introduced, followed by a presentation of their recent applications

2. Fundamental Aspects

2.1. Single polymer chain

Traditional polymers are macromolecules consisting of multiple repeating units (monomer) held together by covalent bonds.[73] In the early-to-mid 20th century, Debye, Kuhn, Kramers, and Flory[74] laid the foundation for understanding polymer properties and behavior. Starting from the smallest unit of a polymer (monomer), one is able to calculate the statistical length of a polymer chain by ignoring the long-range interactions between monomers that are far away from each other on individual chain. In subsequent experiments, it was shown that the size of a polymer could be more accurately defined by developing techniques to account for the long-range monomer interactions.[75,76] To allow an even more accurate description of the polymer chains, individual monomers could be thought of as being grouped together as unit, which can be considered a "blob". In each blob, the structure of the polymer chain is considered to be unaffected by the environment. One of the most common theories used to predict the chain conformation in good solvent is Flory theory,[77] which makes rough estimations of both the energetic and entropic contribution to the free energy. The predictions are in good agreement with both experiments and other more sophisticated theories.[73] Although, there are limitations of Flory theory it is still useful as it is simple and provides reasonable information. In addition, it reveals the universal power law dependence of polymer size R on the number of monomer unit *N*: $R \sim N^{\upsilon}$. The quality of the solvent is accounted for by the exponent υ (υ = 1/2 for Θ-solvent, and υ = 3/5 for athermal/good solvent and υ = 1/3 for poor/non solvent). More recently, computer simulations have attracted the attention of researchers due to their ability to bridge theory and experiment, with molecular dynamics[78] and Monte Carlo[79] simulations being the most commonly employed.

The behavior of stimuli-responsive polymers in solution is not easily predicted by scaling laws that are used for non-responsive polymers due to the additional specific monomer/monomer and monomer/solvent interactions. By selectively choosing a monomer, responsivity can be engineered into a polymer chain. For example, the electromagnetic field (light)-induced *cis-trans* isomerization of azobenzene can be used to affect the conformation of polymer chains.[79] As mentioned above, *N*-isopropylacrylamide (NIPAm) can be used to generate thermoresponsive polymers. PNIPAm is one of most extensively studied responsive polymers, which has an LCST ~32 ^{o}C. As the temperature increases, the entropy change (mainly a result of water association with the polymer) overcomes the dissolution enthalpy of pNIPAm, which resulted in a positive free energy changes unfavorable for the dissolution.

Heskins and Guillet,[14] Kremer,[80,81] Wu,[82-84] Tanaka,[44,85] Kubota,[86] have spent many years understanding the fundamental behavior of pNIPAm chains in solution. We will not include the details of each here since there have been many reviews already published on this topic. [45,87]

Experimentally, several techniques are available to study the behavior of single polymer chains in solution. Atomic force microscopy (AFM) is a common technique that is used to study individual single polymer chains. Hashimoto's group first reported the observation of a two-dimensional random coil conformation of a polymer chain by using the Langmuir-Blodgett technique to cast polymer solutions onto a substrate.[88, 89] In addition, AFM can also be used characterize the elasticity of polymer chains.[90] However, the isolated chains that AFM probes are normally in a quasi-two dimensional or diluted state. Therefore, it cannot be compared with various macroscopic phenomena in real systems, which consist of a number of polymer chains entangled with each other in a three-dimensional bulk state. Fluorescence imaging is a technique that can be used investigating the behavior of single fluorophore-labelled polymer chains in a bulk medium without the modification of its chemical and physical properties.[91, 92] Light scattering is another powerful technique that can provide detailed information on polymer conformations in solution. Light scattering, like X-ray scattering and neutron scattering,[93,94] is a result of the difference of contrast between polymer chains and the surrounding solvent. In polymer science, the most common application of light scattering is to measure polymer molecular weight and polydispersity. However, light scattering can provide information about polymer chains that is not available using other methods, e.g., the mean square radius, conformation (random coil v. globule)[82,87,95] and diffusion coefficients.[96,97]

2.2. Polymer brush

Polymer brushes (PB) are collective assemblies of macromolecules that have one end tethered or grafted onto a surface.[98] The conformation of the polymer chain on a surface depends on the polymer composition, chain length (molecular weight), as well as the grafting density on the substrate. Due to the irreversible attachment to a surface, polymer brushes endure entropy loss relative to polymers in solution, and therefore exhibit very distinct behavior. As illustrated in Fig. 1, there are three common conformational regimes for polymer chains tethered to surfaces, which depend on the solvent quality, affinity of the chain monomer to the substrate, as well as the proximity to other polymers attached to the surface (crowding). When the distance between two neighboring grafting sites is larger than the chain size, the polymer chain will adopt a "pancake" conformation (as shown in Fig. 1b) if the monomer has strong affinity to the substrate. Otherwise, it will form a "mushroom" conformation (as shown in Fig. 1a) if the interaction between polymer chain and substrate is weak. In the high grafting density case, where the polymer chains are crowded on the surface, they can interact with one another, resulting in individual chains stretching away from substrate and leading to the "brush" regime as shown in Fig. 1c. The behavior of polymer brushes is dictated by the combination of excluded volume interaction (entropic repulsion), free energy of the polymer chain, conformational entropy loss as a result of chain stretching, frozen constraints of irreversible grafting and the geometry of the substrate.[9]

The theoretical modeling of polymer brush behavior was pioneered by Alexander de Gennes, and Milner.[99-103] One of the molecular modeling theories used to predict polymer brush behavior is scaling law, which considers a section of stretched polymer as a tension blob (as shown in Fig. 2). The number of monomers and size of the section is carefully chosen such that the tension blobs exhibit a random walk, and that most of the conformation entropy of the chain is dictated by local conformation freedom of tension blobs. When the distance $\xi \sim \sigma^{-1/2}$ (σ is the grafting density) between neighboring tension blobs is smaller than the chain radius $R \sim aN^{\nu}$ (a: Kuhn length, N: number of monomer, ν: exponent unique for each system) the polymer chains starts to interact with each other and the grafted polymer chain will exist in a brush-like configuration. When σ is small, the chains are effectively isolated and act independently of one another, there is no additional osmotic pressure causing the chains to stretch away from the surface, and the chains form isolated islands or mushrooms. For forming a brush, the critical value for grafting density σ^* is $a^{-2}N^{-2\nu}$. For an ideal chain with no interactions between monomers, $\nu = 1/2$; for a real chain in good solvent, which monomer-solvent interactions are dominant, $\nu = 3/5$. As the monomer distribution in the scaling law is dimensionless, it cannot quantify the monomer density along the polymer chain in the brush configuration. To deal with this issue, Skvortsov et al.,[104] Zhulina et al. [105] used density functional theory to probe the internal structure of the PB layer, although a more detailed mathematical description will not be discussed here. In addition, self-consistent field theory and mean-field theory were also used to model and predict the behavior of polymer brushes. The basic idea of these theories is to examine each molecular species with as much molecular detail as possible while treating intermolecular interactions with a mean-field approximation. All of these approaches have shown good predictive power, however, there are still some limitations such as lack of intermolecular correction and the assumption of system homogeneity. From a practical perspective, the kinetics of polymer chain conformation changes under external stimuli is more relevant as it sheds light on the designing principles for rapidly responding systems.

Polymer chains are able to adjust their conformation accordingly to their surroundings, which allow them to collectively respond; this is much different than a single chain on a surface. For example, by altering the solvent quality from good to poor, the interaction between polymer chains and the surroundings switches from attractive to repulsive, and eventually results in conformation change from swollen to collapse. Such unique properties make responsive

polymer brush coatings great candidates for various applications, such as modulating cell growth and release,[106] protein capture,[107] surface wetting and dewetting,[108] and coatings in micro-valve for specific ions transportation.[109]

As polymer brushes are polymer chains tethered/grafted onto surfaces, their behavior can be studied experimentally by techniques that can probe interfaces, such as surface plasmon resonance spectroscopy (SPR),[110] reflectance spectroscopy,[111] AFM,[112] and surface force apparatus.[113] Balamurugan et al.[110] found that thermally responsive pNIPAm brushes in water exhibit a density vertical phase separation. That is, near the surface the dense brush undergoes dehydration and collapse over a broad range of temperatures, while the polymer segments in the outermost area remain highly solvated even above the LCST of ~32 ^{o}C. The Leckband Group[114] also studied pNIPAm brush topography dependence on grafting conditions and temperature by AFM (as shown in Fig. 3). They found that the pNIPAm brushes exhibit complex collapse behavior in a poor solvent, which have micelle transition state from mushroom to pancake regime. The collapse of pNIPAm chains above the LCST depends on the grating density as well as the molecular weight.

2.3. Polymer networks

Gelation is the crosslinking of polymer chains, physically or chemically. When this occurs, polymer chains linked together lead to progressively larger branched polymers. As the crosslinking process continues, still larger branched polymers are obtained. Such a large molecule in the system will not dissolve in a solvent but may swell in it. This "infinite polymer" is called a gel. The transition from a system with dispersed branched polymers to a system containing also an infinite molecule is called the sol-gel transition[115] The sol becomes a gel when the system can support an elastic stress, which is defined as the gel point. Early studies of the sol-gel transition dates back to the dawn of polymer science. The first quantitative theories of gelation were mean-field theories, which were formulated in the 1940 by Flory and Stochmayer.[77] Critical percolation theory was successfully applied to gelation in the 1970s.[116,117] A number of growth models (diffusion limited aggregation, cluster-cluster aggregation, kinetic gelation) have been developed in the 1980s to describe the kinetic aspects of aggregation and gelation.[118,119] When the polymer crosslinking reactions are driven far beyond the gel point, nearly all species are attached to the gel network system. Experimentally, the measurement of gelation is difficult to precisely define, although Sacks and Sheu[120] developed an approach that can fairly accurately measure gelation, which measures the viscoelastic responses of the formed gel as a function of shear rate.

Gelation can occur either by physical or chemical crosslinking. Examples of strong physical bonds are glassy and microcrystalline phases, or double and triple helixes. Thermoplastic elastomers are examples of strong physical gels.[121,122] Weak physical gels have reversible links between polymer chains. These associations have finite lifetimes, breaking and reforming continuously. Examples of weak physical bonds are hydrogen bonds, ionic associations, and block copolymer micelles above their glass transition.[122] In contrast, chemical gelation involves formation of covalent bonds throughout the network and always results in a strong gel. There are three main chemical gelation processes: condensation,[123] vulcanization,[124] and addition polymerization.[125]

Another interesting property of polymer networks is their ability to change volume manifold when exposed to certain solvents. For example, a hydrogel is a type of polymer network that swells upon exposure to water. The ratio of the swollen volume to the dry volume of the polymer matrix is often referred to as the "degree of swelling," and is a common parameter for describing many hydrogels.[126,127] In the late 1970s, Tanaka and co-workers reported swelling/collapse phenomena in polyacrylamide gels reminiscent of vapour/liquid phase transition.[128] Later, the Tanaka group showed that thermoresponsive ionic gels exhibit a discontinuous transition compared to a continuous transition exhibited by non-ionic gels. They also reported that the deswelling rate of the ionic gels is inversely proportional to the square of the smallest dimension of the material.[129] The equilibrium swelling theory of neutral, isotropic polymer networks in the presence of small molecules was first described by Flory and Rehner.[130] When an unconstrained macroscopic network polymer is swollen in a solvent, it undergoes uniform swelling by the same amount in all directions. At swelling equilibrium, the elasticity of the polymer network is balanced by the osmotic pressure of a semidilute solution of uncrosslinked polymer chains. Since the modulus is proportional to the elastic free energy per unit volume, any gel swells until the modulus and osmotic pressure are balanced.

3. Applications of stimuli-responsive polymers

Stimuli-responsive polymers are playing an increasingly important part in a diverse range of applications, such as sensing and biosensing, controlled drug delivery, and actuation (among many other areas). In this section, we will review recent advances in the development of stimuli-responsive polymeric materials in these specific areas.

3.1. Sensing and biosensing

The fact that stimuli-responsive polymers are able to convert environmental stimuli to an observable chemical or physical change has made them attractive for use as sensing motifs. A comprehensive review on responsive polymers for sensing application is given elsewhere[131] and here we limit our discussion on novel applications in the area of sensing and biosensing over the most recent 5 years.

Stimuli-responsive polymers can be used as building blocks for generating photonic crystals (PCs), and have been

used extensively for sensing and biosensing. [132] Recently, label free systems have been employed for the detection of pathogens. More specifically, recognition between host-cell surface carbohydrates and microbial surface proteins has been the topic of immense research. An alternative approach that reverses this process would be more general and specific. As a proof-of-concept for exploiting recognition between a carbohydrate binding protein (lectins) and microbial cell surface carbohydrates, Asher and coworkers generated a 2D photonic crystal (PC) for detecting microorganisms in aqueous environments.[133,134] They developed a 2D PC- Concanavalin A (Con A) pathogen sensing material for the detection of *C. albicans*, a fungal pathogen. The detection mechanism is based on a cell-surface mannan binding to hydrogel-Con A sites. This results in crosslinking and an eventual shrinking of the Con A hydrogel volume, leading to a decrease in the 2D array particle spacing (Fig. 4). The result is a visible color change.

The Serpe group has fabricated etalons (1D photonic materials) that respond to a variety of stimuli, such as pH,[135] light,[136] electric field,[137] temperature,[59] nerve agents,[138] and various biomolecules.[139] Etalons are constructed by depositing a thin layer of Au (typically 15 nm) on top of a glass substrate followed by the deposition of a subsequent layer of Au on top of a deposited microgel layer. This structure allows light to enter the dielectric cavity and resonate between the two reflective Au layers. This resonating light yields constructive and destructive interference, allowing certain wavelengths of light to be reflected. The wavelength of reflected light can be predicted using equation (1):

$$\lambda m = 2nd\cos\theta \quad (1)$$

where the specific wavelength maximum of the reflected peak (λ) depends on the peak order (m), refractive index of the dielectric (n) and the spacing between the mirrors (d), as well as the angle of incidence (θ). For etalons, the Au and pNIPAm-based microgels serve as the mirrors and the dielectric layer, respectively. The ability of the recognition element to penetrate through the porous gold layer and interact with the dielectric medium (microgel) has been exploited for sensing glucose,[140] proteins,[139] and DNA.[141] By taking advantage of the electrostatic interaction between negatively charged microgels (pNIPAm-*co*-AAc) and positively charged biotin modified poly (allylamine hydrochloride) (PAH), a sensor for streptavidin was developed, as can be seen schematically in Fig. 5. [139] Using a similar approach, etalons composed of positively charged microgels were fabricated and used to sense the presence of target DNA.[141]

Recently, Kim and co-workers[142] reported a pH sensor that can respond to a wide range of pH changes from 1 to 7. This sensor system was fabricated by grafting responsive polymers, e.g., poly(acrylic acid) (PAA) (pKa=4.5) and poly(2-vinylpyridine) (P2VP) (pKa=3.0), on quantum dots (QDs). The modified QDs, which exhibited blue and orange emission, were subsequently deposited on a single graphene oxide (GO) sheet (MQD-GO). The responsive polymer was capable of tuning the efficiency of Forster resonance energy transfer (FRET) from the QDs to the GO that modulated the photoluminescence emission from the QDs. The sensing motif is shown schematically in Fig. 6. At the low pH of 1, the color of the solution was dominated by orange emission at 580 nm. In contrast, the color of the MQD-GO solution at pH 7 was blue because of the dominant emission at 440 nm. The nearly equal emission from both the QDs at pH 4 were responsible for a near white light emitting solution. These results can be explained well by the pH-dependent conformation changes of PAA and P2VP polymers that determine the distance between the QDs and the GO surface. Specifically, the pKa of P2VP is ~3, and is therefore protonated and swollen with water at pH < 3. Similarly, the pKa of PAA is ~4.5, and are deprotonated and swollen with water at pH > 4.5. Therefore, when the solution pH is greater than 4.5, the PAA chains are extended and the emission from their associated QDs can be seen, while the emission from the QDs modified with P2VP is quenched due to their proximity to the GO. In contrast, when the pH is below 3, the PAA chains are collapsed and the emission from their associated QDs is quenched, while the emission from the P2VP-modified QDs can be observed. When the pH was between these two pKa values, both emissions can be observed, leading to the "white" light emission.

In another example that uses light emission, Qi and coworkers[143] developed a fluorescent polymer ratiometric nanothermometer that combines gold nanoclusters and thermoresponsive polymer units. In this sensing device, transferrin protein modified Au nanoclusters were used for targeting the cancer cell, while a fluorophore-labeled thermosensitive polymer was used for ratiometric temperature sensing. These so-called nanothermometers were taken into HeLa cells and the ratiometric temperature sensor could provide information on intracellular temperature, which can lead to a better understanding of the relationship between intracellular temperature and ion channel function.

While stimuli-responsive polymers have great potential be applied for sensing and biosensing, there are still many challenges that lie ahead. For example, there is always room to improve sensor sensitivity, selectivity, stability, and to design simpler ways to analyze samples, and to design improved signal readout mechanisms. However, we believe that the benefits of stimuli-responsive-based sensors (i.e., their ease of fabrication, and versatility) far outweigh the negatives, and one will find these sensors being employed in evermore diverse environments.

3.2. Controlled drug delivery

Living systems respond to external stimuli by adapting themselves to changing conditions. Polymer scientists have been trying to mimic this behavior by creating so called smart polymers.[144,145] Smart polymers are very promising for biomedical applications, and have found use as controlled/triggered/targeted drug delivery vehicles, tissue engineering scaffolds, cell culture supports, bioseparation devices, sensors, and actuators/artificial muscles. The concept of stimuli-

responsive polymer-based drug delivery systems was first reported in the late 1970s with the use of thermosensitive liposomes for the local release of drugs via hyperthermia.[146] Subsequently, a great deal of research has been carried out on stimuli-responsive materials for drug delivery, especially concerning the design and application of responsive polymers.[9,16,147-149] The design of new systems and approaches must meet the challenges associated with administration in the body. The systems must be: (i) simply administered, (ii) capable of delivery to the desired locations in response to a stimulus, (iii) composed of non-toxic, biocompatible and biodegradable components. A variety of stimuli-responsive polymer-based materials have been used for this application, including crosslinked gel networks, and non-crosslinked block copolymer assemblies. These, as well as other systems, are shown schematically in Fig. 7. In this section, we will discuss recent progress using these and related materials for controlled/triggered/targeted drug delivery.

One of the most important classes of stimuli-responsive polymers used for controlled drug delivery is crosslinked polymer networks, e.g., hydrogels and microgels. Hydrogels have been shown to be useful for a wide range of biomedical applications because of their porous structure and water swellability. Their porosity permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. In addition, many hydrogels can change their degree of swellability in response to changes in their environment as mentioned earlier. In recent years, researchers investigated microneedle array systems for enhanced transdermal and intradermal delivery of vaccines and pharmaceutical agents.[150-152] Hydrogel-forming microneedle arrays can rapidly imbibe skin interstitial fluid to form discrete in situ hydrogel bulbs to control drug administration at a rate faster than traditional patch systems used for controlled drug release. The most important feature for hydrogel-forming microneedle arrays is the swelling induced release mechanism.[153] By incorporating stimuli-responsive units into microneedles, one is also able to trigger drug release on-demand by applying external stimuli, e.g., electricity.[154,155] Recently, the McCoy group combined the hydrogel-forming microneedles and light responsive drug conjugates to generate a novel devices for on-demand transdermal drug delivery (shown in Fig. 8).[156] For this device, poly (2-hydroxyethyl methacrylate) (HEMA) was used and crosslinked by ethylene glycol dimethacrylate (EGDMA). Microneedles were generated utilizing micromolding, and exhibited desirable mechanical properties. The devices were shown to release ibuprofen over a prolonged period of time (up to 160 h) in response to light. The release could also be turned on and off by turning the light on and off, respectively.

Similar to bulk gels, microgels can also be made biocompatible, however, due to their small size, they exhibit many advantages over bulk gels when used as biomaterials. One major advantage is that the rate of microgel response to external stimuli is much faster than bulk gels.[148,157] They can also be modified chemically such that they circulation in the blood stream for long periods of time, and biodegrade for sustained release. The degradability also allows the microgels to be quickly cleared from the body. In addition, microgels can be used as building blocks for the fabrication of biomedical devices with improved and/or new functionalities. These many advantages make microgels ideal candidates for building controlled drug delivery systems.[148,149,157-160] As a drug carrier, pNIPAm-based microgels combine the advantages of both hydrogels and nanoparticles. PNIPAm microgel particles have a sponge-like structure with interstitial spaces filled with water. Drug molecules can be loaded by equilibrium partitioning between the solution and microgel phases. Electrostatic interaction, hydrophobic interaction, and/or hydrogen-bonding may play an important role for drug loading. The Serpe group developed a novel microgel-based assembly (reservoir device) as a new platform for drug delivery.[161-165] The structure of this device and the release mechanism is shown in Fig. 9. The device is usually composed of a pNIPAm-**co**-AAc microgel layer sandwiched between two thin Au layers (all on a glass support) and was used as a novel platform for controlled and triggered small molecule delivery. Tris (4-(dimethylamino)phenyl)methylium chloride (crystal violet, CV), which is positively charged, was loaded into the microgel layer of the device and released in a pH dependent fashion, at a rate that could be controlled by the thickness of the Au layer coating the microgel.[161] The model drug could be released in an "on-off" fashion, by systematically varying the solution pH. Furthermore, by modifying the top layer Au surface, we can control the drug release with a lower thickness of Au.[162] By combing two oppositely charged microgel, we can control the microgels' aggregation behavior to control the drug release. In this case, the microgels copolymerized with acrylic acid exhibit a negative charge above pH 4.25, while the microgels copolymerized with *N*-[3- (dimethylamino)propyl]methacrylamide exhibit a positive charge below pH 8.4; these microgels are neutral outside of these pH ranges. We show that aggregates form when the two independent sets of microgels were exposed to one another in a solution that renders them both charged. In solutions of pH outside of this range, the microgels disaggregate because one of the microgels becomes neutralized. This behavior was exploited to load (aggregation) and release (disaggregation) a small-molecule model drug.[164] This aggregate based system provides evidence how the charged pNIPAm-based microgels applied in controlled/triggered drug release.

Recently, we showed that the microgel-based reservoirs devices could be used for sequential and controlled release of more than one small molecule.[170] By incorporating the mixed microgels into reservoir devices, and varying their ratio, the small molecule release rate and release amount (dosage) can be easily tuned. Furthermore, two different small molecules can be loaded into the two distinct microgels, which allows for their sequential release at particular pHs

(shown in Fig. 10). PNIPAm-*co*-AAc microgels (AAc-MG) and poly(*N*-isopropylacrylamide-3-(acrylamido)phenylboronic acid) (pNIPAm-*co*-APBA) microgels (APBA-MG) were composed into the devices to load the drugs, MB and CV, respectively. At pH 10.0, methylene blue (MB, positively charged) exhibited strong electrostatic interactions with both the negatively charged AAc and APBA-modified microgels. This resulted in MB uptake into both of the microgels. At pH 7.0, the APBA groups were neutralized, allowing MB to be released from the APBA-MG only. When the solution pH was again lowered to 3.0, the AAc groups are neutralized allowing MB to be released from the AAc-MG. Furthermore, we demonstrated that two different small molecules could be delivered to a system when triggered at specific pHs. These systems represent a versatile approach to sequentially delivering small molecules to a system, in a triggered fashion, with tunable release kinetics. Importantly, their release behavior can be easily tuned by simply changing the microgel chemistry, e.g., by generating reservoir devices from microgels that ionize at different solution pH. This would allow one to deliver various small molecules to a system triggered by a variety of solution pHs. This, combined with the tunable release kinetics and the ability to array these devices on a single substrate, makes this delivery platform extremely versatile, powerful, and unique.

Another important stimuli-responsive polymer architecture in controlled drug delivery systems are block copolymer self-assembled structures, such as liposomes, micelles, and vesicles. Temperature responsive polymeric micelles have attracted a lot of attention due to the sharp change of properties in response to a small change of temperature of responsive polymer. When using a temperature responsive polymer as the hydrophobic core-forming segment, a core-shell micelle structure forms above its LCST due to the hydrophobic interaction among the dehydrated polymer chains.[166-169] For example, Discher and Yang [170] used poly(ethylene oxide)-block-poly(*N*-isopropylacrylamide) (PEO-b-pNIPAm) block copolymers to generate micelles capable of releasing small molecules as a function of temperature. The polymers become amphiphilic in water above body temperature (37 ^{o}C) and self-assemble into micelles that can encapsulate both hydrophilic and hydrophobic molecules. With a decrease in temperature, micelle disassembly is triggered with release of encapsulates. In another example, Xu and co-workers developed a block copolymer with one water-insoluble diselenide-containing polyurethane (PUSeSe) block and two water-soluble polyethylene glycol (PEG) blocks and its self-assembly behavior in water was studied. [171] It was expected that the Se-Se bonds would undergo a structural dissociation, inducing the disassembly of the aggregates in the presence of oxidants or reductants. This is the first report to introduce diselenide group into a diol structure to possess desirable solubility compared to traditional diselenide-containing polymers, which exhibit low solubility. [172] It is worth noting that these PEG-PUSeSe-PEG block copolymer based micelles were quite stable for more than one month in an ambient environment since the active Se-Se groups were buried in the core. However, it is quite sensitive to external redox stimuli, and the incorporated species could be released under the effective oxidants or reductants, like H_2O_2 or GSH as shown in Fig. 11.

The wide range of stimuli able to trigger drug release at the right place and time, and the diversity of responsive materials and other functional materials that can be assembled in different architectures, allow great flexibility in the design of stimuli-responsive drug delivery systems. As we have shown in this section, building up novel structures from stimuli-responsive polymers can yield materials with important applications to solve problems related to human health. The next section will describe their utility as artificial muscles and actuators.

3.3. Artificial muscles and actuators

Electricity responsive polymers (or electroactive polymers (EAP)),[173] can be subdivided into two groups: ionic EAPs and electronic EAPs.[174] Ionic EAPs include ionic polymer-metal composites (IPMCs)[175] and conjugated polymers,[176] and their response depends on ion and solvent transport in fluids to effect volume changes of polymers. Electronic EAPs include piezoelectric polymers, electrostrictives, and dielectric elastomers,[177] which require high voltages and must therefore be shielded from the fluid environment.[174] A common example of an ionic EAP is the conjugated polymer polypyrrole (PPy.[178] PPy is characterized by alternating single and double bonds along the polymer backbone. PPy can be either p- or n- doped by chemical and/or electrochemical processes, which affects the number of electrons associated with the polymer backbone.[179] Specifically, positive charges are delocalized along the polymer chains after removal of electrons (oxidation) by the application of a positive potential or reacting with oxidants. To maintain charge neutrality of the polymer chains, negatively charged anions are incorporated into the polymer to compensate for the delocalized positive charges, which is called p-doping. The positively charged polymer backbones can be rendered neutral when a potential is applied to reduce the polymer. Therefore, the small, mobile anions will be expelled from the polymer resulting in the collapse of the polymer. However, incorporated large, immobile anions are in the polymer, results in swelling of the polymer chains due to the higher osmotic pressure of the more highly charged species.[180-182] PPy possesses many advantageous properties that allows it to be used in myriad applications, e.g., artificial muscles and actuators,[183] biomimetic devices,[184] and biomedical applications.[185] Specifically, they are light weight, exhibit a large strain, can be operated in liquid electrolytes at room temperature, and can be activated by applying low voltages.

Most conjugated polymer-based actuators are bilayers, although many other formats exist. For years, Otero,[186,187] Inganäs,[188,189] and MacDiarmid[190,191] have conducted numerous investigations on bilayers composed of a single actuating conducting polymer film deposited on an electromechanically inert layer. In a few examples, artificial muscles with tactile sensitivities were constructed from electrochemo-mechanical and macroscopic devices using films

of PPy electrogenerated on double-sided tape to generate bilayers and trilayers.[192-194] Natural muscles are biological organs that transform chemical energy into mechanical energy. The process is quite complex, and involves an electrical pulse from the brain that triggers the liberation of ions inside the sarcomere, chemical reactions (ATP hydrolysis), and eventual conformational changes along the natural muscle fibers. This whole process is shown in Fig. 12a. Similarly, conducting polymer-based artificial muscles provide motors with the ability to sense and respond to electrical pulses. This is shown schematically in Fig. 12b. In this example, a PPy layer is doped with small ions ClO_4^-. As the current flows (5 mA), the left PPy film acts as the anode and swells, and the right PPy acts as the cathode and shrinks in aqueous solution. Fig. 12c shows that the electrically stimulated muscle movement is able to move an object by bending; the artificial muscle bending continues until the applied potential is removed. PPy-based actuators and microactuators have many possible applications, particularly in cell biology and biomedicine because they can operate in various salt solutions, blood plasma, urine, and cell culture medium. [195-197]

Serpe and coworkers[198,199] have demonstrated novel humidity responsive self-bending bilayer based actuators made by depositing layers composed of poly(N-isopropylacrylamide)-based microgels and the polyelectrolyte polydiallyldimethylammonium chloride (pDADMAC) on a flexible substrate. The responsive materials bend upon drying and the degree of bending depends on the atmospheric humidity. The dried PDADMAC layer is composed of both amorphous and crystalline phases. The amorphous layer can readily absorb water, which results in actuation, while the crystalline phases template the bending characteristic of the device. They worked on applying them as artificial muscles and humidity sensors based on understanding of the bending mechanism, which is shown in Fig. 13.

Photoresponsive polymer-based materials can also be used to generate shape memory polymers, polymer gels, and liquid crystalline polymers (LCP).[200,201] They are responsible for converting light energy into mechanical work. Generally, polymers are equipped with light responsive groups, which induce photochemical reactions and a visible macroscopic effect on the polymer. In a specific example, photoresponsive unit crosslinked liquid crystalline polymers have been used as actuators.[202-206] Warner and coworkers introduced azobenzene moieties into monodomain nematic LCP as crosslinkers and generated films, which were shown to exhibit significant contraction upon exposure to of 365 nm radiation.[207] Terentjev and coworkers also worked on incorporating various azobenzene derivatives into LCPs and examined the deformation of the system upon exposure to UV light.[208] This was accomplished in a study published by Ikeda and coworkers. They showed that light-driven bending of azobenzene LCPs could be achieved by creating an asymmetric deformation between the surface and the bulk of a film.[209-211] They found that the deformation of the polymer is dependent on the manner of alignment of the LCP mesogens.[200] The monodomain LCP with in-plane alignment of mesogens bent along the alignment direction towards the irradiation source. On the contrary, homeotropically aligned monodomain LCP films underwent the bending away from the irradiation direction of the irradiation source, as shown in Fig. 14. They further fabricated the light driven soft actuators from azobenzene LCP/polyethylene laminated films.[212] The film was mounted on a home-made pulley system. By introducing UV light from the top right and visible light from the top left simultaneously, a rotation of the belt drives the two pullys move in a counter clock wise direction.

Another very important class of actuators are composed of hydrogels that change volume in response to stimuli. Stimuli responsive hydrogels are 3D networks that can absorb water and swell and shrink in response to various external stimuli including temperature, pH, ionic strength, chemicals, electricity, light, et al.[213,214] Hydrogel actuators produce macroscopic changes upon swelling and shrinking.[127,215-217] In a recent example, Aida and coworkers developed a layer hydrogel consisting of cofacially oriented electrolyte nanosheets. This unusual geometry leads to significant anisotropic electrostatic repulsion in the hydrogel interior. They showed that the material could be operated by modulating its electrostatic anisotropy in response to changes of electrostatic permittivity. The electrostatic permittivity could be controlled by varying the material's solvation state, which depended on solution temperature. They realize the actuation by using alternating cycles of heating and cooling, which is shown in Fig. 15.[218]

In summary, polymer-based actuators are materials capable of converting energy from external stimuli (e. g. heat, light, and electricity) to mechanical forces, thus exhibiting shape changes. Polymer-based actuators can be generated from a variety of materials (hydrogels, liquid crystal polymers, and shape memory polymers). The material that is used depends on the intended application, e.g., soft hydrogels could be used for delicate biological applications, while hard shape memory polymers could be used for lifting/moving heavy masses. It is this versatility of materials properties, combined with the diversity of material responsivities, that makes this research area vibrant for exploration and research.

5. Conclusions and Future Perspectives

Although stimuli-responsive polymer-based systems have been known for many decades, it wasn't until relatively recently that their behavior could be understood at a level deep enough to fully exploit their behavior. This was initiated early on by theories used to describe the behavior of polymers and polymer-based materials,[219] later supported by experiment. Stimuli-responsive polymers have been synthesized using a variety of techniques, and employed for myriad applications; we describe only some of their applications here. In the future, combining stimuli responsive

polymers with biological systems, and nanoscale materials, a variety of new functions (and properties) will be accessible. This development needs to be supported by new theories that can describe the newly found behavior such that the development of new materials can be done in a smart fashion to meet the needs of a specific application. Another challenge is to develop systems that respond to multiple external stimuli in an "intelligent" and predictable manner. These materials are required to support the development of biomimetic systems with long-term stability and durability. The concepts presented in this review encompass both the introductory theory needed to understand polymers, and some of their applications. A more complete picture of this broad and complex topic can be obtained from the referenced articles.

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Schemes and Figures

Figure 1. Various conformations of of polymer chains on surfaces; a) mushroom, b) pancake, c) brush.

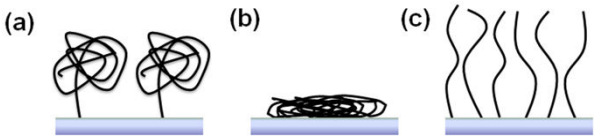

Figure 2. Alexander-de Gennes brushes. Each of the circles is a tension blob. ξ is the center-to-center distance between two adjacent tension blobs. Reprinted with permission from ref. 99 Copyright 1980, American Chemical Society, ref. 101 Copyright 1977, EDP Sciences and ref. 103 Copyright 2006, American Chemical Society.

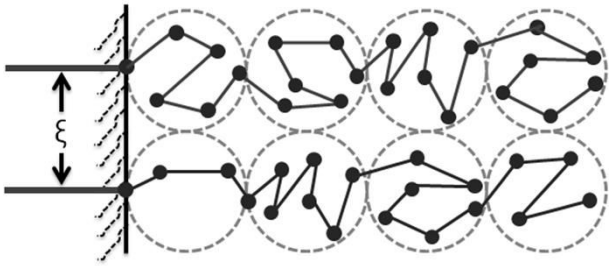

Figure 3. Predicted conformation of surface-bound pNIPAm as a function of distance between grafting sites at (A) T lower than LCST, and (B-E) at T above LCST as a function of distance between chains. Reprinted with permission from ref. 114. Copyright 2013, American Chemical Society.

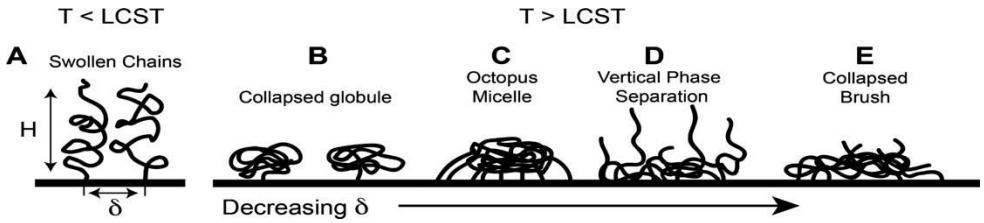

Figure 4. Schematic illustration of Con A-*C. albicans* binding. Reprinted with permission from ref. 133. Copyright 2015, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

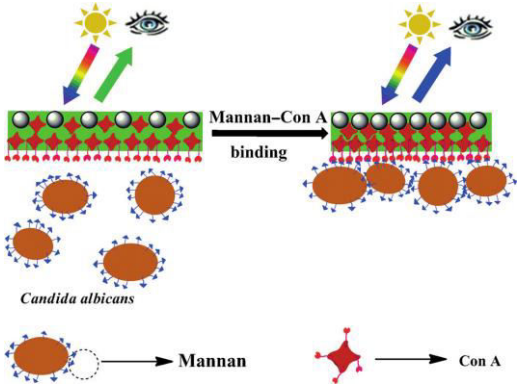

Figure 5. Schematic representation of streptavidin binding to excess PAH-biotin. The excess PAH-biotin can be isolated and added to etalons composed of pNIPAm-*co*-AAc microgels, yielding a response that can be related to the amount of streptavidin in the original solution. That is, the extent of the etalon response is inversely related to streptavidin concentration in solution. Reprinted with permission from ref. 139. Copyright 2014, Elsevier.

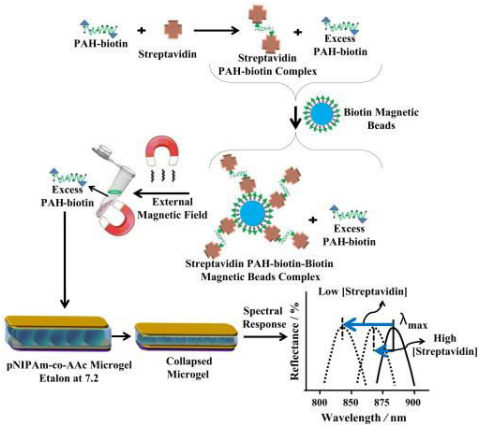

Figure 6. Structure of (a) P2VP-Orange-QD and (b) PAA-Blue-QD. (c) Schematic illustration of the conformation and behavior of pH sensor device at a given pH value. Reprinted with permission from ref. 142. Copyright 2014, American Chemical Society.

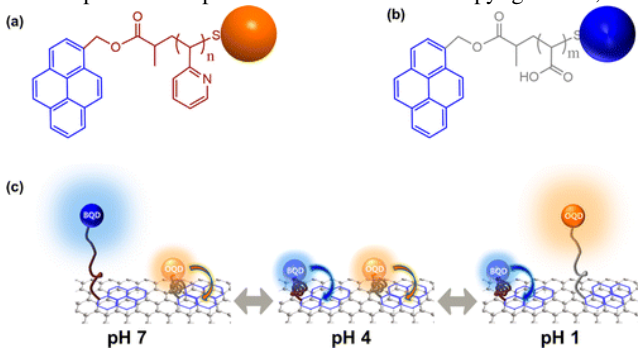

Figure 7. Various stimuli-responsive polymers that have been used for drug delivery applications.

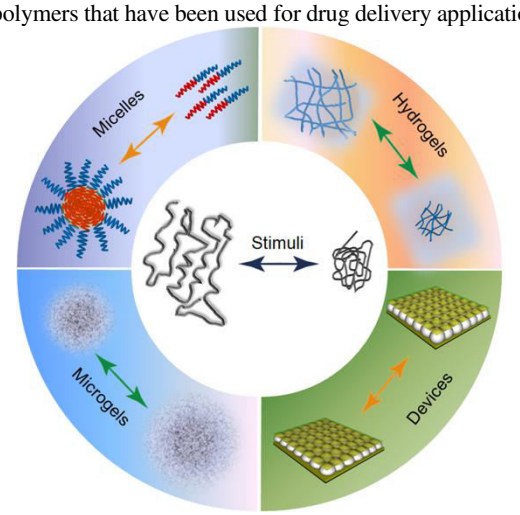

Figure 8. Hydrogel-forming microneedle array system for controlled drug delivery. (a) hydrogel-forming microneedle types used for controlled drug release, (a1) hollow, (a2) coated, and (a3) dissolvable microneedle patches. (b) Schematic illustration of the mechanism of light-responsive ibuprofen release from hydrogel-forming microneedle arrays drug reservoirs. Reprinted with permission from ref. 155, Copyright 2015, American Chemical Society and ref. 156, Copyright 2016, American Chemical Society.

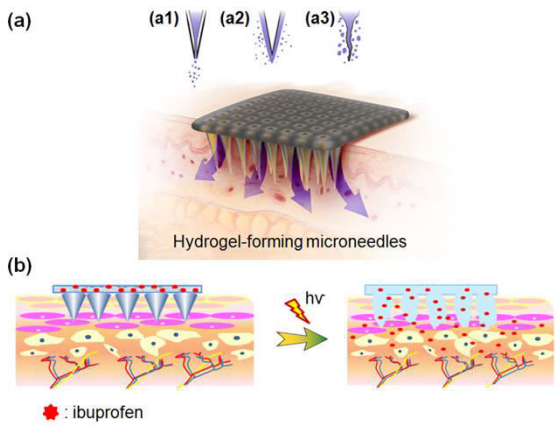

Figure 9. The structure of microgel-based assemblies and their pH triggered release profile with a 500 nm Au overlayer. The dark regions show where the solution pH was changed to 3.0, while the white regions are where the solution pH was 6.5. As mentioned, the solution pH was varied by adding either HCl or NaOH. Reprinted with permission from ref. 161. Copyright 2013, American Chemical Society.

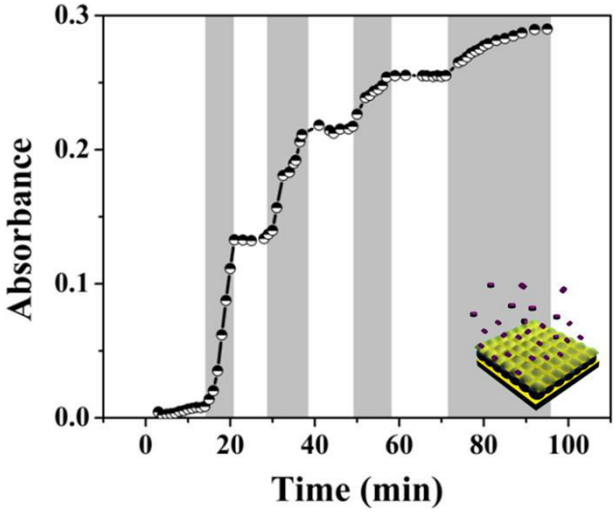

Figure 10. (a) Schematic of pH triggered MB release from APBA-MG and AAc-MG. As each microgel is neutralized, the electrostatic interactions between the microgel and the MB are diminished, and the MB is released from the microgel. (b) Sequential release of MB from a reservoir device with 1 : 1 APBA-MG and AAc-MG and 50 nm Au overlayer at 37 ^{o}C. The arrows indicate when the solution pH was changed to (i) 7.0 and (ii) 3.0. (c) The release profile for a device made of APBA-MG and AAc-MG loaded with MB and CV, respectively. The arrows are the time that pH adjusted. Reprinted with permission from ref. 163. Copyright 2016, Royal Society of Chemistry.

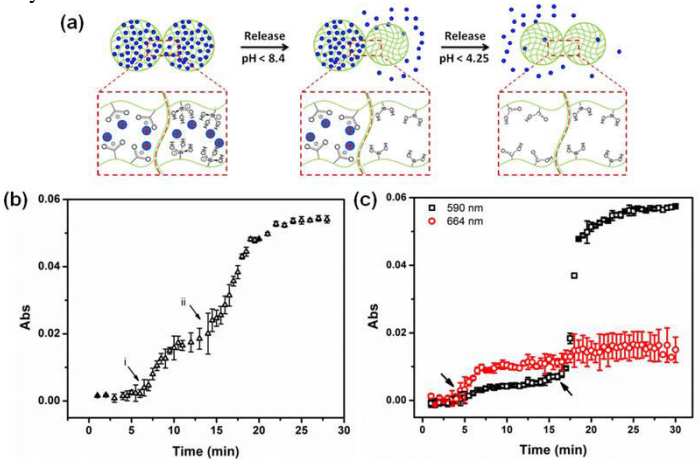

Figure 11. Structure of PEG-PUSeSe-PEG and schematic of the redox initiated disassembly of PEG-PUSeSe-PEG micelles. Reprinted with permission from ref. 171. Copyright 2009, American Chemical Society.

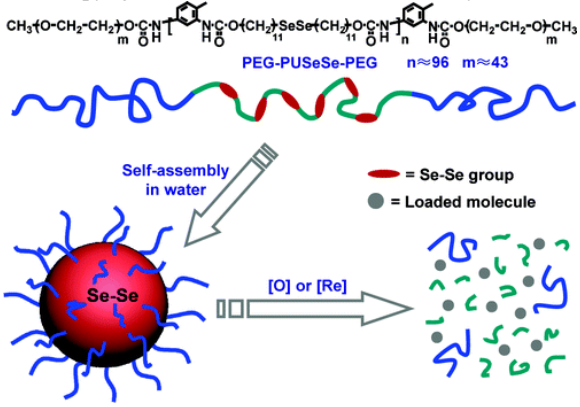

Figure 12. (a) A theoretical model is proposed for the cooperative operation of muscles after brain stimulation and the electrochemical equipment, electrical contacts, and the scheme of the triple layer (PPy/non-conducting and adhesive film/PPy) and (b) the triple-layer muscle initiates its movement under a constant current. Reprinted with permission from ref. 187. Copyright 2003, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim and ref. 194. Copyright 2012, American Chemical Society.

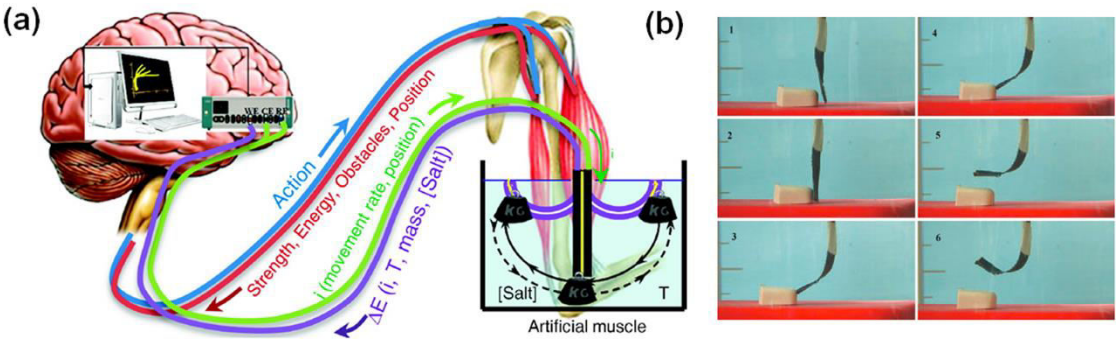

Figure 13. a) Use of the polymer-based devices as artificial muscles. A curled substrate (~2 inches long) was hung from an arm and cycled between low and high humidity. b, left) Schematic depiction of the experimental setup used to measure resistance and LED light intensity as a function of device bending b, right) light intensity (left axis) and resistance (right axis) changes induced by the bending of the bilayers coupled to the strain sensors. Reprinted with permission from ref. 198 Copyright 2013, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim and ref. 199. Copyright 2016, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

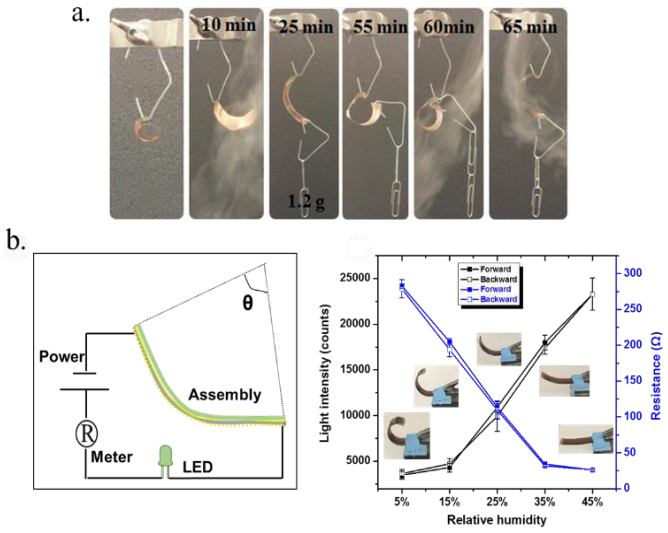

Figure 14. (a) CLCP film with in-plane alignment and photographs and plausible mechanism of photoinduced bending behavior. (b) Photographs and plausible mechanism of photoinduced bending behavior. Reprinted with permission from ref. 212. Copyright 2008,

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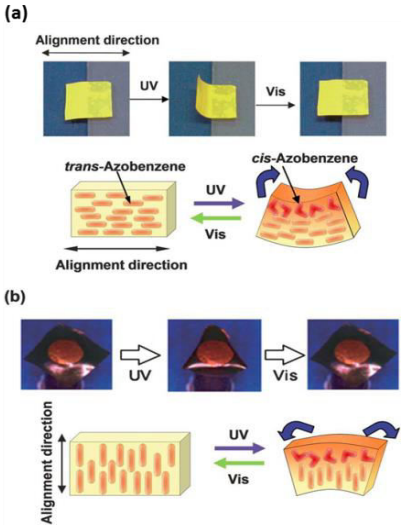

Figure 15. Unidirectional procession of an L-shaped symmetric PNIPA/TiNSk hydrogel actuator. a, Internal design of the actuator (5mm thick) and its ideal processing mechanism. b, c, Snapshots of the actuator (b) and its processing profiles (c) on a flat, horizontal base with alternate heating and cooling between 25 and 45 ^{0}C. In c, the positions of the forefoot (magenta), backfoot (green) and centroid (brown), as well as the fore foot–back foot distance (navy), are shown. Reprinted with permission from ref. 218. Copyright 2015, Nature publication.