Liquid-crystal materials find a new order in biomedical applications

With the maturation of the information display field, liquid-crystal materials research is undergoing a modern-day renaissance. Devices and configurations based on liquid-crystal materials are being developed for spectroscopy, imaging and microscopy, leading to new techniques for optically probing biological systems. Biosensors fabricated with liquid-crystal materials can allow label-free observations of biological phenomena. Liquid-crystal polymers are starting to be used in biomimicking colour-producing structures, lenses and muscle-like actuators. New areas of application in the realms of biology and medicine are stimulating innovation in basic and applied research into these materials.

SCOTT J. WOLTMAN[1], GREGORY D. JAY[2,3] AND GREGORY P. CRAWFORD[1,2]*

[1]Department of Physics, Brown University, Providence, Rhode Island 02912, USA
[2]Division of Engineering, Brown University, Providence, Rhode Island 02912, USA
[3]Department of Emergency Medicine, Brown Medical School and Rhode Island Hospital, Providence, Rhode Island 02903, USA
*e-mail: gregory_crawford@brown.edu

Liquid-crystal materials have often been referred to as a curious phase of matter, but their impact on modern technology has been profound. With the roots of their discovery in derivatives of cholesterol, liquid crystals are materials that biologists and biomedical engineers observe and manipulate daily. Their science and technology is truly interdisciplinary, combining basic aspects of physics, chemistry, biology and engineering. Composed of anisotropic organic molecules, liquid crystals interact with external fields and surfaces, which strongly influence their structure and properties (see Box 1). But the primary scientific and technological revolution brought about by this intriguing set of materials has been in the field of information displays, rather than the biosciences.

With the maturation of the liquid-crystal display market, the question of 'what's next?' pervades the research community. Liquid-crystal science is ripe for translation into new and exciting domains of knowledge. There is perhaps no direction more appropriate for researchers in liquid crystals than the field from which their knowledge first came — the biosciences. From a basic science perspective, the fundamental theories and models of liquid crystals have percolated through many scientific communities; for example, the concepts of orientational order and collective molecular behaviour are central to the modern understanding of the biosciences, contributing to the dynamics of cell membranes, functioning muscles and morphogenesis[1,2].

Here, we focus on early successes for new liquid-crystal material applications with notable biomedical implications. Three primary areas of application are presented: optical devices using liquid-crystal materials for integration into spectroscopy, microscopy and imaging systems; biosensor devices directly interfacing with liquid-crystal materials for improved optical imaging and diagnostics; and liquid-crystal materials that mimic biological materials and systems. Although these areas are not a complete description of the potential of liquid-crystal materials for biology and medicine, they represent a gateway to further advances. In conjunction with the primarily experimental developments discussed here, there have been widespread advances in theoretical modelling and computer simulation of liquid-crystal systems, with a particular emphasis on the biomedical interface.

HISTORICAL PERSPECTIVE

The origins of the liquid-crystal field lie within the study of biological materials. In 1888, the Austrian botanist Friedrich Reinitzer observed the melting behaviour of an organic substance related to cholesterol, specifically cholesteryl benzoate[3]. Discussion with Otto Lehmann led to the identification of a new phase of matter, termed the liquid-crystal phase. Soon afterward, Lehmann confined this unusual material to droplets[4], which would become the basis for a modern-day technology known as polymer-dispersed liquid-crystals (PDLCs), developed more than 80 years later[5,6].

Liquid-crystal science grew rapidly in the 1960s and 1970s, during which its promise for display technologies largely drove the basic and applied research. The outcome is well known — the liquid-crystal display field has expanded dramatically, beginning with laptops and desktop monitors and now penetrating the large-area television market. These systems are found not only in the hands of many consumers, but also in nearly every modern hospital around the world as the primary modality for displaying diagnostic images.

In terms of the ties between biology and liquid-crystal materials, Nageotte laid the early groundwork[7] by drawing attention to the similarities between nervous tissues and liquid crystals, at first in binary systems and then in more complex amphiphile systems composed of lecithin, fatty acids, water and other solvents. The connection between liquid crystallinity and biology advanced further with Needham's observation[8] that "the aspect of molecular patterns most underestimated in the consideration of biology phenomena is that found in liquid crystals." Subsequent research by Neville, Bouligand, Brown and others led to the understanding

of the principle that many biological systems exist as ordered, liquid-crystalline materials.

This early work has sparked more recent developments as liquid-crystal research starts to move into and combine with many of the fundamental aspects of the biosciences to generate new areas of application. In this review we look at the implications of manmade liquid-crystal materials for biological and medical applications; new liquid-crystal devices will no doubt drive forward new research in these fundamental and applied sciences.

ELUCIDATING INFORMATION: SPECTROSCOPY AND IMAGING

Biology and medicine rely heavily on the optical investigation of samples and specimens; the switchable electro-optic properties of

Box 1 What are liquid crystals?

Thermotropic liquid-crystal materials consist of anisotropic molecules that self-assemble into phases with orientational order, but often no positional order, in their simplest form. These phases exist between the conventional crystalline phase and the isotropic liquid phase. The molecules show a high degree of shape anisotropy (for example, rod-like or disk-like), which manifests itself in many ways, such as dielectric and optical anisotropies. The material may pass through one or many different liquid-crystal phases, characterized by order and symmetry, before transforming into a truly isotropic fluid (the liquid phase). There are two generic classes of liquid crystals: those whose transitions are driven by thermal processes, known as thermotropics, and those strongly influenced by solvents, known as lyotropics. Lyotropic liquid-crystal materials may not necessarily possess a shape anisotropy, but rather self-assemble based on their concentration in a solvent. This class of materials is found throughout many biological systems and represents an important subsection of the liquid-crystal materials field, but we focus here on the use of thermotropics.

Thermotropic liquid-crystals are catalogued as either rod-like (calamitic) or disk-like (discotic). Thermotropic calamitic liquid-crystal materials are used throughout the research discussed in this review. The optical anisotropy of a liquid-crystal molecule gives it a birefringence, which is exploited for nearly all optical devices using these materials.

The most common liquid-crystal phase is the nematic, where the bulk system has an orientational order, but lacks positional order. The direction along which the axes of the liquid-crystal molecules align is known as the nematic director, *n*. The nematic phase is compared with the crystalline and isotropic phases in Fig. B1a. Cholesteric liquid crystals contain an intrinsic helicity, as the molecules do not possess mirror symmetry and so must rotate slightly when placed on top of each other to minimize the free energy of the system.

Liquid-crystal materials can be well aligned using surface alignment techniques, as shown in Fig. B1b. Most commonly in display and optical applications, a polyimide is spin-coated onto a glass substrate and uniaxially rubbed with a velvet cloth. Such a procedure creates microgrooves in the polyimide material and it becomes energetically favourable for a liquid-crystal molecule to lie in the grooves; thus resulting in planar and unidirectional alignment. Conversely, homeotropic alignment can be achieved by coating a substrate with a surfactant containing an aliphatic tail. The polar head groups of such surfactants bind or bond to the substrate surface, creating a forest of aliphatic tails; it becomes energetically favourable for a liquid-crystal molecule to stand up amongst these tails.

The dielectric anisotropies of liquid-crystal molecules make them susceptible to electric fields. This is the fundamental property that makes switchable electro-optic liquid-crystal devices possible. Liquid-crystal molecules with a positive dielectric anisotropy will align along the direction of an applied electric field, as shown in Fig. B1c, whereas those with a negative dielectric anisotropy will align along a perpendicular direction. The delicate interactions between these field effects, as well as the free energy contributions of the aligning surface and the elastic interactions between individual molecules, dictate the bulk configuration of a liquid-crystal film.

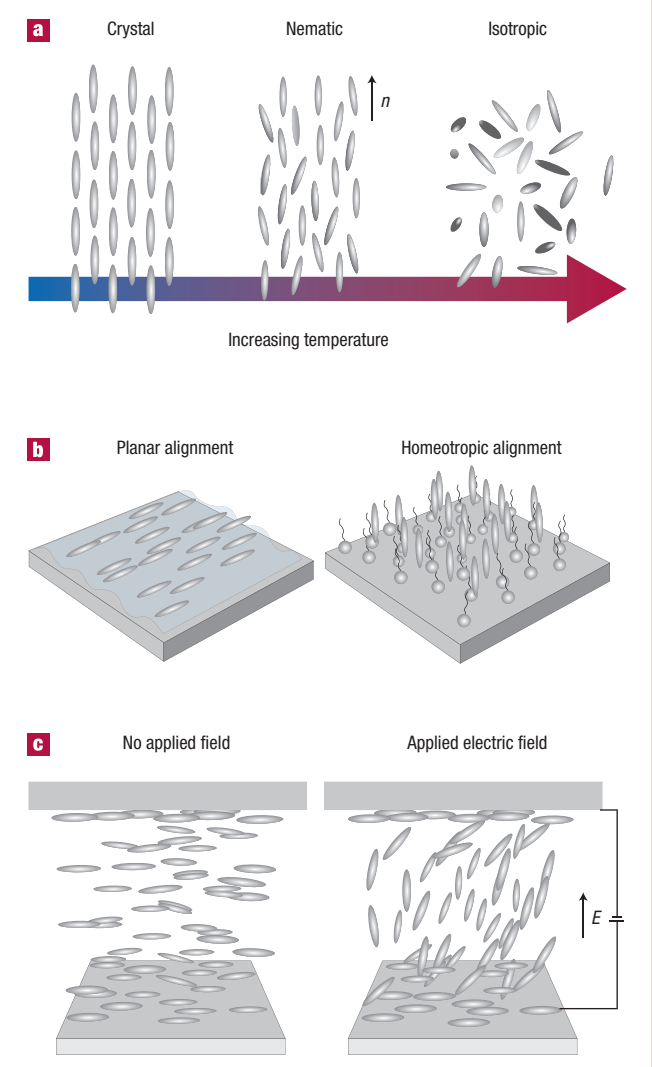

Figure B1 Fundamentals of liquid-crystal materials. **a**, The nematic liquid-crystal phase has an orientational order, but lacks long-range positional order, and exists between the crystalline and isotropic phases. *n* is the nematic director. **b**, The treatment of a surface with rubbed polyimide or a surfactant can induce planar or homeotropic alignment, respectively, in a liquid-crystal film. **c**, Liquid-crystal molecules are susceptible to electric fields; a material with a positive dielectric anisotropy will align along the direction of an applied field.

liquid-crystal materials for optical components make them ideal for the development of biomedical devices. Liquid-crystal tunable filters (LCTFs) and spatial light modulators (SLMs) build on various material configurations and are opening up new pathways for efficient, low-cost optical components and integrated systems. Such components allow the development of small, bedside devices for a rapid optical screening of cells, tissues and biofluids, as well as powerful bench-top tools within the laboratory setting. By simplifying complex microscopy set-ups and adding to their functionality, for example, the incorporation of these components is allowing researchers to probe biological systems in innovative ways. Beyond the nascent LCTFs and SLMs, research focused on liquid-crystal lasers is also producing interesting results with biomedical implications.

TUNABLE FILTERS

Liquid-crystal tunable filters represent a class of optical components that selectively transmit or reflect certain wavelength bands of light, which can often be tuned with an electric field. We will consider several classes of LCTFs, as well as their implications for biology and medicine. The Lyot filter configuration (Fig. 1a) represents one of the most widespread uses of liquid-crystal materials for tunable filters[9–12]. This configuration uses stacks of variable optical retardance filters made by integrating fixed retardance birefringent plates with tunable nematic liquid-crystal retarders. Tuning the retardance of each fixed retarder/liquid-crystal film shifts the transmission profile and, with the integration of multiple stacks, modulates the superimposed sinusoidal transmission peak. Lyot-type LCTFs have been fabricated for ultraviolet, visible and infrared wavelengths (up to wavelengths of about 1,700 nm) and with typical peak transmittance bandwidths (full-width at half-maximum, FWHM) of 10–20 nm (bandwidths as low as 0.1 nm have been reported[13]), depending on the wavelength regime[14]. The research-based spectroscopic reach of LCTFs has also been extended into the regime of terahertz optics, another rising field with potential for new imaging modalities in biology and medicine[15].

Holographic-polymer-dispersed liquid-crystals (H-PDLCs) represent another LCTF geometry[16,17]. Fabricated by exposing a nematic liquid-crystal and photosensitive pre-polymer mixture to an interference pattern generated by a laser source, these grating structures form switchable and tunable reflection gratings with bandwidths of ~20 nm and reflection wavelengths in the ultraviolet, visible and infrared regions, depending on fabrication conditions. Two or more beams from the laser source are used to generate an interference pattern. The exposure of the pre-polymer mixture induces a diffusion process as the reactive material is drawn into the high-intensity regions of the interference pattern, and the liquid crystal counter-diffuses to the low-intensity regions. The resulting structure, depicted in Fig. 1b, possesses polymer-rich (red) and liquid-crystal-rich (blue) layers; the liquid-crystal molecules are generally well oriented in droplets within these liquid-crystal-rich planes. Film thicknesses of H-PDLCs are typically 5–30 μm. Individual H-PDLCs have been shown to be electrically tunable over a 12-nm wavelength range, and several H-PDLCs can be stacked to allow for the observation of multiple distinct spectral ranges[18]. Because of their limited tunable wavelength ranges, H-PDLC filters are most suited for multi-spectral imaging applications, where a stack of filters can be used to monitor select spectral signatures of interest. These grating structures are not limited to simple reflection gratings; given the power of the holographic lithography process, it is possible to fabricate two- and three-dimensional configurations including all 14 Bravais lattices[19], as well as complex quasi-crystal structures[20].

A third LCTF configuration with useful spectroscopic applications[21,22] is the vertically aligned, deformed helix ferroelectric liquid-crystal (VA-DHFLC) structure (Fig. 1c). Ferroelectric liquid-crystals (FLCs) have a smectic-C* phase and are chiral molecules that revolve around a fixed cone angle, which results in highly periodic structures. These materials contain an

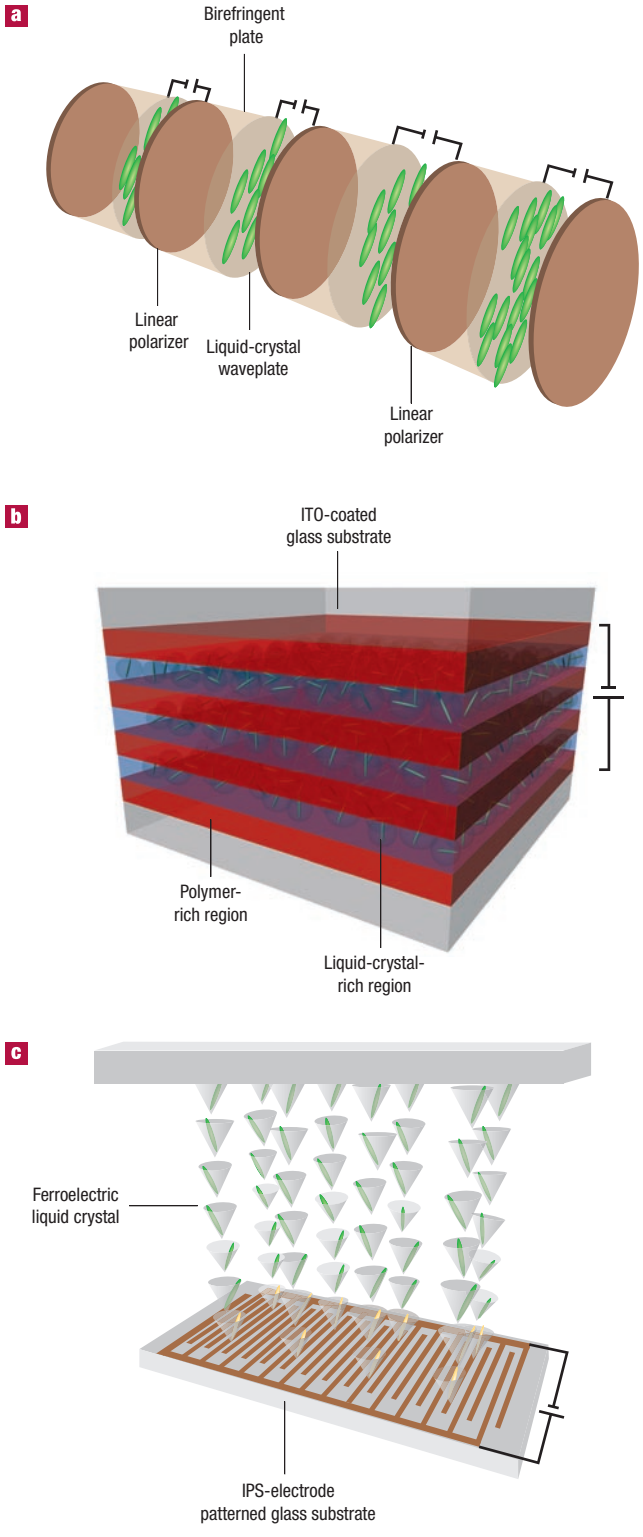

Figure 1 Electrically tunable liquid-crystal filter configurations. **a**, The Lyot filter. **b**, The H-PDLC. **c**, The deformed helix–ferroelectric liquid-crystal.

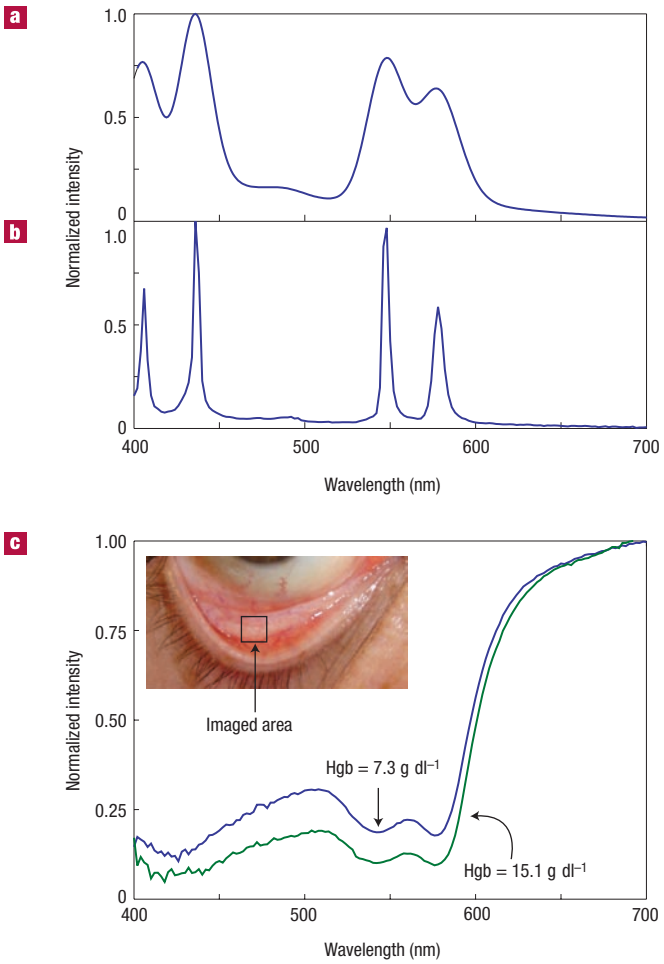

Figure 2 Tunable liquid-crystal films can be used as simple spectrometers in biomedical applications. **a**, The optical spectrum of an incident light source reconstructed by tuning a non-dispersive deformed helix–ferroelectric LCTF. **b**, The same spectrum measured using a higher-resolution dispersive grating spectrometer. **c**, Such a non-dispersive spectrometer is used to image the capillaries beneath the mucosal membrane of the human conjunctiva and determine haemoglobin (Hgb) levels non-invasively. Data courtesy of John W. McMurdy, Brown University.

intrinsic polarization, which gives rise to low threshold voltages for electro-optic applications, rapid microsecond-scale response times and a narrow Bragg reflection notch. Similar to H-PDLCs, VA-DHFLCs have the advantage of narrow reflection bandwidths of around 15–20 nm (a result of the helical periodicity of the material)[21], but also wide electrical and thermal tunable ranges[23,24]. These structures can be tuned using an in-plane switching (IPS) mode, where an electric field is applied along an axis parallel to the substrate surface through the use of an interdigitated electrode design. While tuning the reflection notch of a VA-DHFLC film, a complete wavelength spectrum can be assembled by sampling the reflected or transmitted intensity of light as a function of voltage and using a calibration to map the applied voltage to wavelength. The spectrum of a white light source generated using such a non-dispersive VA-DHFLC spectrometer (Fig. 2a) closely resembles that of a commercial grating spectrometer with a resolution of ~2 nm (Fig. 2b). Although the liquid-crystal spectrometer has a low resolution and does not distinguish sharp spectral lines, the general appearance of the spectrum is accurate.

In biomedical spectroscopic diagnostics, the spectral signature of a specific cell, tissue or other biological sample is of interest. McMurdy *et al.* have investigated the spectroscopic signature of haemoglobin within the blood vessels of human conjunctiva in order to develop an optical approach to measuring haemoglobin levels, useful for the diagnosis of anaemia and other conditions[22]. Their non-dispersive spectroscopic device uses VA-DHFLCs electrically tuned to scan the visible spectrum and assemble a full measure of the reflectance spectrum from a region of interest. The resulting spectra, shown in Fig. 2c, can be processed algorithmically to determine haemoglobin levels. This technique has led to the development of a small, handheld device capable of measuring this vital statistic. Such systems may have further implications for endoscopic diagnostics, for example, with the integration of similar LCTF-based spectrometers into fibre optic systems. Beyond wavelength-measuring spectrometers, non-scanning, Fourier-transform spectrometers are also made possible by using Wollaston prisms based on liquid-crystal materials. This could be extended to Fourier-transform infrared (FTIR) spectrometers — a widely used tool for chemical and biochemical analysis[25,26].

Microscopy also stands to benefit from liquid-crystal-based electro-optic devices. Here, LCTFs allow the selection of narrowband regions of interest over the electromagnetic spectrum. Such electro-optically switchable shutters are useful for fluorescence imaging, where there is a limited range of wavelengths that need to be investigated. LCTFs have been used in the fluorescence imaging of plants[14] and green fluorescent protein[27], among others. LCTFs also allow Raman microscopy, as a Raman spectrum can be scanned using an LCTF to assemble the entire spectrum for each pixel within an optical microscopy image — a form of hyperspectral imaging[10,11,28].

It is in the realm of hyperspectral imaging that we find some of the greatest advantages provided by LCTFs in spectroscopy and microscopy. Here, the spectral signature in each pixel of an image is obtained by using the LCTF to scan across the wavelength spectrum[29,30]. A multi-pixel imaging sensor, such as a CCD camera, can be used to image the intensity of transmitted light at each wavelength; the full spectrum at each pixel is thus assembled in the form of a 'hypercube'. A typical hyperspectral imaging set-up is illustrated in Fig. 3a. A particular advantage of this approach is the ability to investigate multiple spectral regions of interest and compare the two in a single imaging set-up; for instance, diffuse reflectance and fluorescence images (Fig. 3b and c, respectively) can be captured and compared to locate brain tumours[31]. Hyperspectral imaging with LCTFs has been used to map oxygen saturation[32] and hypoxia[33], and in endoscopic techniques[34], among others. Although most LCTF electro-optic devices use the Lyot filter configuration, further advances using other forms of liquid-crystal materials will lead to more advanced devices that are smaller, cheaper and easier to use.

SPATIAL LIGHT MODULATORS

With the maturity of the liquid-crystal display field, these devices (twisted nematic and ferroelectric liquid-crystal displays, for example) have been used as spatial light modulators (SLMs) for a variety of electro-optic devices with biomedical uses. Liquid-crystal SLMs have led to advances in phase contrast[35,36] or scanning microscopy[37,38], and to the ability to create complex diffraction patterns for optical trapping[39,40].

Diffracted wavefronts with arbitrary phase shifts can be generated with variable phase-shifting interferometers based on SLMs. This technique is most advantageous for determining the optical path length of a specimen and, in turn, performing measurements of optical thickness[35] or determining the surface profile of a reflective surface[36]. Phase and interference microscopy

techniques offer new ways to image biological specimens; the use of liquid-crystal SLMs enhances these devices to allow single-pixel amplitude modulation, in the same way each pixel in a liquid-crystal display possesses a different brightness level[38]. Scanning a specimen with phase and amplitude modulations assembles a complex three-dimensional image; this has obvious implications for biomedical microscopy where non-invasive optical investigations are required for real-time observations of biological processes.

Liquid-crystal SLMs also make it possible to control multiple traps simultaneously in an optical tweezers system. In passing a collimated light source through a liquid-crystal SLM acting as a phase-only diffractive optical element, the wavefronts of the incident beam can be focused to controlled diffractive spots[39]. These traps can then be manipulated through computer control to translate a trapped specimen in linear and angular directions. Arrays of traps can also be formed through holographic techniques using SLMs[40]. Translatable and multiple optical traps have widespread applications in biology and medicine, including DNA manipulation, investigations of cellular dynamics and *in vitro* fertilization techniques[41]. Optical tweezers using liquid-crystal materials as a solvent also allow innovative microscopy studies, particularly fluorescence confocal polarizing microscopy for the imaging of nematic director fields around trapped particles[42,43].

LASER SOURCES

Coinciding with the spectroscopic applications, periodic structures of liquid-crystal materials have also been investigated as laser sources. Such periodic structures, including the H-PDLC and FLC geometries described above, as well as the cholesteric and blue phases of liquid crystals, can all form photonic crystals with well-defined bandgap structures. In most cases, the bandgap appears as a reflection notch in the transmission spectrum of the material. Capitalizing on this phenomenon, the introduction of a laser dye into these materials gives us the possibility of optically pumped, distributed feedback dye lasing[44–46].

The advantages of liquid-crystal lasers for biology and medicine lie in their tunability. Being sensitive to electric and thermal fields, these materials can be easily tuned over a wide range of wavelengths[47,48]. Liquid-crystal lasers are also simple to produce and can be fabricated on a large scale for use in a single pumping system; they provide narrow linewidths of emission (as low as 0.1 nm FWHM) and high optical efficiencies (>30% in some instances)[49]. The prospects for liquid-crystal lasers as light sources for biological and medical imaging and therapeutics are improving as research into this young field progresses.

RAPID DIAGNOSTICS: BIOSENSORS

A large subset of the liquid-crystal research community is making use of our new understanding of these materials to develop innovative biosensor devices for bedside diagnostics and laboratory applications. The medical community is moving to translate engineering expertise into the clinical setting and develop useful, clinically relevant tools, the so-called 'lab-on-a-chip', particularly in regard to biosensors and optical diagnostic devices[50]. Liquid-crystal materials, with their birefringent properties and extreme sensitivity to surface interactions, are poised to play an important role in these devices. Optical sensors using liquid-crystal materials could eliminate the need for markers or tags, as the liquid-crystal molecules act to enhance the optical appearance of signals of a biological process or structure.

The study of liquid-crystal materials for diagnostic biomedical sensors relies on the interaction between the sensing liquid-crystal medium, especially thermotropic liquid-crystals, and the biological specimen of interest. It is advantageous that many

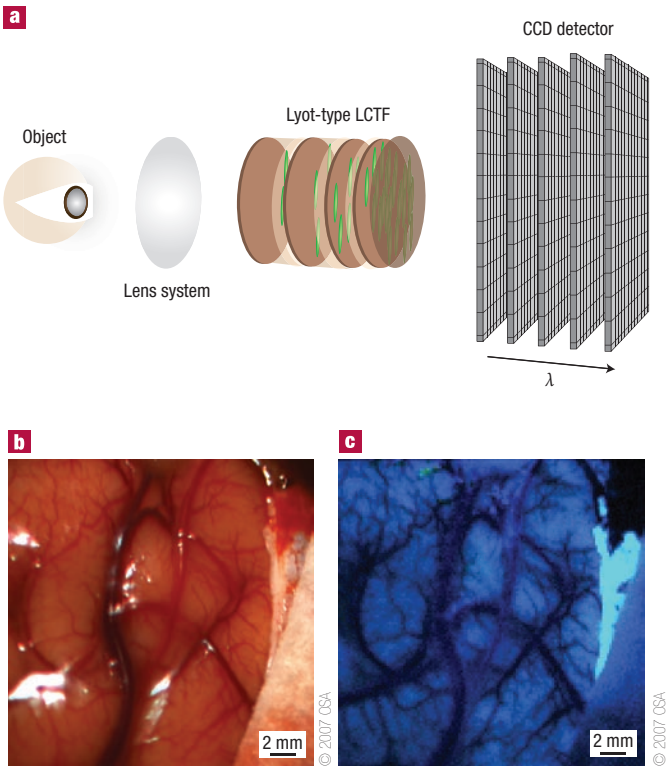

Figure 3 Hyperspectral imaging allows the generation of a complete wavelength spectrum at each pixel of an image. **a**, These devices typically use Lyot LCTFs to scan an entire wavelength region of interest, capturing each wavelength with a CCD sensor array. A single imaging system can be used to capture (**b**) diffuse reflectance and (**c**) fluorescence images of an area of tissue. Images in **b** and **c** reprinted with permission from ref. 31.

biological systems, including cell membranes, phospholipids, cholesterols, DNA and so forth, exist in liquid-crystal phases[1,2]. Critical to this area is a sound understanding of the theory and modelling of liquid-crystal materials at interfaces. Computer simulations of the molecular and mesoscopic interactions between thermotropic liquid-crystal materials and the naturally occurring amphiphilic, lyotropic liquid-crystal systems they are probing are a necessity[51]. Whereas conventional liquid-crystal electro-optic devices are confined between two solid substrates, most biosensor applications use a single solid substrate and a liquid-crystal/air or liquid-crystal/aqueous interface at which the biological specimen is applied. It is important to understand the interactions at these complicated interfaces[52]. In these systems, the 'sensing' liquid-crystal material becomes an active substrate for the biological material.

Brake *et al.* have investigated the alignment change of liquid-crystal materials with the introduction of phospholipids to a liquid-crystal/aqueous interface[53,54]. At the pure liquid-crystal/aqueous interface, the liquid-crystal molecules tend to align planar to the surface. The introduction of phospholipids induces an orientational change of the liquid-crystal material to a homeotropic alignment. Figure 4 depicts the detection of an enzymatic reaction whereby a biosensor containing an enzyme-laden liquid-crystal layer detects enzymatic activity after the introduction of a lipid-containing aqueous solution. The liquid-crystal molecules possess a homeotropic alignment at the aqueous interface before any reaction occurs (Fig. 4a). As the reaction

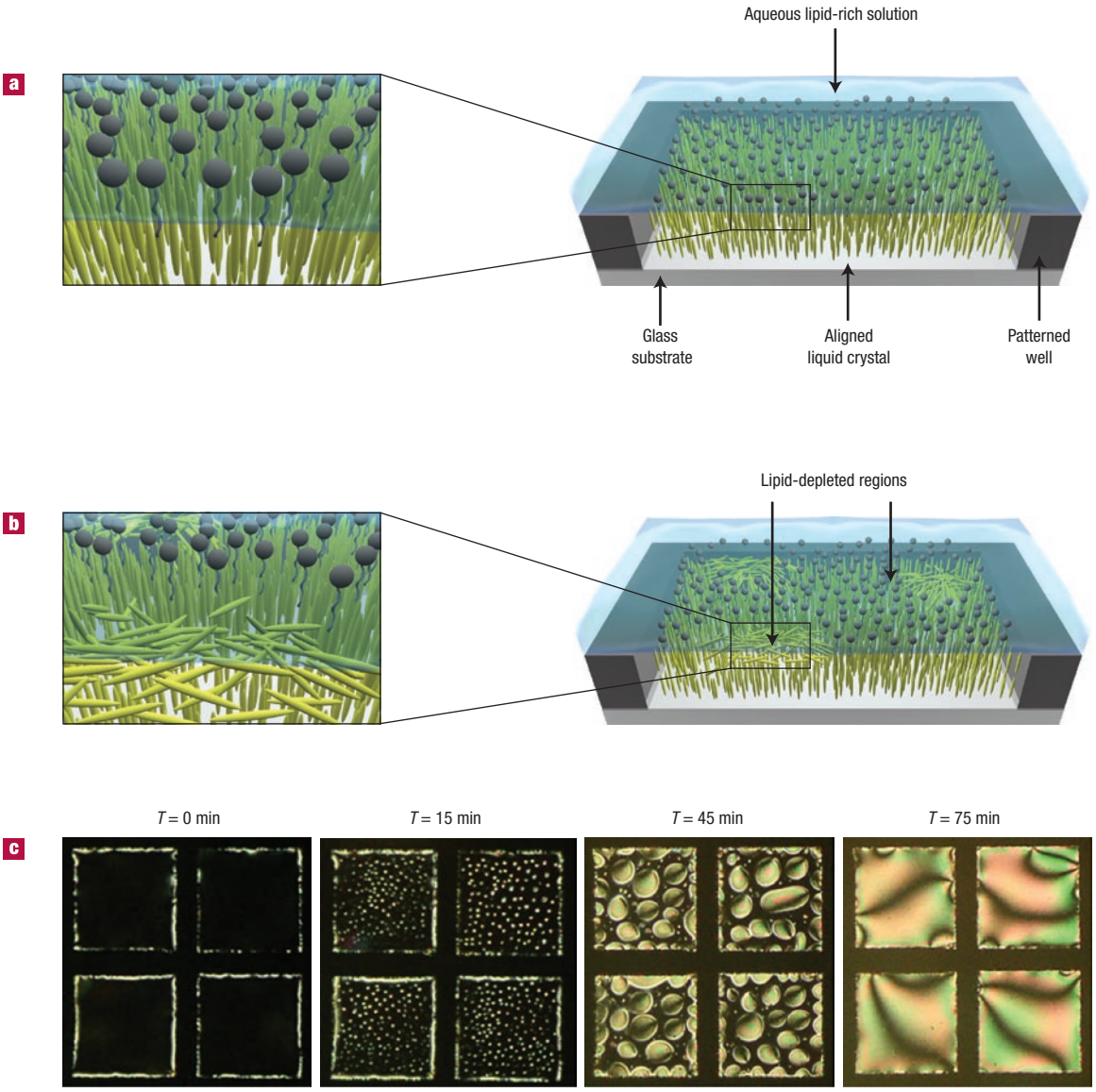

Figure 4 Liquid-crystal biosensors. **a**,**b**, A well-aligned liquid-crystal optical biosensor (**a**) undergoes a change in optical appearance after an enzymatic process removes the aligning lipid material (**b**). **c**, Optical microscopy images show the changes in the optical texture of such a biosensor undergoing an enzymatic reaction; dark regions represent homeotropic alignment, and bright regions represent a tilted or planar alignment. Each of the wells is ~283 μm wide with a depth of ~20 μm. Images in **c** courtesy of Nicholas L. Abbott, University of Wisconsin.

takes place, regions of the interface become depleted of lipids, inducing an orientational change in the liquid-crystal molecules to a planar alignment (Fig. 4b). During this transition, the optical appearance of the biosensor will change when viewed between crossed polarizers (Fig. 4c)[54].

In observing such biosensors, label-free observations of enzymatic action and molecular assemblies are made by detecting an optical change in the transmittance through a liquid-crystal material. Molecular simulations based on the visco-elastic properties of the liquid-crystal materials verify the optically observed interactions[55]. The self-assembly of surfactants and phospholipids at the liquid-crystal interface largely depends on surfactant tail length and molecular branching[56,57]. There is great scope for developing more advanced optical investigations and molecular simulations of the interactions between liquid-crystal materials and different biomolecules; the understanding of the optical appearances of these interactions can be developed for use in diagnostic tools.

Liquid-crystal materials have also been used to image protein-binding events[58,59], the immobilization of peptides[60], and enzymatic processes at a liquid-crystal/aqueous interface[61]. These processes can be initiated through microprinting techniques and the use of self-assembled monolayers. The presence of biological processes can also be investigated within bulk liquid-crystal films. Here, director distortions vary greatly in the presence of a binding event[62]. Optical detection of bacteria and viruses with liquid-crystal materials has great potential for bedside diagnostics[63,64].

Any liquid-crystal-based biosensor must be non-toxic to the cells or tissue it is being used to investigate. To that end, toxicology studies of both thermotropic and lyotropic liquid-crystal materials have been made on living cells [65,66]. Although a number of classes of liquid-crystal materials were found to be

toxic to living cells, several were non-toxic and capable of serving as a culture medium[67]. The surface alignment layer material for a liquid-crystal biosensor must also be biocompatible. Dried low-salt buffer solutions[68] and biomolecules have been investigated as alignment layers. Kim *et al.* have used the protein bovine serum albumin (BSA) immobilized on glass slides and unidirectionally rubbed to align a liquid-crystal material[69]. When the aligned film comes into contact with an anti-BSA IgG analyte, the induced alignment is lost. However, the alignment is maintained in the presence of other analyte solutions. This loss of alignment, for interactions with solutions containing specific biomolecules, offers interesting possibilities for biosensor applications. Arrays of surface treatments acting as alignment layers for liquid-crystal materials can serve as indicators for a wide range of proteins and other biomolecules; exposure of such a system to an unknown analyte solution would allow its constituent materials to be identified through the observation of the liquid-crystal alignment across the array.

Liquid-crystal materials have also been investigated as replacement solvents for gel electrophoresis[70]. The varied anchoring properties of liquid-crystal materials to particles and the complex free energy configurations of these systems generate topological defects. Although the presence of defects is detrimental to an information display application, in the case of gel electrophoresis these defects drive particle motion based on the nematohydrodynamics of the system. The delicate lowest-free-energy configurations of liquid-crystal materials also make them advantageous for directly imaging biological specimens[71]. The birefringence of the anisotropic material greatly enhances the contrast of an image of tissue or muscle as the liquid-crystal molecules align in various configurations around a sample of biomaterial.

FLATTERING NATURE: MATERIALS FOR BIOMIMICRY

Liquid-crystal materials are pushing the boundaries not just of optical and biosensing systems, but of physical systems as well, particularly in the burgeoning field of biomimicking[72]. Anisotropic liquid-crystal materials are often nearly identical to those found throughout nature; for example, the cholesteric liquid-crystal phase is found within the colour-forming structures of the Manuka beetle[73] and is formed in the spinning of spider silk[74]. Liquid-crystal materials can mimic the structural colour and tunable adaptive optics of natural systems, and can be used for innovative actuators, micro-electromechanical (MEM) and biological micro-electromechanical (bio-MEM) devices, such as artificial muscles. In the simplest forms, actuator devices can be used as sensors or to induce fluid flow; on more complex scales, liquid-crystal material actuators are envisaged as artificial muscles capable of carrying out complex tasks.

COLOUR-FORMING STRUCTURES

The natural world is rife with distinct forms of colour generated through a variety of colour-synthesis techniques. Natural colour can result from pigmentation or scattering processes, as well as complex photonic processes, similar to those found in photonic crystals[75,76]. The birefringence and sensitivities of liquid-crystal materials to external fields make them ideal as switchable and tunable photonic bandgap materials[19,77]. The H-PDLC, described earlier in the context of liquid-crystal tunable filters, represents a reflective structure capable of mimicking the brilliant structural colour found throughout nature.

Cholesteric liquid-crystal materials represent another reflective structure for colour reproduction. The presence of a cholesteric structure as the source for the iridescent colour of some species of beetles is a relatively recent discovery[73], but researchers have long been using cholesteric liquid-crystal materials as reflectors

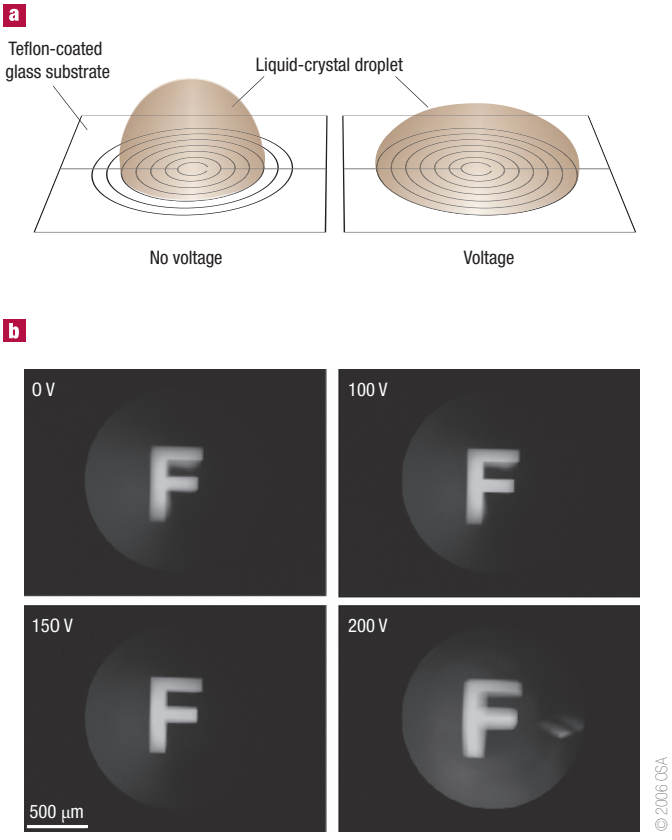

Figure 5 Liquid-crystal lenses. As shown schematically (**a**) and experimentally, looking at an object 'F' at a constant length from the lens (**b**), a liquid-crystal droplet can serve as a tunable lens through the use of a well-designed electrode pattern. Images in **b** reprinted with permission from ref. 83.

for display and filter applications. Biomimicking colour with cholesteric liquid crystals allows for added functionality given the tunable wavelength ranges over which these materials can reflect; Xianyu *et al.* have shown that an in-plane electric field will tune the reflection band of a cholesteric liquid-crystal material film over the visible and infrared regimes[78]. The bi-stability of cholesteric liquid-crystal films is also advantageous for many device applications[79]. Certain cholesteric liquid-crystal materials undergo a thermally induced helical inversion; with such structures it is possible to fabricate a polymerized cholesteric liquid-crystal film with a reflectivity greater than the 50% limit of traditional films[80]. Although cholesteric liquid-crystal materials are not advantageous for LCTFs, given their large typical bandgaps of >50 nm, these materials are well suited for mimicking naturally occurring colour structures and for innovative optical applications.

DYNAMIC LENSES

Liquid-crystal materials can also be used to reproduce the effects of naturally occurring lens systems. The concept of bio-inspired optics builds on millions of years of evolution, in which nature has adapted optical systems for a myriad of applications and environments[81,82]. A single nematic liquid-crystal droplet can act as a simple lens; the focal length of the lens is tuned with an electric field[83], as shown in Fig. 5. Additionally, innovative electrode design schemes make it possible to fabricate tunable liquid-crystal negative lenses[84]. Modelling and simulating the director profiles of liquid-crystal materials in such systems is vital to new device development.

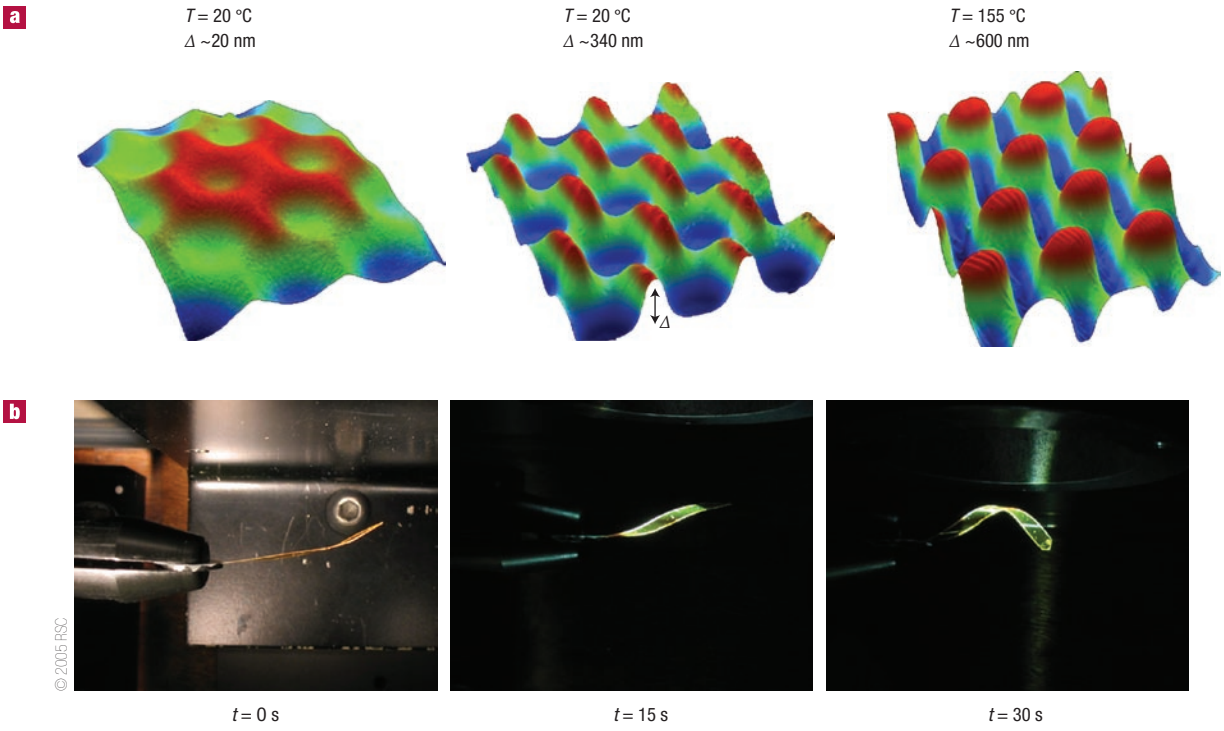

Figure 6 Patterned liquid-crystal-polymer based actuators can undergo radical shape deformations. **a**, Regions of polymerized cholesteric liquid-crystal can rise upwards amongst regions polymerized in the isotropic phase owing to differences in the thermal expansion coefficients (Δ) between the two phases. **b**, Competing surface alignments in an azobenzene-containing film will induce a helical twist with exposure to ultraviolet light. Images in **a** courtesy of Matthew E. Sousa, currently at 3M; images in **b** reprinted with permission from ref. 101.

Microlens arrays can be formed through photolithographic processes to replicate structures, similar to those of a fly's eye, in liquid-crystal and polymer systems including PDLC materials[5,6]. In the case of PDLCs, gradient refractive index lenses are produced through diffusion processes during exposure to a laser source that has passed through a photomask. Electrically tunable focal length microlenses are formed with surface relief structures in polymers using photolithography or microprinting[85,86]. With complex electrode designs, switchable Fresnel lenses incorporating polymer and liquid-crystal composite systems have been fabricated[87]. Bulk liquid-crystal lenses hold promise for the replacement of bifocal eyeglasses, with near-instantaneous switching between focal lengths for near and far vision[88]. The anisotropic nature of liquid-crystal materials could also lead to innovations in contact-lens materials[89].

LIQUID-CRYSTAL POLYMERS FOR ACTUATOR DEVICES

Liquid-crystal polymer materials, including reactive mesogens[90], elastomers[91] and nematic gels[92,93], are opening up new possibilities for MEM and bio-MEM devices. Potential applications range from microscopic gates for controlling fluid flow in microfluidic bio-chips to miniature actuators, and scaling up to artificial muscles[94,95]. Reactive mesogens form the most rigid structures and possess the highest crosslinking densities; elastomers are rubber-like in nature, making them easily deformable; nematic gels possess more fluid-like properties as they contain a weak polymer network saturated with a liquid-crystal solvent.

The simplest conformational changes in any of these materials occur as they are brought through their order–disorder transition temperature, into the isotropic state. A local reorganization of the molecular structure into a completely disordered system can result in a large macroscopic deformation of an entire film. This deformation is carefully controlled by the fabrication conditions of the film. In reactive mesogens, for instance, aligning the pre-polymerized mixture such that the surfaces of the film possess competing alignment conditions results in surfaces with different thermal expansion coefficients[96]. A splay or twist deformation within a nematic reactive mesogen film will force it to bend as it is heated up to and beyond the nematic–isotropic transition temperature. Photo-patterned structures in cholesteric reactive mesogen films have been demonstrated, and well modelled through finite-element analysis, to undergo similar shape deformations in which cholesteric 'islands' rise from an isotropic 'sea' with increases in temperature[97,98], as shown in Fig. 6a. Shape-memory effects can also be written into such materials using smectic liquid crystals, for instance[99].

The addition of dopants containing azobenzene moieties to these materials allows for photo-induced shape deformations. Finkelmann *et al.* have proposed theoretically volume deformation changes as large as 400% through optically driven effects in nematic elastomers[100]. In liquid-crystal polymers, light-induced shape changes are controlled through sample preparation. Fabricated films, with twist structures[101] or uniformly aligned nematic layers[102,103] doped with materials containing azobenzene moieties, controllably bend as the moieties photoisomerize between their *trans*- and *cis*-states in the presence of linear polarized light at specific wavelengths. Figure 6b shows the helical bending of a reactive mesogen film when exposed to ultraviolet radiation. The induced shape deformations can be erased through exposure to light of a different wavelength or polarization state, or by heating the film to the isotropic phase and allowing it to relax to its equilibrium state. Innovative applications can be derived from these effects: Camacho-Lopez *et al.* have demonstrated a

liquid-crystal elastomer film that 'swims' away from a light source while floating on water, its motions resembling those of flatfish[104].

Electric field actuation can also be induced in liquid-crystal polymers. Ferroelectric liquid-crystal polymers can show large lateral electrostriction in the presence of strong electric fields[105]. Doping liquid-crystal elastomers with carbon materials generates even larger electric field effects in these materials[106]. Making use of the conductive properties of carbon nanotubes, a field-induced torque from a low doping concentration of nanotubes in a liquid-crystal polymer induces a large uniaxial stress on the film and a shape deformation. Carbon-coating a liquid-crystal polymer film can also be used to enhance thermal actuation[107].

For more than a decade, liquid-crystal polymers have been considered for actuator and artificial muscle applications[94,112,113]. The stress–strain relationships of these materials are remarkably similar to those of real skeletal muscle[114]. Various material properties and driving methods have been investigated for liquid-crystal polymer muscles, including the thermal and electrical actuation techniques discussed above[115–117]. In the push to use such actuators as artificial muscles, many considerations must be taken into account. An artificial muscle must undergo the greatest shape change with the least amount of energy. Developing the transduction pathways to translate a neurological signal into a conformational change in the artificial muscle is perhaps the greatest hurdle to be overcome. Other applications for liquid-crystal actuators have been proposed, including micro-pumps, mixers and valves[118], as well as cantilevers for flow sensors in microfluidics. Further uses may include tactile sensors[95], inkjet heads for printers or micro-positioning devices for optical systems.

TO THE BEDSIDE AND BEYOND

As researchers continue their endeavours, we can expect both incremental advances and technological leaps. Liquid-crystal materials will help to usher in a wide range of advanced biomedical materials and devices, and to bring about changes in the medical setting. The field of liquid-crystal materials will greatly benefit from improvements in theory and modelling. The advances will take one of two paths: (1) research techniques in the laboratory will benefit from the use of devices based on liquid-crystal materials; and (2) rapid diagnostic tools based on liquid-crystal materials will greatly improve patient care at the bedside and potentially find value in the developing world, because of their portable size and inexpensive manufacturing costs.

Given the impact of liquid-crystal materials on the information display industry, it would be no understatement to declare that a similar revolution is possible for the fields of spectroscopy, imaging and microscopy. New modalities for the study of biological systems will assist in research into fundamental biological interactions and cures for diseases; medical laboratories will be provided with improved optical tools, resulting in greater throughput and precision for arrays that will no longer require adjudication by a human operator. A reduction in wait times for laboratory results will lead to more rapid screening and diagnoses and will substantially improve healthcare. Portable systems will provide developing countries with unprecedented access to medical tools and capabilities, and improve our ability to respond to domestic disasters where healthcare tends to suffer.

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