Smart and functional polymer materials for smart and functional microfluidic instruments

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ABSTRACT

As microfluidic systems evolve from "chip-in-the-lab" to true portable lab-on-a-chip (LoC) or lab-in-a-package (LiP) microinstrumentation, there is a need for increasingly miniaturized sensors, actuators, and integration/interconnect technologies with high levels of functionality and self-direction. Furthermore, as microfluidic instruments are increasingly realized in polymer-based rather than glass- or silicon- based platforms, there is a need to realize these highly functional components in materials that are polymer-compatible. Polymers that are altered to possess basic functionality, and even higher-functioning "smart" polymer materials, may help to realize high-functioning and self-directing portable microinstrumentation. Stimuli-responsive hydrogels have been recognized for over a decade as beneficial to the development of smart microfluidics systems and instrumentation. In addition, functional materials such as conductive and magnetic composite polymers are being increasingly employed to push microfluidics systems to greater degrees of functionality, portability, and/or flexibility for wearable/implantable systems. Functional and smart polymer materials can be employed to realize electrodes, electronic routing, heaters, mixers, valves, pumps, sensors, and interconnect structures in polymer-based microfluidic systems. Stimuli for such materials can be located on-chip or in a small package, thus greatly increasing the degree of portability and the potential for mechanical flexibility of such systems. This paper will examine the application of functional polymer materials to the development of high-functioning microfluidics instruments with a goal towards self-direction.

Keywords: smart materials, functional materials, composite polymers, nanocomposite polymers, microfluidic systems, microfluidic packaging, polymer MEMS, polymer microfluidics, magnetic MEMS, hydrogels

1. INTRODUCTION

Microfluidics and biomedical microelectromechanical systems (MEMS) are revolutionizing laboratory methods, as well as diagnostic monitoring techniques and equipment. Such complex systems offer high levels of functionality, offering new capabilities for multiple areas such as DNA analysis, single cell analysis, immunology, point-of-care medicine, personalized medicine, drug delivery, wearable health monitors, and environmental toxin and pathogen detection. Through a powerful combination of biosensors, microchannel fluid transport, and other micro mechanical, electrical, optical, chemical, and fluidic components, microinstrumentation has spawned research into miniaturized systems for a wide variety of biological, biomedical, and biochemical applications.

Microfluidics can be defined as the design, manufacturing, and formulation of devices and systems that manipulate very small volumes of fluids (e.g., nanoliters or picoliters) and/or have dimensions that are most easily measured in micrometers (e.g., 100 μm wide microfluidic channels). Microfluidic devices can be loosely characterized as passive microfluidics devices, such as microfluidic channels, reaction chambers, interconnect structures between microfluidic-channel containing substrates, filters, and non-actuated physical trapping mechanisms; and active microfluidic devices that involve a sensor and/or actuator structure as part of the microfluidic device, and includes devices such as microfluidic valves, pumps, biosensors, and cell counters. Microfluidic instrumentation combines passive microfluidic structures, together with microsensor and micromechanical or microelectromechanical systems (MEMS) structures, often including actuation mechanisms or other transduction devices such as heaters. In addition, microelectronics is usually required for providing read-out and control for the overall system or for parts of the system. Furthermore, micro-optics may be required depending on the instrument's application, as optical detection is still the gold standard for many biological, biochemical, and biomedical sensors and processes. These often very different components may be fabricated using a wide range of disparate materials and fabrication techniques, and must often be interconnected together in order

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to result in a microinstrument that performs one or more complex and useful functions. The instrument shown in Figure 1[1] shows a general microinstrument concept, and is applicable for both microfluidic-based instrumentation and biomedical MEMS instruments that may or may not have a microfluidics component.

Functional microfluidic instrumentation can be defined as microfluidics-based systems that incorporate functions of sensing, actuation and control to perform complex functions. In addition to such functionality, microfluidic systems may also require some degree of self-direction. In conventional laboratory processes, one or more human operator must direct, interpret, and control overall laboratory function as well as that of individual pieces of equipment. In microfluidics instrumentation, this direction is usually provided by electronic feedback control. Functional microfluidic instrumentation that is also capable of making decisions based on available data in a predictive or adaptive manner may be termed *smart microfluidic instrumentation*. Conventional decision-making is performed via electronic and feedback control. Such control may be aided by functional and smart materials with local stimulus control, which may become an integral part of or even replace the conventional electronic feedback loop. In this paper, we discuss various applications of polymers with magnetic and/or conductive functionality, as well as stimuli-responsive materials such as thermally-responsive hydrogels, with applications to functional and smart microfluidic systems. The paper is not intended as a full review paper, but is intended to introduce the concept of smart and functional materials for smart and functional microfluidics through a small number of important, yet non-exhaustive, examples. We further limit the discussion to polymer materials with a view toward easier integration with trends in polymer-based microfluidics[2] and wearable, flexible biomedical sensor systems[3].

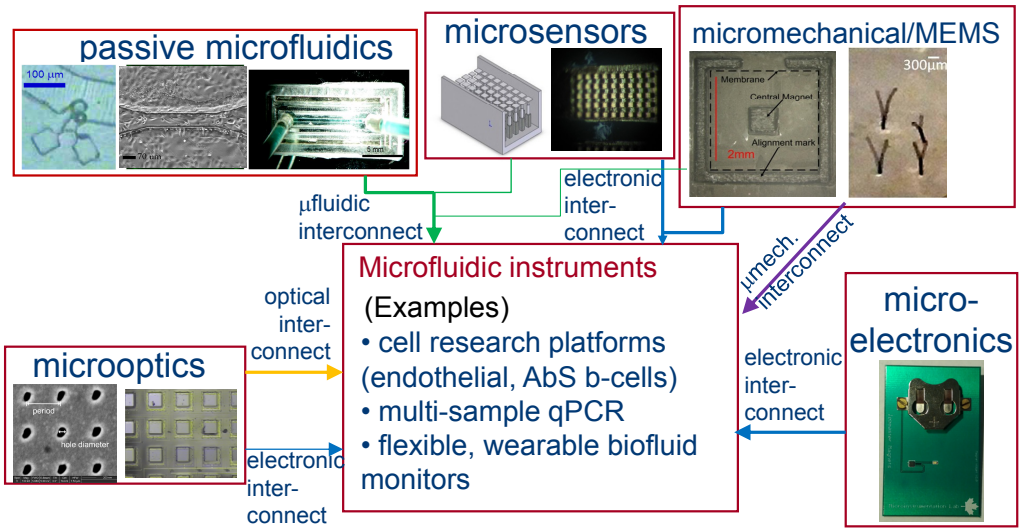


Figure 1. General conceptual microinstrument, showing potential subcomponent types, their required interconnect, and examples of functional microfluidic instrumentation that may result from the integration of these multiple subcomponents (similar to[1]).

2. SMART AND FUNCTIONAL MATERIALS

2.1 Stimuli-responsive hydrogels

Hydrogels are a class of cross-linked polymers that can hold large volumes of water and have been investigated extensively in biomedical and microfluidic applications due to their degree of controllable swelling/shrinking. Stimuli-responsive swelling and de-swelling can result from changes in temperature, pH level, electromagnetic fields (to induce temperature changes), or ionic strength. Stimuli-responsive hydrogels make excellent actuators and have often been utilized to construct microfluidic valves or pumps in microfluidic systems.

The hydrogel PNIPAAm is a thermo-sensitive polymer that exhibits a reversible phase transition from a swollen hydrated state to a dehydrated state in the presence of a temperature change[4]. It is also pH-responsive[5], and is the most well-researched hydrogel for microfluidics and biomedical applications. Figure 2[6] illustrates a PNIPAAm hydrogel sample that shows the transition from transparent to opaque during a change from room temperature to its phase

transition temperature. This change in volume with temperature is substantial, and can be used for a wide variety of actuation mechanisms. PNIPAAm has also been employed on polymer surfaces (polystyrene) for cell capture using hydrophobicity control, and for coating of magnetic and gold nanoparticles, or on substrate surfaces, to aggregate particles or hold biomolecules. Figure 3 shows the chemical structure of the monomers and cross-linker used for synthesis of this particular hydrogel[6].

Examples of other hydrogels of interest to biomedical MEMS and microfluidics are those based on poly(acrylic acid) sodium salt (PAAS)[7], poly(HEMA-co-DMAEMA) hydrogel[8], and the electroactive hydrogel 4-hydroxybutyl acrylate (4-HBA)[9]. Much research continues in both the microfluidics and MEMS communities using an ever-increasing list of stimuli-responsive hydrogels, and includes many investigations in hydrogel patterning including micromolding[10] and other polymer-compatible methods.

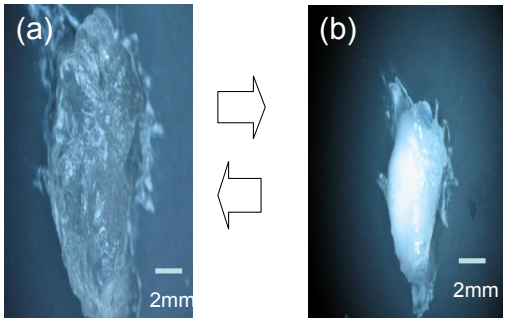


Figure 2. PNIPAAm hydrogel in: a) cooled, swollen state; b) heated, un-swollen state[6].

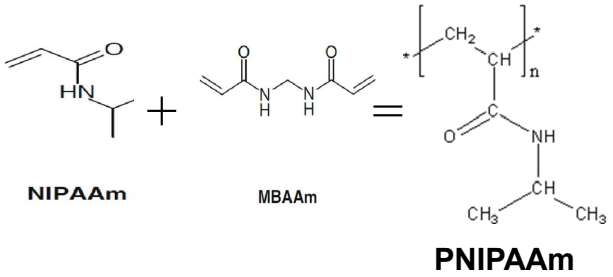


Figure 3. PNIPAAM hydrogel monomer and cross-linker[6].

2.2 Composite polymer materials

Polymer materials are typically insulating, non-conducting, and have low heat transduction. In microfluidics and biomedical instrumentation, they typically serve as the passive microfluidic channels and chambers, and/or the insulating substrate material. Many different polymers are used for microfluidics and biomedical microdevices and systems, and include a wide variety of thermosetting and thermoplastic polymers[2]. A thermosetting polymer is one that irreversibly cures, and covers materials such as epoxy-based materials, including SU-8 photopatternable epoxy; as well as polyimide, and polydimethylsiloxane (PDMS) and other thermosetting silicones, that are used widely in MEMS and microfluidics. Thermoplastic polymers turn to liquid when heated and freeze to a glassy state when cooled. Thermoplastic polymers are widely used in commercial microfluidics, and include materials such as polystyrene, polycarbonate, polymethlymethacrylate (PMMA), cyclic olefin polymer (COP) and polyimide. Polyurethane is a widely known thermoplastic elastomer.

One way in which polymer materials can be rendered functional is through embedding nanoparticles or microparticles into a polymer which forms the base, or matrix, of the functional composite polymer (CP) material. For example, conductive nanoparticles such as silver spheres or flakes may be employed to create conductive nanocomposite polymers (C-NCPs), NdFeB-based microparticles may be employed to create magnetic composite polymers (M-CP), and carbon nanotubes (CNTs) may be employed for C-NCPs that have a strong sensitivity to pressure or polymer swelling due to analyte in a microfluidic sample. Examples of nanoparticles are metal or carbon nano-sized flakes, spheres, cylinders, needles or tubes with at least one dimension typically less than 0.1 μm in average size. Microparticles may be, e.g., metal or alloy flakes or spheres typically 1 to 10 μm in average size. Metal-based particles include silver, gold, aluminum, tungsten, copper, platinum, iron and its oxides, nickel, and rare earth particles based on SmCo or NdFeB, Particle shapes include flakes, rods, spheres, and random assortments that may contain all of these shapes[11]. Early work on carbon-based nanoparticles involved the utilization of carbon black to make conductive polymers for employment as electrodes or sensors, or for improved polymer mechanical properties[12]. CNTs, which are now regularly used for C-NCPs, usually fall into two categories: single walled CNTs (SWCNTs) and multi-walled CNTs (MWNCTs). They may also be semiconducting, metallic, or most typically will contain a mixture of both types in a given sample[13].

The properties of a CP strongly depend on the volume fraction of particles in the polymer matrix, known as the fill factor. Weight percent (wt-%) is equal to the weight of solute divided by the weight of solution multiplied by 100%, and is the most typical method in which fill factor is specified (volume percent, or expression in fractional amounts, are also used). The filler density can have a large effect on mechanical and other properties of the composite polymer, e.g., the material will typically become stiffer (higher modulus of elasticity) with increasing fill factor, which is an important consideration if employing the CP as an actuator or actuator electrode that must undergo large deformations. The wt-% of nanoparticles in a C-NCP is very important to its electrical behavior due the existence of a *percolation threshold*, which is the point at which the first continuous chain of linked conductive filler particles is present, and can be explained using percolation theory[14,15]. The percolation threshold is a function of both polymer and nanoparticle properties, with aspect ratio of the particles (ratio of length to diameter of nanoparticle) being a very important consideration, with high aspect ratio nanoparticles typically resulting in lower thresholds. Despite the importance of aspect ratio, most percolation theory was historically derived using spherical particle models. Figure 4 shows an example of a typical reversed "S-shaped" curve for resistivity versus wt-% of nanoparticle filler for a C-NCP (COOH-functionalized MWCNT/PDMS C-NCP)[16]. It is observed that as concentration of nanoparticles increases, the percolation paths via the conductive particles are set up with the result that the resistivity decreases sharply near approximately 1.5 wt-% (the percolation threshold, which can be defined as the maximum change of slope of the curve). The small size and large aspect ratio of many nanoparticles, such as CNTs and silver rods, are generally helpful in lowering the percolation threshold. Percolation threshold generally increases as particle size decreases[17]. However, the degree of convolution and entanglement in very high aspect ratio fibers significantly complicates predictions: CNTs may have aspect ratios from 100-10000, and very low percolation thresholds (e.g., less than 5 wt-%) as a result[18].

Wt-% is also important to the properties of M-CPs, with higher wt-% typically resulting in an increase in magnetic force important for, e.g., actuator applications. Many materials exhibit ferromagnetic behavior and possess high magnetic susceptibility, which indicates a strong attraction to magnetic fields. Soft magnetic materials are those such as Fe, Ni, and Co, which can be readily magnetized but lose their magnetization easily. Hard magnetic materials can produce stronger magnets than soft magnetic materials, and include materials such as hard ferrites (e.g., strontium ferrite), and materials based on rare earth elements, such as neodymium (Nd) or samarium (Sm). Nanoparticles consisting of soft magnetic materials are readily available, while hard magnetic materials are typically microparticles[19]. However, a lower wt-% of hard magnetic particles typically results in higher magnetic attraction to magnetic fields. Hard magnetic materials may also be permanently magnetized in high (e.g., 2T) fields, which is an important consideration if bi-directional actuation is desired using a single, reversible-field electromagnet.

Micropatterning of CPs typically follows whatever microfabrication method has been established for the particular base polymer in the microfluidics and MEMS fields. CP microfabrication methods include photopatterning of SU-8 epoxy, PDMS, and some thermoplastic polymers; soft-lithography of PDMS; and other micromolding/casting methods, often against a sacrificial mold, of a wide variety of both thermosetting and thermoplastic polymers. Other microfabrication methods under investigation include ink-jet printing, screen-printing, micro-contact printing, nano-imprinting, embossing, and post-fabrication filling with nanoparticles[11,19].

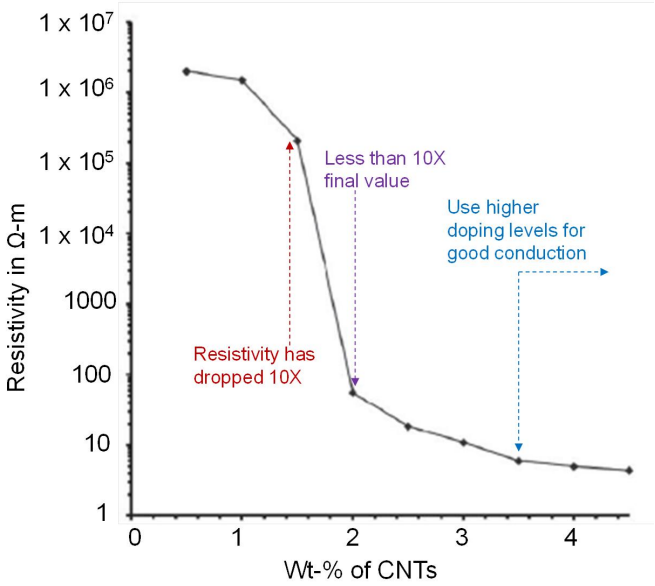


Figure 4. A typical (reversed) "S-shaped" curve for resistivity versus wt-% of nanoparticle filler in C-NCP (adapted from[16]).

2.3 Other smart and functional polymer materials

Many other smart and functional polymer materials have been investigated for biomedical MEMS and microfluidics applications. A short list of such polymers includes the following:

- Stimuli-responsive shape memory polymers undergo a reversible crystallinity transition in resposne to temperature, and include materials such as the biocompatible and biodegradeable polymer poly(3-caprolactone) (PCL)[20].
- Electroactive polymers (EAPs) such as dielectric elastomers have also been employed for actuator structures in microfluidics, called dielectric elastomer actuators (DEAs). DEAs consist of a polymer film sandwiched between two compliant electrodes. A voltage difference is applied between the compliant electrodes, causing compression in thickness and stretching in area of the polymer film[21,22].
- Poly(vinylidene fluoridetrifluoroethylene) is a well-described electroactive polymer that can be employed for a wide variety of microfluidic and biomedical MEMS applications as either a sensor responding to pressure, or as an actuator that can be electrically controlled[23].
- Electrorheological (ER) fluid, and giant ER (GER) fluid can provide reversible transformation from liquid-like to solid-like behavior on the order of milliseconds, and operate via a reversible viscosity change from liquid to gel, and back, in an electric field[24,25].
- Condutive polymers such as polypyrrole and polyaniline are EAPs that swell in response to an applied voltage; however, very high currents are often required which is not desirable for portable systems[21].
- Magnetosrictive materials are a class of materials that change shape in the presence of a magnetic field[26].

Many other EAPs and other smart and functional polymers exist, e.g., various ionic gels, but have not been fully exploited for use in microfluidics and bioMEMS, although they may be under intense investigation for other applications in, e.g., non-biomedical MEMS and robotics.

3. EXAMPLE APPLICATIONS

In this section, we discuss various applications of polymers with magnetic and/or conductive functionality, as well as stimuli-responsive materials such as thermally-responsive hydrogels, as applied to functional and smart microfluidic systems. The following short section is not intended as a full review, but is intended to introduce the concept of smart and functional materials for smart and functional microfluidics through a small number of non-exhaustive examples, primarily centered around examples from the Microinstrumentation Laboratory at Simon Fraser University. For more thorough reviews of applications of functional and smart materials, the reader is referred to the following reviews for: magnetic composite polymer materials[19]; conductive nanocomposite polymer materials[11]; stimuli-responsive hydrogels[5,27]; and electro-active polymers[28]. Reviews specifically of stimuli-responsive polymers for microfluidics are also available[5,29].

3.1 Flow control

In any microfluidic system, flow control is required in order to move a sample between operations and perform fluidic manipulations on the sample such as mixing it with other reagents, which can be difficult in microfluidic systems as fluid flow is laminar. Microfluidic flow control typically employs microfluidic devices such as valves, pumps, and other devices that alter channel or chamber geometry; mixers; filters; hydrodynamic steering of flow streams; and interconnect between microfluidic channel-containing devices.

Stimuli-responsive hydrogels have been used extensive for flow control in microfluidic systems, especially as the basis for microfluidic valve or pump actuation schemes[30,31]. One of two different mechanisms is usually employed for valve actuation: use of the hydrogel to actuate a flexible polymer membrane, or diaphragm; and use of the hydrogel as a plug that is in contact with the sample fluid and can shrink or swell in response to heat or pH level. Membrane-type actuators are also applicable to microfluidic pumps, as the most common type of microfluidic pump involves actuating a membrane with input and output check valves (or diffuser/nozzle input and output structures) so that actuation of the pump results in flow primarily in one direction. Figure 5[6,10] shows a plug-type thermally-responsive PNIPAAm hydrogel valve that is different from other hydrogel-based valves in that all of its components, including its heater element, are mechanically flexible. Microvalve technology for mechanically flexible polymer microsystems remains a largely unexplored area; however, not only are mechanically flexible polymer microvalves generally applicable to polymer microsystems, they further enable microfluidics to be applied to flexible wearable and implantable microsystems, or those located in flexible packaging such as textiles[3] or contact lenses[32]. While the copper metal on a flexible printed

circuit board can be employed for the flexible heater element[10], an even better solution, from the standpoint of materials integration and fabrication simplicity, is to employ flexible C-NCP heater elements doped with metallic or carbon-based nanoparticles, such as tungsten[6]. PDMS can be employed as the base polymer for all other components of the valve, including microfluidic channels, heater element, and electronic routing to the heater, or between heaters when an array of valves is used.

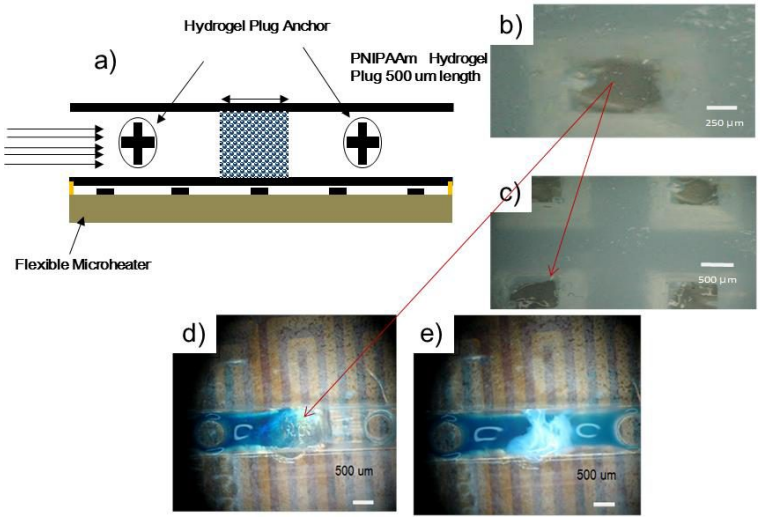


Figure 5. Mechanically-flexible plug-type PNIPAAm hydrogel valve with W-doped PDMS C-NCP, or flexible PCB metal, flexible heater element: a) schematic of valve showing subcomponents of device; b,c) hydrogel plug microfabrication via micromolding; d) normally-closed valve operation with heater off; e) open valve with heater on showing fluid flow from left to right (adapted from[10]).

Many different M-CP actuators have been proposed in recent years for microfluidic valves and pumps, with most typically falling into one of four categories based on actuation structure: membrane, beam, cilia, or rotary[19]. Many membrane-type actuators intended for use in microfluidic valves and pumps have been proposed. In one example, membranes ranging in size from 1 to 8 mm in diameter were fabricated from PDMS with 75 wt-% 5 µm $(Nd_{0.7}Ce_{0.3})_{10.5}Fe_{83.9}B_{5.6}$[20] rare-earth magnetic particle filler[33]. Deflections up to 1 mm under a 70 mT oscillating electromagnetic field were demonstrated, as well as deflections of 100 µm under fields as small as 6.2 mT for larger membranes. This work was followed up with a valve designed to employ the actuator, resulting most recently in demonstration of pairs of fully operation microfluidic valves with fast and efficient flow switching under magnetic fields up to 80 mT[34]. Biomimetic cilia consist of small cantilevers or "hairs" that can be actuated in a way that mimics the cilia that line the inner surfaces of the trachea of mammals to expel mucus from the lungs. M-CPs make excellent cilia actuators as high-aspect ratio structures can be formed in highly flexible polymers and easily controlled by global or local magnetic fields. M-CP cilia have been demonstrated for microfluidic mixing, fluid manipulation, and for manipulation of small objects. Figure 6[35] shows an example of microfabricated cilia structures for microfluidic mixing that was fabricated using the same materials as the membrane-type actuators mentioned previously. Due to the high magnetization level of the composite polymer, miniature electromagnets were employed to provide relatively small magnetic fields of 7mT to actuate the cilia microstructures over a very wide motion range. Iron-doped magnetic nanocomposite polymers have also been employed as microfluidic interconnect structures[36]. A recent review[19] provides a more thorough discussion of employment of M-CPs in microfluidics.

Many other smart materials have been employed for microfluidic flow control, including EAPs for microfluidic valves, pumps, and control of microfluidic channel geometry. The most typical EAPs employed are DEAs[21,22] and PVDF[23] for membrane-type actuators. ER and GER[24], and stimuli-responsive shape memory polymers[20] have also been employed to realize valve operations and microfluidic channel re-organization toward smart microfluidic systems. Furthermore, C-NCPs have been employed as GER actuator electrodes[25], as an example of a functional CP combined with a stimuli-responsive polymer material.

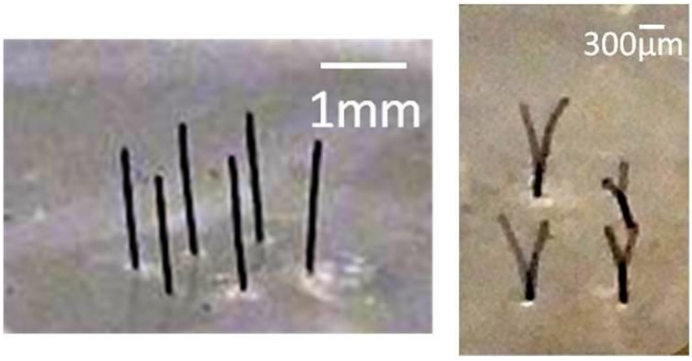
3.2 Surface control

PNIPAAm hydrogel has been extensively used for modification of surfaces of substrates and nanoparticles for assays and diagnostics, as well as control of hydrophobicity for biological cell culture, and controlled absorption and release of biomolecules[27,37]. For example, when PNIPAAm is coated on magnetic nanoparticles and gold nanoparticles, it can act to aggregate the different nanoparticles together when the temperature is raised[27]. Temperature-responsive and photosensitive wettability has also been demonstrated for microfluidic channel surfaces, for defining areas for biological cell immobilization[27,29].

3.3 Sensors and electrodes

C-NCPs have been employed for microfluidic applications such as sensor electrodes, direct analyte detection, and as flow sensors. Figure 7[38] shows C-NCP for use as electronic routing and electrodes using a silicone base material (PDMS) doped with Ag. Such sensor electrodes can be chloridized to result in Ag/AgCl electrodes which are useful for microfluidic and biomedical MEMS applications. C-NCP electrodes have also been employed as flow sensors, where the electrodes are operated as heaters and the heat conduction away from the electrodes due to passing fluid flow can be monitored[39].

When a C-NCP matrix containing CNTs is exposed to an analyte, the reaction between the molecules and the C-NCP matrix material changes the physical properties and dimensions of the polymer, causing it to swell; this physical distance change between CNTs has been suggested as the mechanism of resistance increase. Such sensors have been demonstrated for detection of biohazardous solvent vapor, using functionalized CNTs embedded in a PMMA matrix[40]. Other example sensors detect various sorts of biohazardous gases and vapors using primarily carbon black or CNTs in a wide variety of different thermoplastic and thermosetting polymer base materials.



a) b)

Figure 6. Magnetic composite polymer cilia: a) six cilia at rest; b) four cilia of different heights under a 7mT oscillating field[35].

Figure 7. C-NCP electrodes fabricated via micromolding from PDMS filled with Ag nanoparticles[38]. Substrate has been twisted to show flexibility.

Other stimuli-responsive materials such as hydrogels and halochromic polymer materials have also been employed for pH level sensors and for biosensors[41] where the stimulus is provided by the quantity that is to be measured, and is an active and intense area of research.

4. SUMMARY AND FUTURE DIRECTIONS

Functional microfluidic instrumentation may be defined as microfluidics-based systems that incorporate functions of sensing, actuation and control to perform complex analyses. Functional microfluidic instrumentation that is also capable of making decisions based on available data in a predictive or adaptive manner may be termed smart microfluidic instrumentation. Conventional decision-making is performed via electronic and feedback control. Such control may be aided by functional and smart materials with local stimulus control, which may become an integral part of or even replace the conventional electronic feedback loop. Polymers with magnetic and/or conductive functionality, as well as stimuli-responsive materials such as thermally-responsive hydrogels, are finding applications in functional and smart microfluidic systems. C-NCPs have further been combined with stimuli-responsive polymer materials such as hydrogels and GER fluid to create microfluidic flow control devices.

One existing example of a smart microfluidic system employing stimuli-responsive materials is a thermally-adapting cooling system that employs thermally-responsive hydrogels to automatically deliver coolant to areas most in need, while minimizing the system shear stress[42]. The microfluidic system automatically adjusts via thermally-responsive hydrogel flow control devices in the fluid network.

Another example of a smart and functional microfluidic system that could benefit from functional and smart materials is an instrument in which microfluidic transport can be altered to optimize microfluidic-based operations to be performed on one or more samples. Droplet-based microfluidics devices perform fluid manipulation via electro-wetting (electronic control of surface hydrophobicity) to offer versatile fluid steering of multiple samples. Electro-wetting-based systems include smart fluid networks that can be reconfigured[43,44]. Similar in concept is work presented by other researchers[45] in which a theoretical switching network could be controlled for smart fluidic routing between operation chambers that may include mixing, reaction, and detection. Recent work presented a rapid optofluidic technique to create, move, and remove arbitrary solid regions in a microfluidic flow simply by illumination with an optical pattern[46]. It is clear from all of this work that smart methods of fluid control are desired, for which functional and smart materials could play a significant role for surface modification, sensing elements, and/or flow control.

A third example of a smart and functional microfluidic instrument is designed to trap, monitor, and extract biological cells of interest. For this instrument, arrays of microfluidic wells capture individual biological cells via sediment-based trapping[47]. The goal is to trap a single antibody-producing cell at the bottom of each well. Although only a small array of wells was demonstrated for proof-of-concept, arrays of a thousand or more wells could be employed[48]. After cell trapping, each well has a larger microfluidic chamber aligned to it that contains an optical transmission-based surface plasmon resonance sensor on the "top" of the chamber that sits opposite the trapped cell and monitors its anti-body production. Wells producing antibodies of interest (perhaps 0.1 to 1 % of the population) could be identified and extracted using a smart microfluidics system, for which smart and functional microfluidics materials could play a central role in microfluidic flow control or cell immobilization.

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