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Synthetic bio-actuators and their applications in biomedicine

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Abstract. The promise of biomimetic smart structures that can function as sensors and actuators in biomedicine is enormous. Technological development in the field of stimuli-responsive shape memory polymers have opened up a new avenue of applications for polymer-based synthetic actuators. Such synthetic actuators mimic various attributes of living organisms including responsiveness to stimuli, shape memory, selectivity, motility, and organization. This article briefly reviews various stimuli-responsive shape memory polymers and their application as bioactuators. Although the technological advancements have prototyped the potential applications of these smart materials, their widespread commercialization depends on many factors such as sensitivity, versatility, moldability, robustness, and cost.

Keywords: smart hydrogels; shape memory polymers; bioactuators; surgical tools; artificial cornea; glucose sensors; artificial muscles; drug delivery.

1. Introduction

A characteristic feature of living systems is their ability to convert one form of energy to another. For instance, living tissues convert chemical energy to mechanical energy, which is necessary for their survival and function. A similar phenomenon is observed in plants, in which the sun's heat energy evaporates water from the surface of leaves, creating a pressure gradient that draws water upward into the plant (Fraztl *et al.* 2009). This pressure is induced by the chemical conversion of energy to mechanical energy via turgor pressure developed by cells. Similarly, in animal muscle cells, molecular motors convert chemical energy to mechanical energy resulting in movement (Fraztl *et al.* 2009). There has been extensive research in an effort to create bio-inspired synthetic actuators as functional synthetic mimics that can imitate the processes of energy conversion to perform work. Although many of the early efforts were focused on metal-based systems, the invention of stimuli-responsive hydrogels and shape memory polymers has created a new avenue for soft-wet actuators.

One of the advantages of hydrogel systems is that from a structural perspective, they are very similar to soft tissues. Nature has many gel-actuators such as jelly fish, sea cucumbers, sea anemone, etc. that can function (move, change shape, and protect themselves from enemies) similar to other living organisms. Similarly, most mammalian soft tissues are water-filled networks comprised of polysaccharides and proteins. In this review, we will discuss the actuating properties of stimuli-

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responsive hydrogel and their role in cell biology and medicine. Specifically, we will discuss the fundamental principles that govern the stimuli-responsive behavior of synthetic hydrogels and shape memory polymers, their actuating properties, followed by their applications in cell biology, medical devices, prosthetics, and drug delivery.

2. Stimuli-responsive polymers

Stimuli-responsive hydrogels are characterized by their ability to undergo reversible, discontinuous, and large volume changes when subjected to one or more stimuli such as temperature (Frimpong *et al.* 2006, Hu *et al.* 1995, Lendlein and Langer 2002, Leong *et al.* 2009, Weissman *et al.* 1996, Tanaka, 1978), pH (Beebe *et al.* 2000, Dong *et al.* 2006, Shin *et al.* 2009*)*, chemical triggers (Leong *et al.* 2009), electric field (Osada *et al.* 1992), magnetic field (Frimpong *et al.* 2006), and light (Irie *et al.* 1993). These stimuli can be either external and/or internal. Such stimuli-responsive hydrogels have been creatively utilized in a number of applications in biomedical and pharmaceutical industry ranging from sensors (Holtz and Asher 1997) to artificial muscles (Osada *et al.* 1992, Hirai 2007). The stimuli-responsive behavior of hydrogels is mainly attributed to the various types of interactions between the polymer chains and the solvent. Amongst the various stimuli-responsive hydrogels, temperature-sensitive hydrogels are probably one of the most extensively studied systems.

Temperature-sensitive (or thermoreversible) hydrogels undergo large, reversible volume changes in response to subtle temperature variations about the lower critical solution temperature (LCST) of the corresponding linear polymers. This thermoreversible behavior is strictly regulated by two competing forces: hydrophilic and hydrophobic forces. The volume phase transition observed at their LCST is attributed to the release of water molecules bound to the hydrophobic moiety of the polymer, followed by enhanced inter and intramolecular hydrophobic interactions. Changing the chemical composition to modify the hydrophilic-hydrophobic balance of the polymer chains can modulate the transition temperature. For instance, incorporation of hydrophobic comonomers decreases the transition temperature, while addition of hydrophilic comonomers increases the transition temperature (Badiger *et al*. 1998). This allows for the precise tuning of their transition temperature; thus, their swelling-deswelling kinetics is highly attractive for applications where temperature is an important consideration. The fundamental interactions that regulate this behavior and its kinetics are mainly secondary interactions such as hydrophobic interactions and hydrogen bonding. However, the macroscopic applications of these hydrogels are often limited due to their slow response time. A number of structures such as comb-like architecture with dangling chains have been adopted to overcome the diffusion limited swelling of hydrogels to improve their swelling-deswelling kinetics. Compared to temperature-responsive hydrogels, electric field responsive hydrogels exhibit faster response times that are required for various applications such as artificial muscle (Fuhrer *et al.* 2009), responsive valves (Beebe *et al.* 2000), and sensors (Holtz and Asher 1997).

Since the first report of electric field-induced deformation of hydrogels in 1982, hydrogels responsive to electric fields have been extensively explored as chemo-mechanical systems. In 1992, Osada *et al*. devised a mobile hydrogel from weakly crosslinked acrylamido methyl propane sulfonic acid (AMPS) polymers. The AMPS strips were first immersed in a surfactant solution causing the gels to swell. Each end of the strip was attached to an electrode and activated with 20 V in surfactant solution with the polarity flipped every 2 seconds. This caused the gel to reversibly bend and stretch in a looping movement (walking motion). The velocity of movement was

determined by the current applied, the concentration of salts in solution, and the molecular size of alkyl chains in surfactant molecules. The AMPS-based electro-driven chemo-mechanical hydrogel walked at a speed of 15 mm/min by applying on–off cycles of electric field (35 V, direct current) (Osada *et al.* 1992). This reversibility in deformation was dictated by the complexing of surfactant molecules to the gel under an electric field, which caused shrinkage. Swelling occurred due to osmotic pressure changes and ions freely moving in the gel and solution. As such, the swelling could be manipulated by changing the number of fixed charges in the gel. The direction of bending was controlled by the cathode and anode placement. Positive charges in the surfactant solution moved towards the cathode, complexing with the cathode, but when the polarity was switched, the surfactant molecules were released and moved to the opposite side, which was now the anode. New surfactant molecules attached to the anode side, straightening the gel. The gel was reversibly bent and straightened thus causing it to displace in the direction of bending. As made obvious by the large displacement, translational movement, and cyclical deformation, such hydrogels can be used as molecular machines or soft-actuators controlled by electrical energy to manipulate movement and direction of bending.

Like electric field-responsive hydrogels, pH-sensitive hydrogels usually contain ionic groups that change their ionization responding to differences in external pH. As the degree of ionization increases, the electrostatic repulsion between ionized groups adjacent to each other increases causing a chain expansion. Such pH-sensitive hydrogels have been explored as sensing actuators. Bebee *et al.* have creatively manipulated flow regulation in microfluidic systems by photopatterning pH-responsive hydrogels in the liquid phase *in situ* to create both sensing and actuation capabilities. Theses microactuators are valve systems with microchannels allowing control over flow with response times shorter than 10 seconds (Beebe *et al.* 2000). Similarly various other stimuli-responsive hydrogels can change their shape, volume, or size in response to other stimuli such as chemicals, magnetic field, and light. Magnetic field-responsive hydrogels, or ferrogels, are a classical example of shape memory gels in which both magnetic and electric properties are coupled. Upon exposure to an external magnetic field, ferrogels undergo an instantaneous and significant change in shape, which disappears abruptly upon removal of the external magnetic fields (Xulu *et al.* 2000).

Hydrogels can also be designed to respond to internal stimuli. Internal stimuli-mediated oscillating hydrogels were developed by harnessing the principles of the Belousov–Zhabotinsky (BZ) reaction, a non-equilibrium thermodynamic process that exhibits temporal oscillation of redox potential in a closed solution. Combining these nonlinear oscillatory chemical reactions along with the ability of poly (N-isopropylacrylamide) (PNIPAM) hydrogels to undergo reversible swelling-deswelling in response to subtle changes in temperature results in self-oscillating hydrogels without external stimuli. These spontaneous, self-oscillating hydrogels create a dynamic rhythm similar to a beating heart muscle (Yoshida 2005).

Another unique aspect of stimuli-responsive hydrogels is their shape memory, where the hydrogels can self-organize into specific, programmed shapes in response to an external stimulus (Osada and Matsuda 1995). Due to their ability to respond to a wide variety of external signals and to control their mechanical properties and moldability, stimuli-responsive hydrogels have been proposed for various applications including shape memory gels for valves and artificial muscles (Beebe *et al.* 2000), drug delivery (Wu *et al.* 2006), gene delivery, self-cleaning biosensors (Gant *et al.* 2008), cell sheet engineering, and microgrippers (Leong *et al.* 2009, Feinberg, *et al.* 2007).

3. Shape memory polymers

Shape memory polymers belong to the class of stimuli-responsive materials. As mentioned in the above section, most of the stimuli-responsive hydrogels are shape memory materials in which they restore their original shape upon removal of the environmental stimuli. Shape memory effects were first observed for metal alloys, (Chang and Read 1951, Bühler *et al.* 1963) which undergo martensitic phase transformations that enable them to switch from a "temporary" shape to a "parent" shape. The shape transition of these materials is tuned using temperature, where the shape of the material can be switched from the transient state to their original state by heating and cooling them across their transition temperature. Such shape memory metal alloys can be used in various industrial applications. For instance, Song *et al.* have developed an active jet engine intake prototype using Nitinol-based shape memory alloy actuators (Song *et al*. 2011). Studies have also shown that self-healing metallic materials can be developed by harnessing the shape memory ability of metal alloys (Faravelli and Marzi 2010).

Unlike the homogenous stimuli-responsive hydrogel strip that exhibits reversible bending and straightening (shape memory effect), heterogeneous hydrogels containing modulated structures can perform complex shape changes that are completely reversible. For instance, bigel strips consisting of temperature-responsive PNIPAM and nonresponsive polyacrylamide moieties have been used to create reversible alphabets and soft grippers (Hu *et al.* 1995). Such hydrogels have been proposed to find applications as robotic fingers. Adapting the same principle, Hu *et al*. have created complex shape memory structures where they integrated two stimuli-responsive gels that reacted to temperature and solvents (Hu *et al*. 1995). The shape memory gel was composed of the PAAM gel with NIPA gel located at four locations to allow gel bending at only these sites. At 22°C, the gel was straight, but as the temperature increased, the gel bent creating a pentagon structure at 39°C (Fig. 1(a)) and a quadrangle at 41°C (Fig. 1(b)). In instances where heating is not possible, this gel can also be modified by using pH-sensitive polyacrylic acid moieties with PAAM in an environment with controlled pH. As such, the large strains produced make these gels applicable for use as switches and valves.

Most of these aforementioned hydrogels exhibit shape memory by swelling or collapsing along the length to form different shapes. In a study using the presence of metal ions as an external stimulus, hydrogels were shown to self-organize starting as cylindrical hydrogels that transformed into a completely hollow spherical or ellipsoidal shape responding to external transition metal ions (Varghese *et al.* 2001). These hollow, self-organized constructs returned to their original shape upon the decomplexation of the transition metal ions from the gel.

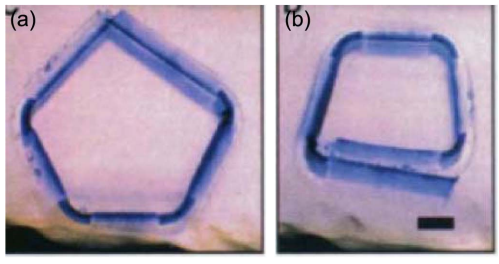

Fig. 1 Shape memory gel produced as a result of the modulation of the PAAM gel with NIPA gels at four locations (darker regions). The separation between adjacent NIPA gel pieces is about 12 mm. The gel shape at various temperatures: (**a**) 39°C, (**b**) 41°C. The scale bar is 6 mm. (Reproduced, with permission, from Hu and Zhang 1995)

In addition to stimuli-responsive hydrogels, Osada and Matsuda created a different class of temperature-responsive shape memory polymers, where the shape memory is attributed to a reversible order-disorder transition of the polymer components present in the gel (Osada and Matsuda 1995). However, one of the major concerns of shape memory hydrogels is their weak mechanical properties. Lendlein *et al.* created a series of responsive shape memory polymers that are not only mechanically robust but also biocompatible and biodegradable (Lendlein and Langer 2002). Unlike hydrogels, these shape memory polymer networks do not swell in water; however, they can respond to the same external stimuli as hydrogels. In general, mechanically robust shape memory polymers are achieved by copolymerizing precursors that have varying thermal properties, such as melting transition temperatures. The two main components of these polymers are molecular switches and netpoints. The former is a precursor that determines the temporary shape in response to external stimuli, while the latter defines the permanent polymer shape (Lendlein and Langer 2002). In addition to temperature responsive shape memory polymers, these authors have also developed photo-sensitive shape memory polymers harnessing the ability of cinnamic groups to deform and attain a temporary shape responsive to UV-light at ambient temperature (Lendlein *et al.* 2005).

4. Smart polymers in biomedical applications

4.1 Surgical tools

The ability of shape memory polymer-based biomaterials to attain a transient shape in response to the magnitude and type of stimuli, while maintaining their ability to return to their parent state upon a change in stimuli, makes them an ideal candidate for various surgical tools. During minimally invasive endoscopic surgery, sewing wounds and tying sutures into knots are one of the most challenging tasks since it requires a specific tension to hold the lips of tissue together without tightening excessively; otherwise, tissue necrosis can result. Conversely, if the tension is too little, scar tissue will form and increase the risk of hernia formation due to tissue weakness. As made apparent, shape memory polymers offer a solution. For instance, Lendlein *et al*. have shown that the biodegradable sutures made of thermoplastic polymers can be used to tighten the loosely sewn sutures by exposing them to suitable stimuli like temperature, (Fig. 2), (Lendlein and Langer 2002).

These shape memory copolymers could be stretched up to 1000% before fracture, with a maximum deformation of 400% between temporary and permanent shapes compared to Ni-Ti alloys, which exhibits a maximum deformation of 8%. This high elasticity and shape memory properties make them optimal for such surgical applications.

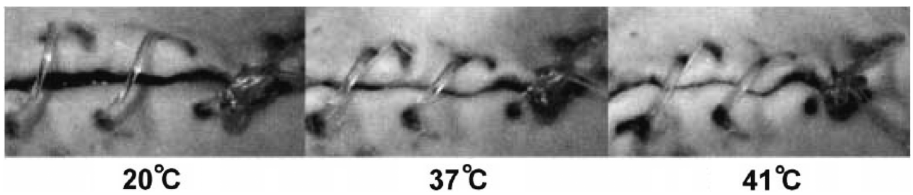

Fig. 2 Degradable shape-memory suture for wound closure. The photo series from the animal experiment shows (left to right) the shrinkage of the fiber while temperature increases (Reproduced, with permission, from Lendlein and Langer 2002).

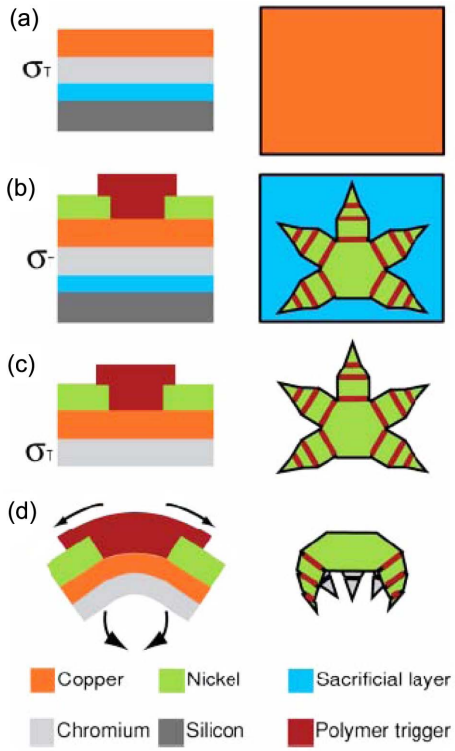

Fig. 3 Schematic diagram depicting side and top view of the key steps in the fabrication and operation of the microgripper trilayer joints. (**a**) The bimetallic joint component (orange and light gray) was evaporated above the sacrificial layer (blue) and silicon (dark gray) substrate. The Cr layer (light gray) developed residual tensile stress during evaporation, denoted by σ_T. (**b**) The Ni phalange (green) and the polymer trigger layer (red) were then patterned above the bimetallic layer. (**c**) The sacrificial layer was dissolved to release the microgripper from the substrate in a planar, open configuration. (**d**) When heated or exposed to selected chemicals, mechanical property changes in the polymer trigger allowed the stressed bimetallic layer to flex. (Reproduced with permission, from Leong *et al.* 2009. Copyright 2009 National Academy of Sciences, U.S.A.)

Such shape memory biocompatible polymers have also been proposed to assist the implantation of bulky implants through small incisions. During synthesis, they can be shaped to deform into a complex bulky shape. These structures can then be exposed to environmental stimuli to create a compressed temporary shape that regains its original bulky shape after minimally invasive administration. Research has also been driven towards smaller scale tissue manipulation by targeting applications in cell and tissue isolation. In a recent study, Leong *et al*. created tetherless microgrippers that can be actuated using temperature or chemical stimuli (Leong *et al.* 2009). They were designed with three-layer joints made of polyvinyl alcohol (PVA) and bimetallic chromium-copper thin films thermally evaporated onto sacrificial layers that were spin coated onto a silicon wafer (Fig. 3). Nickel and gold were electrodeposited followed by photolithographic patterning of trilayer joints. The microgrippers were released into water in an opened state, dissolving the PVA layer, causing an irreversible release of residual tensile stress in the Cr/Cu thin film, allowing flexation of the bilayer and closure of the microgrippers. Any chemical reagent causing a decrease in the polymer's elastic modulus increases the joint angle of grippers, thus improving their gripping ability. The authors have demonstrated *in*

vitro that these biologically compatible microgrippers can be used to capture clusters of cells (L929 fibroblast cells) from a cell mass. The cells can then be removed from microgrippers using mechanical disruption without damaging the cells. In addition to manipulating and capturing cells, stimuli-responsive hydrogels (synthetic actuators) can also be used as synthetic, multifunctional matrices for stem cell culture where the matrix can provide multiple physical cues to the embedded cells while providing three-dimensional structural support (Lim *et al*. 2011).

Similar to the thermally activated microgrippers discussed above, Feinberg *et al*. have created muscular thin films or autonomous soft robotic grippers by using a rectangular strip made of polydimethylsiloxane (PDMS) elastomer thin films (Feinberg *et al.* 2007). Anisotropic myocardium aligned lengthwise such that the ends contracted towards each other under application of an electric field using platinum wire electrodes to sandwich the gripper. Under electrical stimulation, the gripper contracted until the ends made contact. Unlike the microgrippers synthesized by Leong *et al.,* these were reversible grippers that opened and closed by increasing the pacing rate until the muscular thin films reached tetanus (5 Hz) at which point the cardiomyocytes were fully contracted. The gripper ends could also be shaped and bound with proteins to enable binding to and manipulating single cells and biological samples.

4.2 Artificial cornea

The human eye focuses its vision by changing the lens shape using ciliary muscles (Toates 1972). Traditional optical systems focus on images by manipulating lenses and focal points. However, recent technological advances have made miniaturization possible using microlens arrays with fixed focal lengths (Popovic *et al.* 1988, Yang *et al.* 2005) or adjustable microlens (e.g., tunable liquid lens) focal lengths. In the case of tunable liquid lenses, changes in external pressure can be used to manipulate the shape of the liquid lens, which in turn adjusts its optical properties for focusing. Integration of liquid lenses with stimuli-responsive hydrogels in a microfluidic system has been used to achieve autonomous focusing of liquid lenses (Dong *et al.* 2006). The microfluidic component stores the liquid droplet while the hydrogel detects the external stimuli and changes in shape accordingly, altering the droplet focal length. The meniscus between water and oil are used as the optical lens, such that manipulating the meniscus curvature changes the focal length.

These pH-responsive hydrogels were comprised of acrylic acid (AA) and 2 (dimethylamino)ethyl methacrylate (DMAEMA), shaped into a ring, placed within a microfluidic channel, and sandwiched between a glass plate and an aperture slip with cutouts for the hydrogel ring and meniscus (Fig. 4). To ensure that the water-oil meniscus remained stationary, the top surface of the aperture was designed to be hydrophobic, while the sidewall and bottom surfaces were designed to be hydrophilic. A microlens array inspired from the compound eyes of insects was designed by combining two microlenses in one microchannel. This allowed dynamic focusing on two areas. One hydrogel was made of AA while the other from DMAEMA, which reacts oppositely to AA in pH buffers. The AA hydrogels shrank in acidic solutions (<5.5 pH) and expanded in basic solutions (> 5.5 pH), while DMAEMA expanded at pH < 7.0 and shrank at pH > 7.0. The ring size was manipulated by exposing the outside perimeter of the gel to pH buffers flowing in the microchannel. For AA gels, the meniscus bulged upward when the pH value increased, decreasing the focal length of the microlens to the aperture. At high pH, the DMAEMA gels caused the meniscus to shrink, increasing the focal length (Dong *et al.* 2006). Thus, the two functioned antagonistically, allowing each microlens to focus on one area while having the ability to vary focal lengths by changing

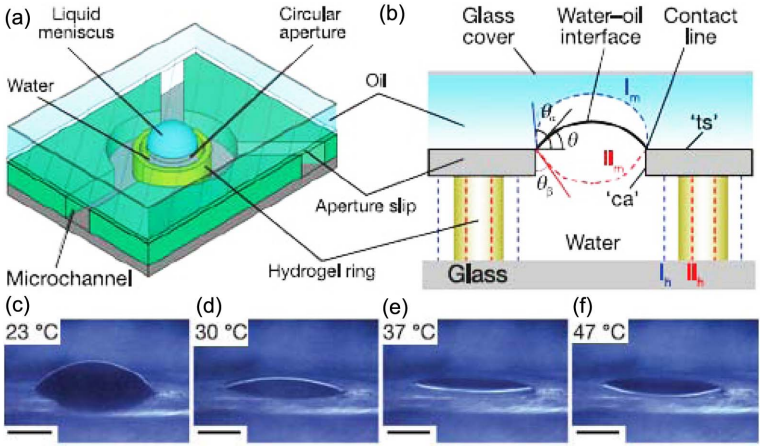

Fig. 4 Smart microlens using a pinned liquid-liquid interface. **(a)** The water-oil interface forms the liquid microlens. The microchannels allow the flow of fluid to the microlens structure. **(b)** Smart variable-focus mechanism. The hydrophilic sidewall and bottom sidewall and bottom surface ('ca') and hydrophobic top surface ('ts') of the aperture pin the water-oil meniscus along the contact line 'ca-ts'. The expansion and contraction of the hydrogel regulates the shape of the liquid meniscus by changing the angle θ of the pinned water-oil interface. The blue dashed lines show the expanded state of the hydrogel ring ('I_h') and the corresponding divergent microlens ('I_m') at $\theta = \theta_\alpha$. The red dashed lines show the contracted state of the hydrogel ring ('II_h') and the corresponding convergent microlens ('II_m') at $\theta = -(90^o - \theta_\beta)$. **(c-f)** The shape of the liquid microlens varies with local environmental temperature. Scale bars, 1.0 mm. (Reproduced, with permission, from Dong *et al.* 2006)

ambient pH. This microarray system can be made with any smart hydrogel to build optical systems capable of capturing images. It is possible to image a larger field of view by building a 3D array system on polymer substrates integrated with an optical-electronic system.

3.3 Glucose sensors

Materials that exhibit reversible color changes are an important component of smart sensors. Weissman *et al.* developed hydrogels encoded with optical conversion functions, where a mesoscopically periodic smart material was created by utilizing crystalline colloidal arrays along with a reversible volume change of temperature-responsive hydrogels (Weissman *et al.* 1996). By altering the periodicity of the crystalline colloidal array (CCA; polystyrene spheres) using temperature-stimulated reversible volume transition of the hydrogel (PNIPAm), the authors were able to create wavelength tunable diffraction devices. The mesoscopically periodic smart materials diffracted light at wavelengths dictated by the lattice spacing, giving rise to color change. Combining the CCA with stimuli-responsive hydrogels provided a new knob for controlling color, where the lattice spacing could be dictated by the reversible volume change of the hydrogel.

Holtz *et al*. have developed intelligent chemical sensing materials utilizing these smart materials where the hydrogel was armed with a molecular recognition group to undergo reversible volume change by binding specifically to the analyte (Holtz and Asher 1997). The molecular recognition-induced swelling increased the mean separation between the colloidal spheres and thereby the Bragg peaks of the diffracted light to longer wavelengths. The authors have demonstrated the potential application of these smart systems as optical sensors for different metal ions (Holtz and Asher 1997).

They also fabricated stimuli-responsive hydrogel-based glucose sensors by attaching enzyme glucose oxidase spaced 25 nm apart to the polymer CCA of the polystyrene colloids. The gels only swelled in glucose solutions and caused the length of diffraction to shift into red visible light. The diffraction wavelength returned to its original length once the glucose was removed by soaking in deionized water for a few minutes. At a high glucose concentration the high ionic strength caused a decrease in Donnan osmotic pressure and a swelling saturation. Decreasing the CCA thickness (from 125 μm to 10 μm thick) and the hydrogel polymer and cross-linker concentration cause the response rate to increase from seconds to milliseconds. Additional work has been conducted by Asher *et al.* who harnessed the ability of glucose-responsive reversible swelling of hydrogels to construct glucose sensors, while Kataoka *et al.* have utilized glucose-sensitive hydrogels for on-off release of insulin responding to the changes in external glucose concentrations (Kataoka *et al.* 1998).

4.3 Artificial muscles

Living organisms directly convert chemical energy into mechanical work to power muscle movement without producing energy waste in the form of heat. Muscles are linear actuators driven by actin-myosin motors controlled via excitation-contraction coupling. They have the ability to change in stiffness in response to a given load (Madden *et al.* 2004). Since their invention, stimuli-responsive hydrogels have been extensively explored for their potential application in artificial muscles. This is mainly attributed to the ability of these polymers to undergo large reversible volume changes or strain in response to external stimuli. The rate of swelling-deswelling kinetics of the gel system plays an important role in determining their actuation efficiency. The swelling of hydrogels is diffusion limited and is therefore proportional to the square of the linear dimension. Due to their slow responsiveness along with weak mechanical properties, most of the polyelectrolye hydrogel-based actuators (or artificial muscles) are in their prototype stage. For instance, studies have produced faster gel responses by utilizing biochemical principles, e.g., ATP-driven hydrogels. Kakugo *et al*. have reported the development of a soft gel machine comprised of actin and myosin fragments (Kwon *et al.* 2007, Kakugo *et al.* 2002). These ATP-driven synthetic actuators (chemically crosslinked actin gels) were found to move along the myosin gels with a velocity as high as that of native F-actin. In another study, Shen *et al*. have developed ATP-independent forisome-based smart actuators that can expand and contract anisotropically in response to changes in pH and calcium concentrations (Shen *et al*. 2006).

Another approach to improve both the response time and mechanical properties of synthetic bioactuator systems is through the use of nanotechnology. A number of techniques have been adopted to decrease the response time of gels such as the incorporation of nanosized particles and carbon nanotubes (Tong *et al.* 2007, Haraguchi and Takehisa 2002), although these additives can increase gel fragility (Sakai and Yoshida 2004, Jin and Hsieh 2005). Shin *et al.* have shown these gels can support external tensile loads, which is essential for most hydrogel actuator applications (Shin *et al.* 2009). Additionally, other studies make use of nanofillers to decelerate crack propagation to delay composite hydrogel failure while enhancing hydrogel swelling properties (Haraguchi *et al.* 2002). The smaller the particle, the larger the surface area exposed for nanofiller-polymer matrix interactions, thereby improving mechanical properties. Another study used ferritin-nanoparticles embedded within a pH-sensitive, PVA hydrogel matrix (Shin *et al.* 2009). Composite nanofibers enhanced hydrogel toughness and increased gel elastic modulus by 230%, mechanical strength by 170%, and elongation at break by 440%. Ferritin was shown to enhance bulk PVA hydrogel properties by exhibiting a faster equilibration response time of 100 seconds to change the pH from 4 to 9, under a 0.5 MPa

isotonic stress. This enhanced response was attributed to increased cation-water cluster diffusion rates due to the open, porous structure provided by nanofiber arrays. In addition, swelling and contraction was completely reversible for PVA/ferritin hydrogels. The ferritin nanoparticles acted as nanosprings connecting the ferritin core and polymer matrix through hydrogen bonds, preventing the separation of core and PVA chains in the matrix. Proposed applications for this hydrogel are artificial muscles and valves since the performance of ferritin-based hydrogel nanofiber structures can be further improved to model natural muscle properties.

Similarly, magnetically activated hydrogels have also been extensively explored in artificial muscles (Fuhrer *et al.* 2009). Such magnetic field-responsive hydrogels are typically modified using magnetic micro- or nanoparticles embedded within a polymer matrix. This enables manipulation of gel mechanical properties including stiffness, elasticity, and shape memory using an external magnetic field. The strength of actuation force depends on the amount of magnetic particles (mass of particles per volume) and the force per particle (particle saturation magnetization) (Fuhrer *et al.* 2009). Metallic cobalt and iron are optimal metals, but as small particles they are unstable. As such, magnetite (Fe_3O_4), also known as iron oxide, is most commonly used for emulsion, suspension, or precipitation polymerization (Jian *et al.* 2008, Huang *et al.* 1996). Under application of an alternating magnetic field, iron oxide magnetic nanoparticles generate heat, triggering volume changes in temperature-sensitive hydrogels such as NIPAAm (Frimpong *et al.* 2006). However, as the particle concentration increases the polymer system becomes more brittle and less functional (Fuhrer *et al.* 2009).

Manipulation of these particles was conducted by Fuhrer *et al.* who used poly(2 hydroxyethyl methacrylate), commonly used for optical lenses, to develop a polymer matrix with magnetic nanoparticles to enhance gel mechanical properties (Fuhrer *et al.* 2009). Nanomagnets made of metallic cobalt nanoparticles were encapsulated in 1-2 nm thick carbon shells to protect against oxidation or corrosion. The nanomagnets were covalently modified with a vinyl group to copolymerize with 2 hydroxyethyl methacrylate. Crosslinking these nanomagnets into the polymer backbone increased the mechanical stability and decreased the brittleness as compared to physically mixed nanoparticles in polymer solution. Under a gradient of variable magnetic fields, the magnetic hydrogels reversibly elongated or contracted very quickly by aligning the gels parallel to the magnetic field. To produce a 123% stretch, the hydrogels required a 60 wt% metallic cobalt nanomagnet composition. This combined high saturation magnetization of cobalt allowed high particle loading without compromising gel mechanical properties. Such magnetically active polymers have potential applications as medical implants, heart pumps, and controlled drug delivery vehicles.

Capadona *et al.* have created stimuli-responsive nanocomposite hydrogels that mimic the functional characteristics of the sea cucumber species *Cucumaria frondosa* by exhibiting similar reversible changes in mechanical properties upon exposure to a stimulus that mediates nanofiber interactions (Capadona *et al.* 2008). This rubbery nanocomposite is an ethylene oxide/epichlorohydrin 1:1 copolymer (EO-EPI) with rigid cellulose nanofibers taken from tunicates, or the mantles of sessile sea animals (Capadona *et al.* 2008). The cellulose was used as the component for reinforcement having nanometer size dimensions and a stiffness of 143 GPa (Frimpong *et al.* 2006). The tensile modulus could be altered by modifying the extent of hydrogen bonding of the cellulose fibers. Chemical regulators including water and isopropanol were used as swelling agents to switch the interactions between fibers “on” and “off”, with the former producing the best dispersion of cellulose fibers and generating up to a 40 fold change in tensile modulus (about 800 to 20 MPa after swelling) with a 19% v/v of cellulose fiber content.

The dynamic properties of these materials were tested for use in brain-device interfaces in which

electrodes are used to treat medical conditions including Parkinson's disease, spinal cord injuries, and stroke. Currently, implanted electrodes exhibit a decrease in signal quality over a period of a few months. Capadona *et al.* hypothesized that this was in part due to the rigidity of implanted electrodes, which damage the soft cortical tissue in the brain and cause damage to surrounding neurons (Rutten 2002). They proposed that a mechanically adapting electrode could be made such that during insertion into the brain, it is rigid, but after implantation in response to the brain's chemical environment, it becomes soft without expanding significantly. They used poly(vinyl acetate) (PVAc) nanocomposites to induce a sharp thermal transition using chemical agents and caused fiber switching. In artificial cerebrospinal fluid at 23°C to 37°C in increments of 2°C, the materials exhibited a phase transition and the fiber network dissembled, decreasing the tensile modulus significantly (Capadona *et al.* 2008). PVAc served to increase the thermal transition temperature from 25 to 40°C such that for *in vivo* applications, the gel would not soften simply upon exposure to body temperature. All of these nanocomposite materials responded to specific chemical agents and mimicked the reversibility in tensile strength of sea cucumbers, making them optimal for brain and spine implants.

4.4 Drug delivery

Since the onset of research in polymer science, stimuli-responsive hydrogels have been extensively explored for drug delivery applications. The ability of stimuli-responsive hydrogels to swell and deswell in response to environmental parameters has enabled sustained or bolus delivery of drug molecules. For instance, pH-sensitive hydrogels have been extensively investigated in oral drug delivery where hydrogels are used to protect encapsulated drug molecules from the digestive tract. Lowman *et al.* evaluated the potential of pH-sensitive poly(methacrylic acid) grafted poly(ethylene glycol) hydrogels for oral insulin carriers (Lowman and Peppas 1999). Such hydrogels were reported to exhibit an enhancement in insulin transport.

In addition to protecting loaded drugs, hydrogels can respond to perturbations in their environmental cues and modify their drug release rates. Studies have also investigated the applicability of dual-stimuli-responsive hydrogels for drug delivery. For instance, Yin *et al*. developed hydrogels containing pH-sensitive (polyacrylic acid) and temperature-sensitive moieties (N-isopropylacrylamide) (Yin *et al.* 2006). These dual-stimuli-responsive hydrogels, which can respond to environmental changes within physiological pH ranges, have been proven to be effective in intracellular drug delivery where subtle pH changes across the endosomal membrane trigger drug delivery. Vakkalanka *et al*. synthesized dual-stimuli-responsive terpolymer hydrogels containing N-isopropylacrylamide, acrylic acid, and 2-hydroxyethyl methacrylate (Vakkalanka *et al.* 1996). These hydrogels were shown to exhibit pulsatile release of drugs under oscillatory pH and temperature conditions. Hydrogel drug delivery systems have also been explored in pulsatile drug delivery necessary for chemotherapeutic agents specific to cell-cycle processes for cancer treatment and hormone therapy (Yoshida 2005). In addition to pH and temperature-sensitive hydrogels, electric field-responsive hydrogels have also been demonstrated to support on-off delivery of encapsulated drugs. Sawahata *et al.* designed a drug delivery system in which drugs in solution were loaded into hydrogel networks as they swelled, then released by an applied alternating current that produced on-off drug delivery (Sawahata *et al.* 1990). Instead of controlling the presence of external stimuli, an alternate approach to manipulate drug release rates is by modifying the hydrogel structure itself. For example, Plunkett *et al.* developed patterned pH-sensitive hydrogels with core-shell structures to control the swelling kinetics. The core and shell could be

swollen independently, altering the swelling profiles significantly while providing a constant maximum diameter. This allowed for controlled release of encapsulated drugs and small molecules (Plunkett and Moore 2004). All of these gels were designed to regulate drug release rate by manipulating stimuli parameters including pH, temperature, electric field, and hydrogel structure itself; however other methods exist.

Another method of modulating drug release is through the use of small molecule stimulating agents. As mentioned earlier, the ability of glucose-sensitive hydrogels to swell in response to changes in environmental glucose concentration can be a powerful tool for constructing self-regulated insulin delivery systems (Cartier *et al.* 1995, Kataoka *et al.* 1998). Glucose-sensitive hydrogels composed of PNIPAM modified with a glucose-sensing phenylboronic acid showed a glucose concentration-dependent swelling-deswelling behavior where an increase in environmental glucose concentration from 0 to 5 g/L induced a shift in the LCST of the hydrogel from 22 to 36^{o}C (Kataoka *et al.* 1998).

Hydrogels have also been developed to respond to large molecules such as proteins, enzymes, and antigens in addition to small molecule-sensitivity described above (Miyata *et al.* 2002). Kurisawa *et al.* have created hydrogels containing moieties that respond to different types of enzymes (Kurisawa and Yui 1998). Such dual-stimuli-responsive hydrogels could be used for targeted tissue-specific delivery of small molecules. In an interesting study, Miyata *et al.* developed a hydrogel that could swell reversibly in the presence of a specific antigen (rabbit IgG) and change its structure. This hydrogel was prepared by encoding the hydrogel network with the antigen and the corresponding antibody (GAR IgG). When immersed in buffers containing free antigens, these hydrogels showed a free-antigen-dependent (in buffer solution) swelling. The advancements in the field of biomolecule-sensitive hydrogels are continuously growing and are expected to result in the development of self-regulated drug delivery systems.

5. Conclusions

Lessons from nature are continuously inspiring the development of micro- and nanosized soft actuators based on stimuli-responsive polymers. Although the advancements in stimuli-responsive hydrogels have enabled the creation of synthetic bioactuators with functional properties characteristic of living organisms, these synthetic bioactuators lack the mechanical properties, thus limiting their biomedical applications. Development of mechanically robust stimuli-responsive shape memory hydrogels will be a key component in the development of next generation, biologically inspired materials. Despite the major advances made in creating responsive materials, with many of them requiring exogenous interference, ongoing challenges remain in achieving rapid response of these synthetic actuators.

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