Hydrogels for Soft Machines

By *Paul Calvert**

Hydrogels have applications in surgery and drug delivery, but are never considered alongside polymers and composites as materials for mechanical design. This is because synthetic hydrogels are in general very weak. In contrast, many biological gel composites, such as cartilage, are quite strong, and function as tough, shock-absorbing structural solids. The recent development of strong hydrogels suggests that it may be possible to design new families of strong gels that would allow the design of soft biomimetic machines, which have not previously been possible.

1. Introduction

As a combination of solid and liquid components, gels differ from conventional solids in their mechanical properties and in their response to external stimuli. In particular, gels can undergo large changes in volume by exuding or absorbing water, and this in turn leads to changes in most other properties. We are familiar with gels in food, in cosmetics, and in medical creams, pastes, and ointments. Gels are also used media for electrophoresis and in a range of fillers, mastics, and paints. In most of these applications, the gel is not called upon to carry significant loads or to function as a gel for an extended time. There has been much recent research into gel applications where they may carry significant mechanical loads, such as muscle-like actuators, as components of batteries and other electrochemical devices, and as medical implants. If we can develop gels that combine good mechanical properties with responsiveness and fast diffusion, we can envision new families of gel-based machines. A recent review has discussed gel responsiveness and current applications, especially in sensors and for drug release;[1] here, I focus on how enhanced mechanical properties might lead to new applications.

The classic gel has a minor fraction, typically less than 10%, of chemically cross-linked polymer, and a major fraction of low-molecular-weight liquid, usually water. Such gels are weak and dry out quickly, so they are really only useful if encapsulated. Plasticized polymers, which are similar systems with higher polymer content and a less volatile liquid, have been widely used for structural applications in the past, but loss of plasticizer has always been a concern. In biology, many examples of structural gels can be found in the marine environment, including seaweeds and the bodies of many invertebrates, such as sea anemones. In the human body, cartilage, cornea, the dermis, and arterial walls are all fiber-reinforced gels. In these materials, the solid content is typically in the region of 50%. Although soft and not very strong, these materials are very tough, and survive the impacts of life in motion better than many hard materials in machines.

Most synthetic gels are a homogeneous, single-phase solution of a polymer network in a solvent. Plasticized polymers are also considered to be a single-phase mixture, although plasticized PVC may present some nanoscale crystal structure, which leads to improved properties. Biological gel tissues are mostly two-phase systems, with micrometer scale or nanoscale fiber reinforcement, or ordered nanoscale regions This structure is probably the source of their better properties.

Engineering materials are generally dry, and there is a reluctance to use materials that may lose liquid and dry out. However, we do work with systems that need to retain liquids, such as foods, cosmetics, paints, and inks. Our experience with houseplants suggests that it would be quite possible to develop long-lived systems that depend on occasional replenishment of a water reservoir, if there were desirable and unique properties. This survey of recent work on gels will focus on whether it is possible to reach a combination of mechanical properties, stability, and activity that would allow more use of gel devices and structures.

2. Natural Gels

Since water is a crucial component of living systems, it is also a major component of many tissues. Thus, the tissues of many marine plants, such as kelp, are polysaccharide gels reinforced with polymeric or inorganic fibers, while the gel tissues of marine animals are combinations of protein fibers and proteoglycans.[2] On land, most bodies require a rigid support structure, for instance, the external chitin skeleton of insects or the internal bone skeleton of mammals, but the remaining connective tissues are fiber-reinforced gels.

Familiar fiber-reinforced composites depend on continuous or discontinuous fibers to stiffen and strengthen a rigid polymer matrix. In general the fibers are the main load-bearing component, even at small elastic strains.[3] In contrast, many

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biological tissues show a ''J-shaped'' tensile stress–strain curve,[2] where the reinforcing fibers initially rotate, as the soft gel is stretched, and then the fibers take up the load, as they become parallel to the stress axis. Other variations occur depending on whether the fibers are bonded to a network. Unbonded fibers can flow with the gel under slow loading, but give rigidity under fast loading.[4]

Articular cartilage is a proteoglycan gel reinforced with about 20% collagen fibers. It has strength of about 1.5 MPa, and an extension to break of about 100%. The structure is layered, and the properties vary greatly with depth below the surface, with strength up to 30 MPa in layers with higher fiber contents.[2,5–8] Costal (rib) cartilage has a strength of 5–7 MPa.[9] The large extension to break and large work of fracture (1 kJ m^{-2})[10] allows cartilage to function effectively under impact, even though the average strength is not high.

An unfamiliar aspect of the mechanical properties of gels is that they tend to lose water under compression, and take up water under tension. As a result, the mechanical properties are different depending on the test speed. Thus, the fast modulus of cartilage is 2.5 MPa, while the equilibrium modulus, measured as water is displaced from the structure, is about 0.7 MPa.[2,7] The transition between these two values will depend on sample size, as the water has to flow out of the gel. Likewise, testing under water will result in properties that differ from those measured in air.

Cornea is another tissue that is reinforced with collagen fibers. As with cartilage, there is an immediate need for a synthetic substitute to replace damaged corneal tissue. Cornea contains about 20% of collagen fibers in a gel matrix. The fiber diameter is of the order of 20 nm, so that light is not scattered and the material is transparent.[11] The tensile strength is about 4 MPa, and the elastic modulus is about 6 MPa at 20% strain on the J-shaped stress–strain curve.[12]

The stipe (stem) of kelp is an alginate gel reinforced with cellulose. The elastic modulus is about 7 MPa, and strength is 3 MPa, with a breaking strain of about 40%.[13–15]

The properties of these soft tissues and marine gels suggest that a combination of a higher polymer content and fiber reinforcement should let us form materials that retain the responsive properties of gels whilst having sufficient mechanical strength to be used in engineering systems. As a target system, we could envision a synthetic gel with a tensile strength of 5 MPa and an extension to break of 100%, but we also need to develop a better understanding of the mechanical properties of gels.

3. Mechanical Properties of Simple, Single-Phase Gels

Because gels are weak, and currently do not have many synthetic applications, there is not a large co-coordinated literature on their mechanical properties. For many materials, we can consider elastic modulus and tensile strength as sufficient to characterize the mechanical properties. The first of these reflects the rigidity or degree of bending under stress, and the second the ability to withstand static stress without breaking or deforming irreversibly. For hard materials that have to withstand impacts, we are also concerned with the toughness, often measured as the energy absorbed in propagating a crack through the material. These concepts are substantially derived from the consideration of metals and ceramics where their stress–strain relationship is essentially linear up to about 1% strain and then yield or fracture occurs. They serve well in most engineering situations, where objects are designed to be rigid.

Many biological tissues operate in a different regime, where large reversible strains are present and substantial impacts can be tolerated without damage. In this case, the energy needed to produce damage may be more important than the strength. The stress–strain curve may be very nonlinear, and the shape of the curve out to large strains becomes important. The same is true for rubbery materials, but these are also not very familiar in structural engineering. Thus, engineering with gels will put us into a regime that is unfamiliar to many mechanical engineers.

3.1. Elastic Moduli

A gel can be seen as a modified rubber. The properties of amorphous polymers change dramatically above the glass transition, when the chains become mobile. Since polymer chains are mobile in solution, and we think of a simple gel as a cross-linked solution, we can regard a single-phase gel as a dilute rubber. Dense polyacrylamide, for instance, is a glassy polymer. We do not want to compare the gel properties with this state, but with the same polymer as a cross-linked rubber, above its glass transition. It has been suggested that the water content of gels is equivalent to temperature in synthetic polymers. Raising temperature in a plastic, or increasing the water content in a gel, results in lowering the modulus from glassy to plastic to rubbery regimes.[16]

Gels are soft materials, so we would expect elastic moduli to be below 10 MPa, and we would expect the modulus to decrease as the volume fraction of solvent increases. As an example, a gelatin gel swollen to five times its dry weight has a modulus of about 0.8 MPa, and a fracture stress of about 70 kPa, with an extension to break of 10%. At a swelling of 40 times, the modulus is only 40 kPa, and the strength 6 kPa, with the extension to break 11%. This soft, weak, brittle behavior is characteristic of most simple gels.

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The initial elastic modulus of a nonionic gel can be derived from rubber elasticity theory, as:

$$G = A\frac{\rho}{\overline{M}_c} RT\left(v_2^0\right)^{2/3}(v_2)^{1/3} \quad (1)$$

where A is a constant close to 1, ρ is the density, M_c is the average molecular weight between cross-links, v_2 is the volume fraction of polymer in the swollen gel, and v_2^o is the volume fraction in the gel as synthesized. Thus, swelling after synthesis decreases the modulus relative to the G_o, the modulus as synthesized.[17,18]

$$\frac{G}{G_0} = \left(\frac{v_2}{v_2^0}\right)^{1/3} = V_r^{-1/3} \quad (2)$$

Many natural gels are highly charged polyelectrolytes. It might be expected that there would be a strong difference in modulus between otherwise comparable ionic and nonionic gels. For weakly charged groups (acrylic acid), there seems to be little effect of charge on elastic properties.[19] Other studies show that charged groups increase the modulus and decrease the dependence of modulus on swelling.[20] The effect of ionic comonomers is complex, because they affect the swelling ratio and indirectly affect the cross-linking reactions. At high swelling ratios, the charged chains become highly extended, which again stiffens the gel, but this is in a regime where they are too weak for structural applications.

3.2. Measurement of Gel Strength

In determining the mechanical properties of gels, there are important factors that can often be ignored in dense materials. Gels often fracture at much higher strains than conventional engineering materials, properties can be very time dependent, and liquid may be taken up or lost during the test. Likewise, the properties of immersed gel samples differ from samples tested in air, as water is normally taken up in tension and exuded in compression. The degree of confinement and timescale of testing is also important, for the same reasons.

At high compressive strains, sample geometry will also be crucial, since friction at the platens will result in shear stresses, which put the sample effectively into hydrostatic compression where failure cannot occur. Thus, properties at high strain in compression must not be regarded as directly comparable to a true strength. This is also true in metals, but the strains are larger in gels, and compression tests are used more often on gels, since attaching samples to grips for testing in tension is quite difficult, especially as linear extension leads to lateral contraction, and the gel pulls loose from the grips. Thus, in discussing gels, it is necessary to keep a clear distinction between compressive and tensile strength.

In hard solids, fracture toughness is often measured by a crack propagation test.[21] In rubbers, a ''trouser'' tear test is often used where the sample geometry resembles a pair of trousers, where the ends of the two legs may be pulled to the left and right or to the front and back.[22] Tensile-impact tests can also be used to measure tearing energy of elastomers.[23]

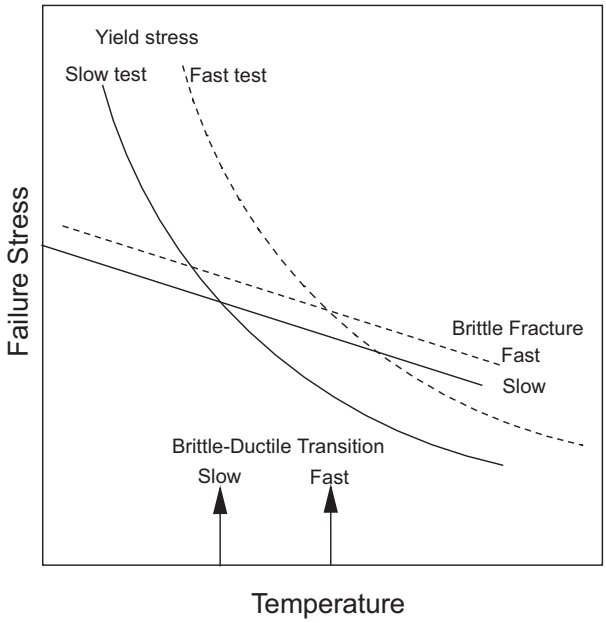

Figure 1. Schematic of the brittle to ductile transition in polymers.

3.3. Strength

Synthetic gels based on cross-linked soluble polymers are mostly too weak to be used in any structural applications. Many natural gel structures, such as those found in marine organisms, seem quite strong. As we discuss next, this difference possibly arises from the microstructure of natural gels, which most synthetic gels lack.

Conventionally, strength can be limited by two competing processes, yield and plastic deformation and brittle fracture.[24] The strength is then the stress at which the first of these processes occurs. As temperature decreases or test speed increases, the yield stress tends to increase, because it depends on significant molecular motion, and the brittle fracture, which is less affected, becomes the first to occur (Fig. 1).

Most hard amorphous polymers under tension show brittle fracture. The strength σ is determined under the Griffith equation (Eq. 1), by the fracture surface energy γ, which in turn depends mostly on the energy absorbed by the plastic deformation and void formation (crazing) that occur immediately at the tip of the crack. E is the elastic modulus and c is the crack length.

$$\sigma = \left(\frac{2\gamma E}{\pi c}\right)^{1/2} \quad (3)$$

Since elastomers are essentially liquid polymers, the elastic modulus is low, and crazing is not believed to occur. Most of the fracture energy probably goes into pulling individual chains out across the fracture, and so the energy increases with the chain length between cross-links.[21] Fracture of rubbers does not follow the Griffith theory because of the higher extensions at fracture, but the role of fracture energy in limiting crack extension still

applies. Most unreinforced elastomers lack significant energy-absorbing mechanisms, and readily tear at any cut or notch.

Based on this comparison with elastomers, we would expect the strength of unstructured gels to be lower than that of rubbers, with a similar cross-link density by factors reflecting the dilution of the gel by water or solvent, and reflecting the degree of pre-extension of the chain due to swelling by the solvent. We thus expect gels to be weak, and to get weaker as they continue to swell.

There are exceptions to the generally low strength of elastomers, where some energy-absorbing deformation can occur. One example is natural rubber, where the crystallization occurs under tension, resulting in increased stiffness at high stress, and a large energy to fracture as chains slip through the ordered crystals. Large fracture energies are also obtained when diene rubber chains slip over the surface of reinforcing carbon-black particles,[25] or through the hard regions of two-phase polyurethane elastomers. It may be possible to build similar energy-absorbing mechanisms into gels.

Theoretical discussions of gel fracture have focused on gelatin gels, which are important in food. Both fracture mechanics and fracture energy approaches have been considered, but understanding is still imperfect.[26–28]

Synthetic gels based on acrylates are unstructured, and would also be expected to be weak. Natural gels, such as agarose[29] and calcium alginates, do seem to form ordered regions of double helix or multiple helices.[30–32] As a result, the mechanical properties are very dependent on the extent of structure developed during gelation.[33] The disruption of these structures during fracture could be expected to be a source of energy absorption, and so increase strength and toughness. Agarose gels (2%) have strength of about 0.14 MPa, and a strain to failure of 40%. In contrast, the strength of similar gelatin gels is about 1 kPa.[34] It is possible that ordered structures, similar to those in agarose, exist in gels of hydrogen-bonding polymers, such as hydroxyethylmethacrylate and vinylpyrrolidone, which do seem to be stronger than less-polar synthetic gels.

One area where there has been vigorous search for improved mechanical properties is in gels for contact lenses, but there is no clear picture of what determines strength.[35,36] Contact lenses have water contents of 30–50% and strengths of 2–4 MPa.[37] Tests on vinylpyrrolidone gels with low water contents (30–40%) gave strengths up to 2 MPa, in the range of cartilage, and could therefore be considered adequate for construction of equipment.[38] On the other hand, contact lens gels made from mixed acrylic and vinylpyrrolidone monomers with 40–70% water content have strengths from 100–600 kPa.[39] There is no simple relationship between polymer structure or water content and gel strength, but gels based on vinylpyrrolidone tend to be stronger. Work on cross-linked acrylic acid gels for microfluidics showed similar strengths, with a dramatic decrease as the gel was swollen at high pH.[40] A cross-linked copolymer gel of hydrophilic and hydrophobic segments was reported to have a strength of 200–500 kPa.[41]

4. Multiphase Gels

Many gels are two-phase composite systems. Polyacrylamide gels are often quite turbid, suggesting phase separation into polymer-rich and polymer-poor regions. The cross-linked structure prevents large-scale separation, so unambiguous evidence for two phases is hard to obtain. Crystallizable synthetic polymers form solvent-containing gels, which apparently contain crystallites connected by segments of solubilized polymer chains. Similar combinations of regions of nanoscale order linked by disordered solutions probably characterize many biological gels, such as gelatin, agarose, and calcium alginate. In principle, one would expect the phase behavior of a lightly cross-linked gel to be the same as that for a high-molecular-weight sample of the same polymer in the same solvent. Heavier cross-linking would further restrict the entropy of the chains, and might induce phase separation.

The search for an artificial cartilage material has long driven the search for strong gels. Various multiphase systems that are much better than simple gels have been found, but, until recent unexpected results on ''double network'' gels, none have been strong enough to be considered promising.

It is has been known for some time that the properties of polyvinylalcohol and mixed polyacrylic acid/polyvinylalcohol gels can be enhanced by a series of freeze-thaw cycles, which drive more extensive aggregation of the polymer.[42] Exactly what happens is unclear, but growth of ice crystals will probably concentrate the polymer in the crystal boundaries, and drive formation of insoluble hydrogen-bonded complexes of the polymers.[43] Addition of dimethyl sulfoxide (DMSO) as a co-solvent enhances the gel strength, possibly by limiting ice-crystal size. Early work on two-phase freeze-thaw modified neutral gels of polyvinylalcohol mixed with cationic and anionic polymers found a strength of 1 MPa at 85% water.[44] More recently, such polyvinylalcohol gels with water contents of around 80% were found to fail in compression at a few MPa.[45] This freeze-thaw process produces a two-phase composite structure, which has recently been studied in more detail.[46,47] Composite gels with polyvinylalcohol and other water-soluble polymers have also been studied.[48]

There have been many recent studies of composite gels produced by irradiation of mixed solutions of polymers, and increases in strength have been reported, compared to single-polymer gels.[49] One would expect that the properties of these disordered systems would follow primarily the water content.

A number of studies have considered reinforcement of gels with inorganic fibers or plates, both added before gelation and grown in situ in the gel, and a significant increase in modulus is certainly seen.[50–52] With exfoliated clays as reinforcement, moduli increased from 4 to 20 kPa and tensile strengths increased from 0.1 to 0.3 MPa as the clay was added were observed.[53–56] Pre-stretching these gels resulted in subsequent moduli of up to 1 MPa, and strengths up to 3 MPa.[57] High strengths in compression have also been seen in hydrogels reinforced and chemically linked with 100 nm particles of denser gel.[58]

One very attractive approach, based on the analogy to collagen-reinforced biological gels, is to reinforce gels with fibrils of rigid-rod polymers.[59] This particular system does show a significant increase in modulus, but from very low values and no strength data were given. Thus, the full potential of composites of this type has yet to be fully explored. A simple variant of this approach is to reinforce a gel with a textile, such as nonwoven

polypropylene, but the properties of these coarsely filled structures have so far been less impressive.[60,61]

It should be noted that the aim of reinforcing an elastomer is to increase the strength and toughness without greatly increasing the stiffness. This is in contrast to engineering composites, where the reinforcing fibers lead to a great increase in stiffness. In conventional composites, successful reinforcement is usually at the scale of 10 μm fiber diameter. In elastomers and gels, examples of successful reinforcement are usually on the nanometer scale.

5. Double Network Gels

Gong et al.[62] have formed gels with compressive strengths up to 17 MPa at 90% water level, by forming an interpenetrating network of ionic and nonionic gels in a two-step process, shown in Figure 2. This compares with the strength of 0.2 MPa in compression for the equivalent single-component gel. These gels are produced by forming a moderately tightly cross-linked network, then swelling this gel in a solution of a second monomer with a low ratio of cross-linking agent, and carrying out a second polymerization. As a result of the high degree of swelling in the monomer solution, the first gel network is highly extended in the final product, while the second network is relaxed. The weight fraction of the second network in the final gel is 10–20 times that of the first network.

Other gels with a more lightly cross-linked first network show yield and necking in tension with extensions to break over $10 \times (1000\% + \text{strain})$ and a strength of 0.3 MPa.[63] Using a tear test, a fracture energy of 300 J m^{-2} was measured, compared to 0.1–1 J m^{-2} for conventional gels.[64] Yielding is characteristic of metals and semicrystalline polymers where molecular slipping sets in at high stresses. It is not normally seen in rubbers or gels, where the permanent cross-linked network prevents slippage.

While the strength was greatly increased by the addition of the second component, the initial modulus was only mildly affected when compared to a conventional gel at the same concentration. If these double gels are made with a linear polymer in place of the second network, the fracture strength and fracture energy rise steeply at a molecular weight over 10^6, where the second polymer becomes highly entangled and these entanglements can act as physical cross-links.[65] Cyclic loading tests do show hysteresis, with a loss of modulus after successive cycles to high strain. This implies that breakage or other irreversible loss of highly strained cross-links is occurring.[66]

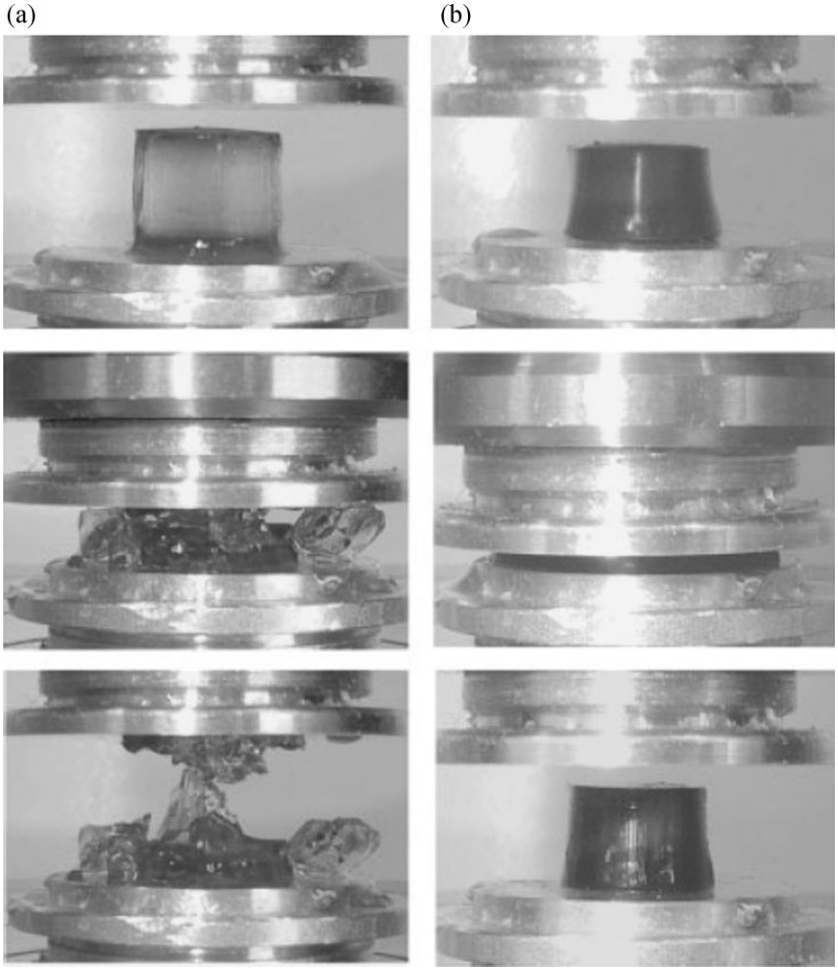

Figure 2. Compression of a a) simple gel and a b) double-network gel. Reproduced with permission from [62].

Other workers have found similar enhanced strengths in polyethyleneoxide (PEO)–polyacrylic acid (PAA) double network gels.[67,68] These gels have tensile strengths that range up to 12 MPa, depending on composition and swelling. Molecular dynamics simulations have been carried out for these PEO–PAA gels, and show that the elastic modulus rises suddenly at strains of about 100%, where the first network becomes fully stretched.[69] This combination of high stress with a large strain to break increases the fracture toughness.

Other interpenetrating networks, formed without the extension of the first network, have not shown similar improvements in strength. For instance, 2-hydroxyethylmethacrylate (HEMA)–gelatin gels reach strengths of 65 kPa, just slightly above gelatin alone,[70] and polyacrylamide/poly(*N*-isopropylacrylamide) (IPN) gels reach strengths of just 10 kPa.[71] Templating gels on a colloidal crystal and then removing the colloid has also been reported to give good toughness, although the modulus and strength remain low.[72] Reinforcing polyacrylamide gels with a rigid-chain polyelectrolyte does lead to a large increase in modulus.[59]

Porous polyethylene glycol gels were formed by templating on a colloidal crystal, which was then dissolved to leave interconnected pores.[72] Moduli of 10–20 kPa were reported, about 1/10 that of the dense gels, and many times that of disordered gels with equivalent interconnected porosities. Strength values were not reported, but the gels were described

as ''robust'', and the porous structure might certainly be expected to resist crack propagation.

5.1. Mechanism Leading to Strength of Double-Network Gels

Of the trio of mechanical properties outlined above, elastic modulus is highly predictable in terms of intermolecular forces and, in two-phase materials, simple composite models. Strength is likewise quite easy to understand in materials where molecular slippage leads to yielding. In contrast, strength in the brittle-fracture regime is very dependent on mechanisms to absorb energy, as the crack propagates through the material and new mechanisms of energy absorption are still being elucidated.

In plastics, the improvement of toughness is usually a question of adding a second phase, such as rubber particles or long fibers. Natural materials, such as bone, tendon, and mollusk shells, clearly have toughening mechanisms, but we are not sure exactly how they work. The question is how these double-network gels are toughened, and whether this can be traced to the microstructure, either in the unstretched state or in a state that develops during stretching, as occurs when natural rubber crystallizes under stress.

Three theories for the origin of the high fracture energies have been discussed, based on extensive fracture of chemical bonds at the crack tip, viscous flow at the crack tip, or on a composite model similar to that applying to hard composites toughened with rubber particles. This last theory was selected as the most promising by the Osada and coworkers.[64] This heterogeneous model has also been discussed by Okumura.[73] Brown has proposed a model resembling fibrillation at the crack tip in amorphous polymers.[74] Extensive cracks in one network are held together by chains of the other network extended across the crack.

The toughness of natural rubber (*cis*-polyisoprene) is attributable to small crystalline regions that form at high strains as the chains straighten and lose entropy, which effectively raises the crystal melting point. These crystals toughen the rubber. Even in a double network gel with chemically identical networks, there are effectively two populations of molecules with different entropies, so one could envisage microscale phase separation occurring under strain, leading to reversible reinforcement. Small-angle neutron scattering at ultralow wave-vectors was carried out at the National Institute of Standards and Technology (NIST). The data show deformation-induced structures that appear at 50% shear deformation, with a periodicity along the stress axis of 1.5 μm in the gels.[75] This implies that the gels may be single phase in the unstretched state, but undergo some kind of phase separation under stress. This two-phase structure then provides the energy absorption. This is certainly indicative of a toughening mechanism, but the key to toughness is what happens at a crack tip, and we still have no information on that. Strain-induced clustering in polyacrylic acid gels has recently been reported and may be a related effect.[76] The role of energy absorption is also shown by the increased toughness of gels with reversible cross-links.[77]

A recent paper by the same group shows that there is a close match between Flory–Huggins Chi parameters in the poly(2-acrylamido-2-methyl-1-propanesulfonic acid) (PAMPS) -polyacrylamide system.[78] Solutions of two polymers usually phase-separate driven by an unfavorable polymer–polymer interaction energy and a very low entropy of mixing. The authors suggest that these two polymers associate in the gel, and that the resulting single-phase mixture is crucial for toughness. Other evidence for phase separation comes from dynamic light scattering, which shows a slow relaxation mode that is thought to be associated with diffusional motions of the coiled chains of the second network, and may also indicate that the gel is near a single-phase to two-phase boundary.[79]

The conclusion from this is that, as Shull has recently emphasized, there is a need to develop better understanding of fracture toughness in these double-network gels and in biological gels.[80] The preceding discussion also shows that microstructure control can lead to greatly enhanced strengths and toughnesses in gels. Improvements obtained by double networks, by freeze–thaw, and by fiber reinforcement suggest that there are many possible routes to better properties. A J-shaped stress–strain curve, which is an increase in elastic modulus at high strain, seems to be one signature of better toughness and strength. In this view, cartilage is a similar cross-linked network of collagen microfibers with a second network of coiled proteoglycan chains that can absorb fracture energy. Thus, it seems we can separately control modulus and strength of networks in order to design suitable mechanical performance into any functional matrix.[81] A useful objective for future work would be to develop some design rules.

6. Properties Needed for Applications

Strong gels would be useful as multifunctional materials. Mechanical robustness can be combined with other properties such as responsiveness, biocompatibility, or actuation.

There are many potential applications for strong gels in medical devices, as will be outlined below. We can also expect that strong gels will be the basis for devices that combine their ability to change shape and respond to the chemical and physical environment with a rugged durability. In the absence of such gel machines, it is hard to define how they might be constructed, and what materials properties will be needed.

In seeking soft, durable models for gel machines of unspecified function, one might take the orange fruit as an example. They survive normal handling and will resist drying for a reasonable time. There have been studies of the mechanical properties of orange peel, which put it in the same range as the gels discussed here.[82] Thus, we can believe that soft machines are mechanically feasible, if novel functions can be developed.

6.1. Chemical Fabrication of Gels

Most materials are available in bulk form ready to be molded or cut to shape. Chemically cross-linked gels must usually be prepared in situ, so that convenience of synthesis is a big factor in the manufacturability of devices. Most of the work on synthetic gels uses gels formed by free-radical polymerization, of the families of hydrophilic acrylate, methacrylate, and acrylamide monomers, plus vinylpyrrolidone. While these methods provide a very versatile family of hydrogels, it is worth noting that the

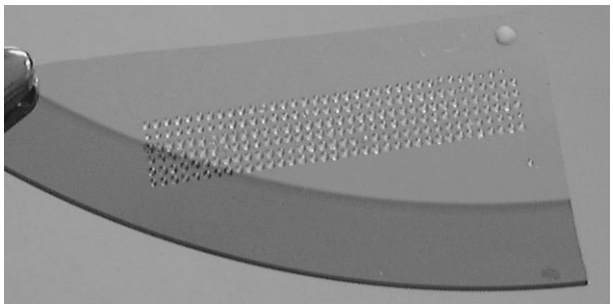

Figure 3. Dots (100 μm) of epoxy gel printed onto a platinized silicon electrode.

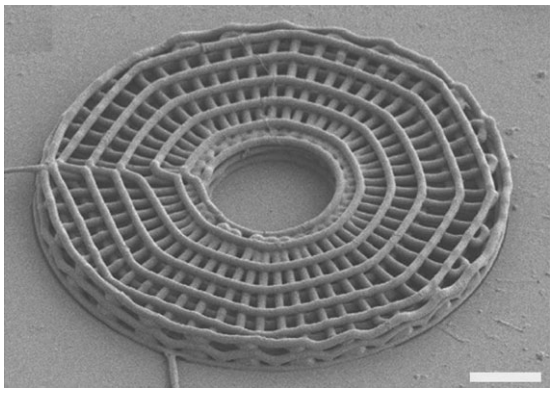

Figure 4. Printed polyelectrolyte complex filaments, written with a micrometer-sized nozzle. Scale bar = 10 μm. Reproduced with permission from [98]. Copyright 2004 Macmillan Publishers Ltd.

polymers are atactic, or otherwise irregular, and this limits formation of microstructures that might give rise to toughness.

Free-radical polymerizations have been studied in great detail for the formation of linear polymers with reproducible properties.[83] Free-radical polymerization is oxygen sensitive, and this can render good control of the gel structure difficult in small or air-exposed devices with samples of gel. Photoinitiated polymerizations are often used for thin films, and these have the additional problem that the light intensity, and so gel structure, varies through the film. Practical production of gel parts for machines will probably require other, more controlled, methods.

For these reasons, it may be valuable to explore other approaches to forming synthetic hydrogels. A recent review discusses other radical polymerization routes for gels for tissue engineering.[84] To avoid the oxygen-sensitivity problem, Yoshioka and Calvert studied epoxy hydrogels for small artificial muscles and sensors (Fig. 3).[85,86] UV-curable epoxies are well known,[83] and epoxies have also been photopolymerized with visible light,[87,88] but these methods do not seem to have been applied to epoxy gels. Water-soluble polymers and hydrogels have also been made by ring-opening metathesis polymerization.[89–92] One would also expect that it is possible to form stable hydrogels based on polyamides and other polymers formed by condensation chemistry, which might form tough microstructures.

It has long been know that many pairs of polymers self-assemble to form gels through interchain bonding. Gelled capsules can be formed by dripping a solution of cationic polymer into a solution of anionic polymer,[93,94] or by dripping alginate into calcium.[95] This process results in a thick-walled capsule with a nonuniform structure. There is no way of simply mixing the two components, so that a uniform block of material is formed. Ionic self-assembly by sequential dipping into anionic and cationic polymers,[96] or by repeated contact printing,[97] does produce uniform thin films of ionic gels in a more controlled fashion. While these systems have been shown to have many potential applications, there has been little work on the structure and properties of the gels themselves. One structural study, by Lewis and coworkers,[98] used a fine capillary to make micrometer-scale 3D structures by extruding a stream of solution into water at a pH that induced gelation (Fig. 4). Such writing systems could be used to make a wide range of gel microdevices.

Natural proteins form structures by a combination of ionic interactions, binding to multivalent cations, and hydrogen bonding. It is possible to design synthetic proteins to form similar structures[99–101] and demonstrate that they gel. Thus, there are considerable opportunities for better characterization of gelation of synthetic ionic polymers and for the study of more structured synthetic gel systems formed by other polymerization chemistries. This should lead to a better understanding of the whole structure–mechanical properties map for gels.

6.2. Transport Properties

Uses of gels for drug release or as battery electrolytes will depend on the transport properties of small molecules or ions.

6.2.1. Water and Small-Molecule Diffusion

Many potential applications of active gels, as muscles, for drug release, or as sensors, depend on their ability to respond to external influences by changing volume or shape or by taking up or releasing small molecules. If this responsiveness is not important, a range of dense elastomers can duplicate their mechanical properties, and we have no reason to employ a gel. Small molecule transport properties are thus crucial.

One would expect that diffusion coefficients of small solutes in gels should be intermediate, between that in solution and in an elastomer. The diffusion coefficients of solutes in dilute gels have been measured, and do not differ dramatically from those in solution.[102] Diffusion processes in gels can also be conveniently studied by conductivity.[45] For low levels of soluble small-molecule additives in an elastomer, the diffusion coefficient can be estimated from the properties of the polymer and the size of the molecule.[103] At the other extreme, for a highly swollen hydrogel, the diffusion of water and of soluble compounds in the water have been shown to be reduced roughly in proportion to the water content of the gel.

Diffusion of water in 5% polyacrylamide gels drops by half from that in pure water.[102] Hirose and Shibayama measured swelling and deswelling of poly(*N*-isopropylacrylamide-*co*-acrylic acid) gels, and also found diffusion coefficients from 10^{-5} to 10^{-7} $cm^2 s^{-1}$ dependent on the degree of swelling and temperature. In contact lens gels with 30–70% water, diffusion coefficients were also in the range of $2–20 \times 10^{-7}$ $cm^2 s^{-1}$.[104] An NMR study of diffusion of water in contact-lens materials

suggests a model with rapid exchange between bound and free water, with the amount of bound water increasing with the hydrophilicity of the gel.[105] The actual values obtained by short-time methods, such as NMR, are generally higher than those measured over longer experimental times, which correspond to bulk diffusion rates.[102]

6.2.2. Large-Molecule Diffusion

Many new drugs from the biotechnology industry are large molecules, for which the transport properties will depend on the relationship between the gel mesh size and molecule size. Measurements of the effect of concentration of protein on the diffusion of a large molecule, serum albumin, in agarose gels showed a coefficient of about $7 \times 10^{-7}\,cm^2\,s^{-1}$, increasing slightly with protein concentration, and dropping about 10% for every 1% increase in gel concentration, up to 2%.[106]

7. Response Time in Swelling and Shrinking

Applications of gels as actuators are generally envisaged as depending on the volume change resulting from uptake or loss of water from the network. This is fundamentally a diffusion process, but one which is coupled to changes of state of the gel itself. The rate of this process is crucial to most potential applications.

7.1. Theory

A significant difference will result when the diffusion process causes swelling or deswelling of the gel. The resulting nonuniform volume changes through the gel will result in highly non-Fickian behavior, and may also cause significant internal stresses or fracture. Shibayama and Tanaka[107] studied many of these interactions. As gel concentration changes in a single-phase gel, diffusion and solubility of a solute will change, such that the resulting changes in permeability can be quite complex. Li and Tanaka[108] distinguish between gels that undergo a continuous volume change with pH, temperature, or solvent, and those which undergo a discontinuous phase transition and pass through a two-phase region. In many systems, there will be a critical point where the behavior changes from continuous to discontinuous.

The kinetics of gel swelling can be treated as a two-step process. Solvent diffuses into the gel causing some regions to swell, and then there is an instantaneous shape change to minimize the elastic energy between the swollen and unswollen regions. For swelling involving small changes in volume in the continuous region of the phase diagram, the kinetics and dependence on the gel shape correspond to those expected for diffusion of solvent. In the two-phase region, or where there is a large volume change, the changes in diffusion coefficient and gel properties will lead to complex kinetics, which depend on the details of the initial and final gel states. As an additional complication, the swelling of gels with physical cross-links, such as hydrogen bonding in starch, has been shown to be affected by deformation prior to swelling.[109] Tanaka and coworkers[110] also pointed out that swelling of ionic gels could be much slower, due to the slow kinetics of ion exchange reducing the effective diffusion rate.

Two-phase gels will be even more complicated, and so should be a source of many complex changes in release or uptake of solutes.

7.2. Thermally Driven Changes

Changes in the chemical environment of a gel are slowed by diffusional processes, while temperature changes can be rapid, so that studies of the response of macroscopic gel samples are simpler. The *N*-isopropylacrylamide (NIPAM) gel system shows a sharp transition from a swollen to a contracted state on heating above 40 °C. The physics of this system was studied in detail by Li and Tanaka.[108] The response time of a long cylinder 1.3 mm is diameter was about 1 h, in agreement with a theory based on the coupling of the diffusion coefficient of water in the gel and the shear modulus of the gel.[111] This model works for a small volume change. On the other hand, a rapidly shrinking gel tends to form a dense skin that inhibits water loss from the interior, slowing the volume change and possibly leading to fracture of the gel under the resulting shrinkage stresses. The effect of such skin formation on deswelling kinetics has been studied by Hirose and Shibayama,[112] who showed that pure NIPAM gels form a dense layer and shrink much more slowly than weakly charged copolymers of NIPAM and acrylic acid, which retain more mobility for water in the collapsed state.

7.3. Porous Gels and Microgels

In answer to the slow response time of macroscopic gels, a number of workers have made the gels porous, so that simple diffusion only occurs over a small distance. For instance, polymerizing the gels under reduced pressure produces a macroporous gel that responds to temperature changes in a few minutes, about ten times faster than normal gels.[113] After freeze drying, this porous gel had an apparent pore size of 20 μm, although the actual structure prior to drying was not studied. Viewed as an actuator, these porous systems have the disadvantage that the forces developed will also be reduced as the porosity increases. Polymerizing gels in the presence of polyethyleneoxide also yields porous, fast-responding gels,[114] as does polymerization of gels on micrometer-scale liquid templates.[115]

A related approach to increasing response time is to prepare a two-phase gel, so that a nonresponsive matrix can allow fluid flow into and out of the gel. This has been shown for solutions of linear NIPAM as a block or graft copolymer with polyethyleneoxide.[116] The collapsed, precipitated state of the graft copolymer is more open than pure NIPAM, and so allows more rapid water penetration and redissolution when the temperature is decreased.

Thin layers of photo-cross-linked gel deposited on silicon do show very rapid swelling responses, corresponding to short diffusion distances.[117] Similar changes can also be seen for small particles deposited on surfaces or suspended in liquid.[118–120] Similarly, plant-derived forisomes a few micro-

meters in diameter shrink in response to increased calcium concentration in less than 1/10 s.[121]

7.4. Drying Time

Drying time is also clearly an issue in gel devices. The evaporation rate of water is very dependent on temperature, humidity, and air flow, but measurements on drying of snails give a rate of about 100 $\mu m\,h^{-1}$ as typical for still air, with an active snail being able to reduce this by about 20-fold, by maintaining a surface coating.[122] If some similar mechanism were available to gel devices with a size of about 1 cm, they would experience 10% water loss in a week, and so would only need occasional rehydration.

7.4.1. Swelling Pressure as an Actuator

One major potential application of hydrogels is as a muscle-like actuator. To act like a muscle, an actuator needs a fast response time and an active strain of 10–50%. It must develop a reasonable force in contraction, and be strong enough to carry these loads in the ''off'' state. Strong gels fill this last criterion, and the force developed can be estimated. For this purpose, we can envisage a gel immersed in fluid and loaded in tension, like muscle, or as a cylinder loaded in compression with surrounding fluid, to work like a jack.

Swelling pressure is a measure of what mechanical force can be delivered by a swelling gel.[19] We can follow the approach of Li and Tanaka[108] and envisage swelling to equilibrium followed by elastic compression under the applied load. For a 10% linear strain from equilibrium with a gel modulus of 1 MPa, a force of 100 kPa is obtained, about 1/3 the peak force of muscle. Ionic gels show higher swelling pressures than neutral gels under conditions where they are charged.[20] The chemical changes causing the volume change can both cause volume and stiffness changes, such that the results of combining pH changes and applied force can be unexpected.[123] This coupling between swelling thermodynamics and mechanical stress leads to a number of other peculiar phenomena, such as negative Poisson's ratios,[124–126] and to strange responses to bending and other complex loads.

In practice, electrically driven gels provide a large strain, but little force and a very slow response.[127,128] Shiga et al. carried out an extensive series of studies on poly(vinyl alcohol) gel actuators driven by electrical and solvent activation.[42,129–134] Even with small forces, gels can be used to transport ''cargo'' as they expand and contract in a tube.[135] The response of a gel in an electrical field is a coupling of electrical, chemical, and mechanical effects. Each separate effect is quite well known and simple, but the combined response can be complicated. Computational models have been developed that agree well with experiment.[136,137]

Chemically driven gels can develop higher stresses, as they are moved from strong acids to strong bases, for instance, but these are inconvenient to build into devices. Forisomes, plant proteins responsible for opening and closing of leaf pores, produce a force of 11 kPa in response to calcium and pH.[121] Suitably stiff synthetic gels can also develop higher forces in response to chemical activation.[138,192] The implication is that energy sources other than simple electrochemical effects will be needed to produce a muscle-like actuator.

7.4.2. Friction and Lubrication

A major target for strong gels has long been an implantable cartilage substitute. One important aspect of the performance of cartilage is the very low friction of articular joints,[139] which is attributed to a lubricating layer of synovial fluid expressed from the cartilage under compressive load. As a result, there is much interest in preparing artificial gels that show similar self-lubrication. Clearly, this effect could be utilized also in machines.

Osada and coworkers[140] prepared double-network gels with an added linear polymer to provide a weeping lubricating layer, and obtained friction coefficients below 10^{-4}. The coefficient of cartilage is difficult to measure under conditions that simulate its natural state, but values of 0.002 have been reported.[141] Freeze–thaw poly(vinyl alcohol) gels have been reported to have friction coefficients down to 0.02.[142] A recent study of implanted specimens of double-network gel shows them to be biocompatible.[143]

7.4.3. Electrical Conduction

Electronically conducting gels of conducting polyoctylthiophene in chloroform have been reported.[144] This is a very interesting observation, because one might expect that the flexibility of chains in solution would eliminate the long, planar conjugated sequences necessary to stabilize charged defects on the chains, and the longer spacing between chains would be expected to eliminate interchain hopping.

Conducting composites of hydrogels and carbon, polypyrrole, or polyaniline have been prepared by various methods.[85,145,146]

While electronics depends on electron conduction in solids, ionic conductivity is key to electrochemical devices such as batteries and fuels cells, and proton conduction is important in many biological processes. Nafion and similar sulfonated fluoropolymers are essentially two-phase proton-conducting gels. Proton conductivities of $5 \times 10^{-3}\,S\,cm^{-1}$ have been demonstrated in gels of polymer in acidified polar solvents.[147] In more dilute gels, conductivities of $1\,S\,cm^{-1}$ have been achieved. At these conductivities, ionic gels are comparable to electron-conducting composites, and could be used as conductors in devices.

8. Potential Applications

Many applications of current hydrogels in biomedical devices were reviewed previously.[1] The availability of dramatically stronger gels would be expected to give rise to a much wider range of applications. Since new materials usually lead to new applications, the applications for strong gels are a matter of speculation. This short survey points out where new applications may arise from new properties.

8.1. Drug-Delivery Systems

Polymers play a role in controlling drug delivery in the form of tablets, capsules, transdermal patches, and subcutaneous depots.

Strong gels may at least be expected to change the design and use of capsules and patches. In addition, protein drugs are liable to be hydrolyzed during oral delivery, and present too-high molecular weights to diffuse through polymers, but should be deliverable from implanted gels or transdermal patches. Uses of hydrogels in drug delivery have recently been reviewed.[148] Here, the focus is on how enhanced mechanical properties might extend these applications.

Gel capsules are widely used for drug delivery. They are most commonly made from gelatin, and can be coated for release at acid pH in the stomach, or a neutral pH in the intestine.[149] Concerns about possible contamination of gelatin with prions have led to a search for strong gels based on starch or other degradable polymers. Hard gelatin capsules are usually filled with powders or microbeads, while soft gelatin capsules are usually filled with solutions of drug in an oil.[150] The drug is released when the capsule ruptures. Soft capsules have strengths of less than 1 MPa, which can be reduced by swelling with the contents,[151] while hard gelatin has a strength of about 20 MPa.[152] There is interest in replacing gelatin with starch or other biodegradable polymers, but matching the strength and swelling properties of gelatin has been a barrier.[152,153]

There is much interest in developing transdermal drug delivery as an alternative to oral routes. These have potential for greater control of the dosage and for the delivery of proteins and peptides. The patch might be applied to the skin or to a mucus membrane, such as inside the mouth. A patch would at least comprise a backing layer, a drug depot layer, and an adhesive. Hydrophobic drugs with low molecular weight transfer best through the skin, and surfactants may be added to increase the skin permeability.[154]

Hydrogels have been used to deliver anesthetics in wound dressings.[155] The preparation and properties of hydrogels for iontophoretic (electrically driven) transdermal delivery have been reviewed.[156] Bond strength is an important factor in transdermal patches, and high strength freeze–thawed poly(vinyl alcohol) gels have been tested.[157,158] Optimization of a polyacrylic acid-HEMA gel for bond strength has also been reported.[159] In both these reports, bond strength (tack) was about 0.1 N mm^{-1}. A number of specifically mucoadhesive formulations have been developed, with adhesion based on ionic or hydrogen bonds and thiolated polymers, which might be expected to form chemical bonds to skin.[160]

Implanted polymeric depots have been used for controlled drug delivery, such as the Norplant contraceptive system,[161] but most such systems are now injectable suspensions of microspheres, which form the depot in situ. Hydrogels may also be used for implantable long-term drug-delivery devices. In this case, the mechanical strength of the gel may be important. In one example, a hydrogel matrix was filled with biodegradable drug-loaded microspheres. After an initial spike, the drug was released over about 60 days, with zero-order kinetics.[162] Unexpectedly, the rate of release from the composite gel was greater than from the microspheres alone. Hydrogels for protein drug release can be injected and polymerized in situ.[163]

While there are good oral administration routes for most small-molecule drugs, peptides and proteins are normally given by injection. The prime example is insulin, where an alternative to injection would be a major benefit to diabetics. Transdermal and other routes for insulin delivery have been reviewed.[160] Hydrogels are a promising matrix material, because diffusion of large molecules is fast and controllable, and gel chemistry can be benign so that proteins are not hydrolyzed or denatured. Hydrogels also allow many specific release strategies, such as composites with drug-loaded polymer particles, drugs bound to the gel by a hydrolysable linkage, multilayer structures, ''smart'' environmentally responsive gels, and degradable gels.[148] The rate of release of a protein, such as the growth factor transforming growth factor (TGF)-Beta in a microsphere-hydrogel composite, depends on the degree of cross-linking of the gel.[164,165] Other growth factors have also been incorporated into gels.[166]

Hydrogels can also be used as carriers for cells for 3D tissue engineering.[1] Photopolymerization with gentle chemistry or self-assembly can be used to entrap cells in gels.[84,167]

Tissue growth is also very sensitive to mechanical stimuli, and it may be that hydrogels allow better control of these stimuli, because they match the elastic properties of tissue.[166] Body movement may produce large stresses at the interface between a hard implant and soft tissue, resulting in cell damage or unwanted mechanical signals. In the long term, it may also be possible to use gel muscles to provide mechanical stimuli.

8.2. Actuators and Artificial Muscles

There are many potential applications for artificial muscles, but the fact that there are currently no effective materials means that most of these applications are now just design concepts. A muscle needs to be mechanically strong to carry a useful load, and the strong gels are a significant advance that may lead to new muscle-like materials. One region where more immediate application seems likely is in valves for the delivery of small amounts of liquids, where electromechanical systems tend to be clumsy and unreliable.[168–170]

Most gel systems bend in an electric field, because the two sides of the gel respond differently to the positive and negative potentials. The actual response mechanisms depend on whether the electrodes are embedded in the gel or are in the fluid.[171,193] As shown in Figure 5, it is possible to form gels that respond to a field by linear contraction, if the composition also varies through the gel so that, for instance, one side shrinks at negative potentials while the other side shrinks at positive potentials. It may be that some composite gel materials will show responses to external fields other than the ionization-induced swelling, which has been widely studied. Moschou et al.[172] reported fast bending responses for carbon-filled gel bars about 0.5 mm thick. The

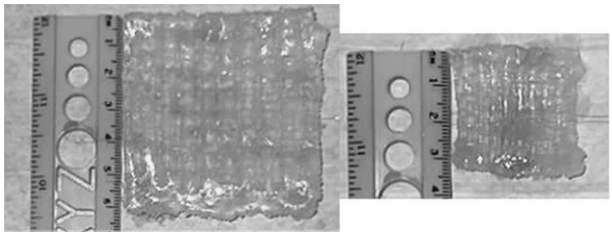

Figure 5. Multilayer, electrically driven gel actuator in the swollen and shrunk states. Note that the large volume change pulls on the embedded wires. Reproduced with permission from [190].

response time of the gel in liquid between unattached electrodes separated by about 1 cm was about 5 s.

A measure of the possible efficacy of gels as actuators or transducers are the mechanical energy density and the power density: the rate at which energy can be delivered by solvent-induced contraction. Gels have achieved 135 J kg^{-1} and 2 W kg^{-1}, which compares to 70 J kg^{-1} and 100–200 W kg^{-1} for muscle, which is in turn similar to the energy storage density of a lithium battery.[173] Thus, gels could be effective actuators if they could be structured on a fine scale, so as to give a more rapid response. There may be special applications in micromachines, but artificial muscles would need to be assemblies of many small actuators.

One answer to a muscle-like actuator would be to reconstitute natural actin–myosin complexes in vitro. Many workers have shown that the complex will respond with relative motion of the chains in the presence of adenosine triphosphate (ATP), but only for complexes on the microscopic scale.[174,175]

8.3. Sensors

There are many applications for gels as thin matrix layers on sensors, but these are normally supported by a stiff substrate, and do not require physical strength. There are also many prototype gel-based sensors for a wide range of chemical and physical stimuli, where the volume change or shape change of the gel itself is detected.[176–178] In general, these have yet not found applications, except in specialized laboratory and medical systems, where strength is not yet a major issue.

Gels containing conducting particles at a volume fraction close to the percolation threshold can also show a large change in resistivity in response to temperature, chemical change, or mechanical force (Fig. 6).[85] The conductivity of gold-particle filled NIPAM gels increases when the gel is heated through the lower critical solution temperature (LCST) and shrinks.[179]

Sensors for continuous use in vivo or in natural environments are prone to biofouling. Hydrogels present a hydrophilic and liquid-like surface, and so are less prone to protein or cell attachment. Hydrogel coatings have been explored for implanted glucose sensors, which otherwise lose sensitivity as dense deposits build up on the surface. The gels can be modified to slowly release drugs, which also slows the fouling process.[180] Hydrogel coatings with slow release of antifoulants can also be used to protect marine sensors from adhesion of bacterial biofilms or barnacles.[181] In such cases, where the gel will ideally protect the sensor for an extended time, the mechanical performance of the gel would be important.

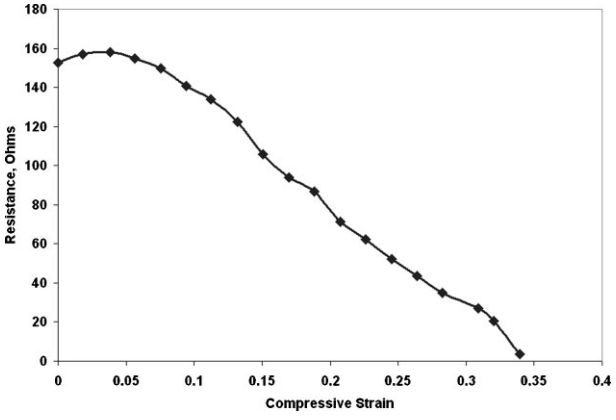

Figure 6. Resistance decrease under compression of a strain-sensing epoxy gel-carbon composite. Reproduced with permission from the author [191].

8.4. Biomedical Materials

The need for prosthetic corneas and cartilage has already been mentioned. In general, there has been great success in making implantable prosthetics to replace hard tissues, but producing materials that work in conjunction with soft tissues has proved more difficult. This may be partially due to inflammatory reactions following the adsorption of proteins and cells to the hydrophobic surfaces of synthetic polymers. Another reason is cell damage at interfaces where there is an elastic-modulus mismatch, and so large shear forces cause the tissues to deform. Other problems may arise from dense materials interfering with the flow of metabolites and cytokines through tissues. Soft, wet gel materials may prove much more biocompatible when implanted in soft tissue.

Hydrogel wound dressings are widely used to keep the wound moist but protected. Hydrogels have been used as an alternative to silicone in plastic surgery, such as rhinoplasty.[182] They may be used as solid materials, or in injectable form with gelation in situ. Prosthetic materials should ideally match the elastic properties of the tissue they replace, but should be stronger than the natural material, because the replacement will leave local damage. For cartilage, this would require a gel strength greater than 10 MPa, and preferably greater than 20 MPa.[5] For cornea, the target strength would be about 10 MPa.[12] These numbers are challenging even for the double-network gels.

8.5. Conductors

The growing interest in soft electronics, and particularly in "smart textiles", has emphasized the difficulty in making electrical connections between rigid electronic packages and flexible conducting fabrics. There is a need for soft, strong conductors based on conducting materials embedded in elastomers or gels.

Strain gauges based on conductive rubber composites have often been described, but are not yet widely used.[183,184] Strong gels could also fulfill this role.

8.6. Photoresponsive Gels

Color changes for camouflage in cuttlefish or mood expression in chameleons suggest that gels can be used to control light. A colloidal crystal contains an ordered array of sub-micrometer particles, which will diffract light at an angle that depends on the spacing of the particles, following Bragg's law. If the array is in a gel matrix, any volume change by the matrix will change the particle spacing and the diffraction angle, and so can be used as the basis of an optical sensor. Many groups have studied this effect since the original work by Holtz and Asher.[176,177,185]

Marder and coworkers developed a hydrogel that responds to UV irradiation with a keto to enol tautomerism, which results in mechanical deflection of a cantilever.[186] A thermal light modulator has been produced by embedding colored particles of a NIPAM gel in a second gel, so that the particles expand on cooling, to block light transmission.[187] Beebe and coworkers have produced gels containing gold nanoparticles that respond by swelling on absorption of selected wavelengths of light.[188]

With the availability of powerful light-emitting devices (LEDs) and solid-state lasers, light seems an excellent way of communicating with gels, in order to drive actuators or read out from sensors. Current results look promising, but do not show the fast or powerful responses that would be desirable.

8.7. Cosmetic and Food Applications

Gels are widely used in the cosmetic and food industries. Mechanical properties are not usually considered to be of first importance, but do have a major effect on the texture of foods. There are also cases where controlled-delivery approaches are used for flavors or fragrances in foods, and strong gels may have some advantages. As in biomedical applications, the particular advantage would seem to lie in the use of strong gels for release of large molecules that are incompatible with or immobile in polymers.

Other cosmetic applications, such as skin creams and hair sprays, might be feasible with strong gels, which were impractical with weaker gel materials.

8.8. Seals and Gaskets

Rubbers find many synthetic uses as seals and gaskets. Strong hydrogels could replace rubber in aqueous environments. Water will tend to be extruded from the gel if it has no impermeable skin, so it might not function well under continuous high load. Addition of a thin impermeable skin, in the form of a bonded polymer film, would control water loss due to evaporation or syneresis under pressure. The fact that a gel can swell to fill any gaps may be a great advantage in some sealing applications.

The transfer of water within gels gives them highly viscoelastic behavior at low speeds, which might find wide use in damping of vibration. In rubber, there is no equivalent mechanism for internal mass transport and low-speed damping.

9. Conclusions and Future Directions

Recent advances in preparation of strong gels suggest that there should be many useful gel materials that have yet to be synthesized. These could be the basis for engineering a range of new soft, wet machines and devices. For this, we need a much-improved understanding of the strength, toughness, fatigue, and creep behavior of gels. A further challenge is to deal with the design of a machine incorporating wet components. This raises questions of encapsulation, sealing, and reservoirs, which have not been part of conventional mechanical engineering. One particular materials challenge will be to develop thin, strong membranes bonded to the gel surface, to prevent fluid loss without significantly increasing the stiffness of the structure.

These new materials should certainly find applications as biomedical materials. There is also a great and unfulfilled need for artificial muscles. Applications in the delivery of drugs, perfumes, and other active molecules in fluidics, damping, lubrication, and sensing are also possible. We have a long history of developing new materials and completely misjudging the potential applications,[189] so it is not clear which of the possible applications outlined above will actually be fulfilled.

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[1] N. A. Peppas, J. Z. Hilt, A. Khademhosseini, R. Langer, *Adv. Mater.* **2006**, *18*, 1345.
[2] S. A. Wainwright, W. D. Biggs, J. D. Currey, J. M. Gosline, *Mechanical Design in Organisms*, Princeton University Press, Princeton, NY **1986**.
[3] D. Hull, T. W. Clyne, *An Introduction to Composite Materials*, 2nd ed, Cambridge University Press, Cambridge **1996**.
[4] J. Gosline, *Am. Zool.* **1969**, *9*, 1115.
[5] V. Roth, V. Mow, *J Bone Joint Surg. Am.* **1980**, *62*, 1102.
[6] V. C. Mow, D. S. Howell, J. A. Buckwalter, in *Cartilage Changes in Osteoarthritis*, (Ed: K. D. Brandt), Indiana University Press, Bloomington, IN **1990**, pp. 22–42.
[7] R. F. Ker, *J. Exp. Biol.* **1999**, *202*, 3315.
[8] G. Bellucci, B. B. Seedhom, *Rheumatology* **2001**, *40*, 1337.
[9] B-y. Guo, D-h. Liao, X-y. Li, Y-j. Zeng, Q-h. Yang, *Clin. Biomech.* **2007**, *22*, 292.
[10] N. K. Simha, C. S. Carlson, J. L. Lewis, *J. Mater. Sci. Mater. Med.* **2003**, *14*, 631.
[11] K. M. Meek, D. W. Leonard, *Biophys. J.* **1993**, *64*, 273.
[12] Y. Zeng, J. Yang, K. Huang, Z. Lee, X. Lee, *J. Biomech.* **2001**, *34*, 533.
[13] B. D. Utter, M. W. Denny, *J. Exp. Biol.* **1996**, *199*, 2645.
[14] M. A. R. Koehl, S. A. Wainwright, *Limnol. Oceanogr.* **1977**, *22*, 1067.
[15] D. L. Harder, C. L. Hurd, T. Speck, *Am. J. Botany* **2006**, *93*, 1426.
[16] I. V. Yannas, *J. Macromol. Sci. Rev.* **1972**, *C7*, 49B.
[17] O. Okay, S. Durmaz, *Polymer* **2002**, *43*, 1215.
[18] M. B. Huglin, M. M. A.-M. Rehab, *Polymer* **1987**, *28*, 2200.
[19] S. A. Dubrovskii, *Polym. Gels Netw.* **1996**, *4*, 467.
[20] F. Horkay, M.-H. Han, I. S. Han, I.-S. Bang, J. J. Magda, *Polymer* **2006**, *47*, 7335.
[21] A. Kinloch, R. Young, *Fracture Behavior of Polymers*, Applied Science Publishers, London **1983**.
[22] K. Tsunoda, J. J. C. Busfield, C. K. L. Davies, A. G. Thomas, *J. Mater. Sci.* **2000**, *35*, 5187.
[23] K. Reincke, W. Grellmann, R. Lach, G. Heinrich, *Macromol. Mater. Eng.* **2003**, *288*, 181.
[24] I. M. Ward, *Mechanical Properties of Solid Polymers*, 2nd ed., Wiley, Chichester **1983**.
[25] G. Hamed, *Rubber Chem. Tech.* **2000**, *73*, 524.
[26] T. vanVliet, P. Walstra, *Faraday Discuss.* **1995**, *101*, 359.
[27] A. Clark, S. Ross-Murphy, *Adv. Polym. Sci.* **1987**, *83*, 57.
[28] A. Bot, I. A. van Amerongen, R. D. Grot, N. L. Hoekstra, W. G. M. Agterof, *Polym. Gels Netw.* **1996**, *4*, 189.
[29] J.-M. Guenet, C. Rochas, *Macromol. Symp.* **2006**, *242*, 65.
[30] E. R. Morris, D. A. Rees, G. Young, *Carbohydr. Res.* **1982**, *108*, 181.
[31] D. Rees, *Pure Appl. Chem.* **1981**, *53*, 1.
[32] R. E. Webber, K. R. Shull, *Macromolecules* **2004**, *37*, 6153.

[33] P. Aymard, D. R. Martin, K. Plucknett, T. J. Foster, A. H. Clark, I. T. Norton, *Biopolymers* **2001**, *59*, 131.
[34] H. McEvoy, S. B. Ross-Murphy, A. H. Clark, *Polymer* **1985**, *26*, 1483.
[35] N. Peppas, W. Yang, *Contact Intraocul. Lens Med. J.* **1981**, *7*, 300.
[36] B. Tighe, *Br. Polym. J.* **1976**, *8*, 71.
[37] J. Stammen, S. Williams, D. Ku, R. Guldberg, *Biomaterials* **2001**, *22*, 799.
[38] O. Guven, M. Sen, *Polymer* **1991**, *32*, 2491.
[39] I. Tranoudis, N. Efron, *Contact Lens Anterior Eye* **2004**, *27*, 177.
[40] B. D. Johnson, D. J. Beebe, W. C. Crone, *Mater. Sci. Eng. C* **2004**, *24*, 575.
[41] I. Isayeva, A. Gent, J. Kennedy, *J. Polym. Sci. Polym. Chem.* **2002**, *40*, 2075.
[42] T. Shiga, Y. Hirose, A. Okada, T. Kurauchi, *J. Appl. Polym. Sci.* **1993**, *47*, 113.
[43] M. J. D. Nugent, C. L. Higginbotham, *J. Mater. Sci.* **2006**, *41*, 2393.
[44] M. Suzuki, in *Polymer Gels*, (Ed: D. deRossi), Plenum, New York **1991**, pp. 221–236.
[45] N. Sheppard, M. Lesho, R. Tucker, S. SalehiHad, *J. Biomater. Sci,Polym. Ed.* **1997**, *8*, 349.
[46] K. Matsumura, S. Hyon, M. Oka, K. Ushio, S. Tsutsumi, *Kobunshi Ronbunshu* **1998**, *55*, 786.
[47] Y. Shapiro, *J. Colloid Interface Sci.* **1999**, *212*, 453.
[48] Y. Nho, K. Park, *J. Appl. Polym. Sci.* **2002**, *85*, 1787.
[49] L. Relleve, F. Yoshii, A. dela Rosa, T. Kume, *Angew. Makromol. Chem.* **1999**, *273*, 63EP.
[50] D. Gao, R. Heimann, M. Williams, L. Wardhaugh, M. Muhammad, *J. Mater. Sci.* **1999**, *34*, 1543.
[51] X. Xia, J. Yih, N. D'Souza, Z. Hu, *Polymer* **2003**, *44*, 3389.
[52] I. Yamaguchi, S. Itoh, M. Suzuki, A. Osaka, J. Tanaka, *Biomaterials* **2003**, *24*, 3285.
[53] M. Zhu, Y. Liu, B. Sun, W. Zhang, X. Liu, H. Yu, Y. Zhang, D. Kuckling, H.-J. P. Adler, *Macromol. Rapid Commun.* **2006**, *27*, 1023.
[54] W. Zhang, Y. Liu, M. Zhu, Y. Zhang, X. Liu, H. Yu, Y. Jiang, Y. Chen, D. Kuckling, H.-J. P. Adler, *J. Polym. Sci. Part A Polym. Chem.* **2006**, *44*, 6640.
[55] K. Haraguchi, L. Song, *Macromolecules* **2007**, *40*, 5526.
[56] A. Okada, A. Usuki, *Macromol. Mater. Eng.* **2006**, *291*, 1449.
[57] K. Haraguchi, H.-J. Li, *Macromolecules* **2006**, *39*, 1898.
[58] T. Huan, H. Xu, Jiao, K. Zhu, L. Brown, H. R. Wang, H. *Adv. Mater.* **2007**, *19*, 1622.
[59] O. Philippova, R. Rulkens, B. Kovtunenko, S. Abramchuk, A. Khokhlov, G. Wegner, *Macromolecules* **1998**, *31*, 1168.
[60] M. Wu, B. Bao, J. Chen, Y. Xu, S. Zhao, Z. Ma, *Radiat. Phys. Chem.* **1999**, *56*, 341.
[61] L. Lopergolo, A. Lugao, L. Catalaini, *J. Appl. Polym. Sci.* **2002**, *86*, 662.
[62] J. P. Gong, Y. Katsuyama, T. Kurokawa, Y. Osada, *Adv. Mater.* **2003**, *15*, 1155.
[63] Y.-H. Na, Y. Tanaka, Y. Kawauchi, H. Furukawa, T. Sumiyoshi, J. P. Gong, Y. Osada, *Macromolecules* **2006**, *39*, 4641.
[64] Y. Tanaka, R. Kuwabara, Y.-H. Na, T. Kurokawa, J. P. Gong, Y. Osada, *J. Phys. Chem. B* **2005**, *109*, 11559.
[65] H. Tsukeshiba, M. Huang, Y.-H. Na, T. Kurokawa, R. Kuwabara, Y. Tanaka, H. Furukawa, Y. Osada, J. P. Gong, *J. Phys. Chem. B* **2005**, *109*.
[66] R. E. Webber, C. Creton, H. R. Brown, J. P. Gong, *Macromolecules* **2007**, *40*, 2919.
[67] D. Myung, W. Koh, J. Ko, J. Noolandi, M. Carrasco, A. Smith, C. Frank, C. Ta, *Invest. Ophthalmol. Vis. Sci.* **2005**, *46*, 5003.
[68] D. Myung, W. Koh, J. Ko, Y. Hu, M. Carrasco, J. Noolandi, C. N. Ta, C. W. Frank, *Polymer* **2007**, *48*, 5376.
[69] S. S. Jang, A. William, I. Goddard, M. Yashar, S. Kalani, *J. Phys. Chem. B* **2007**, *111*, 1729.
[70] M. Santin, S. J. Huang, S. Iannace, S. L. Ambrosio, L. Nicolais, G. Peluso, *Biomaterials* **1996**, *17*, 1459.
[71] J. Djonlagic, Z. S. Petrovic, *J. Polym. Sci. Part B Polym. Phys.* **2004**, *42*, 3987.
[72] A. Stachowiak, A. Bershteyn, E. Tzatzalos, D. Irvine, *Adv. Mater.* **2005**, *17*, 399.
[73] K. Okumura, *Europhys. Lett.* **2004**, *67*, 470.
[74] H. R. Brown, *Macromolecules* **2007**, *40*, 3815.
[75] T. Tominaga, V. R. Tirumala, E. K. Lin, J. P. Gong, H. Furukawa, Y. Osada, W-l. Wu, *Polymer* **2007**, *48*, 7449.
[76] G. Miquelard-Garnier, C. Creton, D. Hourdet, *Soft Matter* **2008**, *4*, 1011.
[77] A. M. Kushner, V. Gabuchian, E. G. Johnson, Z. Guan, *J. Am. Chem. Soc.* **2007**, *129*, 14110.
[78] T. Tominaga, V. R. Tirumala, S. Lee, E. K. Lin, J. P. Gong, W-l. Wu, *J. Phys. Chem. B* **2008**, *112*, 3903.
[79] Y.-H. Na, T. Kurokawa, Y. Katsuyama, H. Tsukeshiba, J. P. Gong, Y. Osada, S. Okabe, T. Karino, M. Shibayama, *Macromolecules* **2004**, *37*, 5370.
[80] K. R. Shull, *J. Polym. Sci. Part B Polym. Phys.* **2006**, *44*, 3436.
[81] H. J. Kong, E. Wong, D. J. Mooney, *Macromolecules* **2003**, *36*, 4582.
[82] K. K. Singh, B. S. Reddy, *J. Food Eng.* **2006**, *73*, 112.
[83] G. G. Odian, *Principles of Polymerization*, 3rd ed, Wiley, New York **1991**.
[84] C. R. Nuttelman, M. A. Rice, A. E. Rydholm, C. N. Salinas, D. N. Shah, K. S. Anseth, *Prog. Polym. Sci.* **2008**, *33*, 167.
[85] Y. Yoshioka, P. Calvert, *Exp. Mech.* **2002**, *42*, 404.
[86] A. Heller, R. Maidan, D. Wang, *Sens. Actuators B* **1993**, 13–14, 180.
[87] J. V. Crivello, U. Bulut, *Macromol. Symp.* **2006**, *240*, 1.
[88] J. V. Crivello, U. Bulut, *J. Polym. Sci. Part A Polym. Chem.* **2005**, *43*, 5217.
[89] D. Rankin, A. Lowe, *Polyelectrolytes Polyzwitterions Synth, Properties, Appl. ACS Symp. Ser.* **2006**, *937*, 117.
[90] B. Bell, J. Hamilton, E. Law, J. Rooney, *Macromol. Rapid Commun.* **1994**, *15*, 543.
[91] J. Hamilton, E. Law, J. Rooney, *J. Mol. Catal. A: Chem.* **1997**, *115*, 1.
[92] W. Feast, F. Cacialli, R. Daik, R. Friend, E. Herzog, B. Heywood, L. Hobson, J. Megson, D. Snowden, *Macromol. Symp.* **1999**, *143*, 81.
[93] F. Simsek-Ege, G. Bond, J. Stringer, *J. Biomater. Sci. Polym. Ed.* **2002**, *13*, 1175.
[94] F. Simsek-Ege, G. Bond, J. Stringer, *J. Appl. Polym. Sci.* **2003**, *88*, 346.
[95] P. Sriamornsak, R. Kennedy, *Int. J. Pharm.* **2006**, *323*, 72.
[96] P. Bertrand, A. Jonas, A. Laschewsky, R. Legras, *Macromol. Rapid Commun.* **2000**, *21*, 319.
[97] J. Xueping, Z. Haipeng, G. Shoshana, P. Hammond, *Langmuir* **2002**, *18*, 2607.
[98] G. M. Gratson, M. Xu, J. A. Lewis, *Nature* **2004**, *428*, 386.
[99] S. Zhang, *Biotechnol. Adv.* **2002**, *20*, 321.
[100] X. Zhao, S. Zhang, *Macromol. Biosci.* **2007**, *7*, 13.
[101] X. Zhao, S. Zhang, *Adv. Polym. Sci.* **2006**, *203*, 145.
[102] L. Pavesi, A. Rigamonti, *Phys. Rev. E* **1995**, *51*, 3318.
[103] D. W. van Krevelen, *Properties of Polymers*, 2nd ed, Elsevier, Amsterdam **1976**.
[104] F. Fornasiero, F. Krull, J. M. Prausnitz, C. J. Radke, *Biomaterials* **2005**, *26*, 5704.
[105] P. McConville, J. M. Pope, *Polymer* **2000**, *41*, 9081.
[106] K. K. S. Buck, S. R. Dungan, R. J. Phillips, *J. Fluid Mech.* **1999**, *396*, 287.
[107] M. Shibayama, T. Tanaka, *Adv. Polym. Sci.* **1993**, *109*, 1.
[108] Y. Li, T. Tanaka, *Annu. Rev. Mater. Sci.* **1992**, *22*, 243.
[109] M. V. Badiger, A. K. Lele, M. G. Kulkami, R. A. Mashelkar, *Ind. Eng. Chem. Res.* **1994**, *33*, 2426.
[110] S. Mafé, J. A. Manzanares, A. E. English, T. Tanaka, *Phys. Rev. Lett.* **1997**, *79*, 3086.
[111] Y. Li, T. Tanaka, *J. Chem. Phys.* **1990**, *92*, 1365.
[112] H. Hirose, M. Shibayama, *Macromolecules* **1998**, *31*, 5336.
[113] X. Zhang, F. Wang, C. Chu, *J. Mater. Sci. : Mater. Med.* **2003**, *14*, 451.
[114] X. Zhang, R. Zhuo, *Eur. Polym. J.* **2000**, *36*, 2301.
[115] J.-T. Zhang, K. D. Jandt, *Macromol. Rapid Commun.* **2008**, *29*, 593.
[116] K. Van Durme, G. Van Assche, V. Aseyev, J. Raula, H. Tenhu, B. Van Mele, *Macromolecules* **2007**, *40*, 3765.
[117] J. M. D. Heijl, F. E. D. Prez, *Polymer* **2004**, *45*, 6771.
[118] J. Wiedemair, M. J. Serpe, J. Kim, J.-F. Masson, L. A. Lyon, B. Mizaikoff, C. Kranz, *Langmuir* **2007**, *23*, 130.

[119] S. Hofl, L. Zitzler, T. Hellweg, S. Herminghaus, F. Mugele, *Polymer* **2007**, *48*, 245.
[120] S. Schmidt, H. Motschmann, T. Hellweg, Rv. Klitzing, *Polymer* **2008**, *49*, 749.
[121] M. Knoblauch, G. A. Noll, T. Müller, D. Prüfer, I. Schneider-Hüther, D. Scharner, A. J. E. V. Bel, W. S. Peters, *Nat. Mater.* **2003**, *2*, 600.
[122] J. Machin, *J. Exp. Biol.* **1966**, *45*, 269.
[123] S. Kim, G. Spinks, S. Prosser, P. Whitten, G. Wallace, S. Kim, *Nat. Mater.* **2006**, *5*, 48.
[124] S. Hirotsu, *J. Chem. Phys.* **1991**, *94*, 3949.
[125] C. Li, Z. Hu, Y. Li, *Phys. Rev. E* **1993**, *48*, 603.
[126] T. Takigawa, Y. Morino, K. Urayama, T. Masuda, *Polym. J.* **1996**, *28*, 1012.
[127] P. Calvert, in *Electroactive Polymer (EAP) Actuators as Artificial Muscles – Reality, Potential and Challenges*, Vol. *PM98*(Ed: Y. Bar-Cohen), SPIE Press, Bellingham, WA **2001**, pp. 123–138.
[128] P. Calvert, in *Electroactive Polymer (EAP) Actuators as Artificial Muscles: Reality, Potential, and Challenges*, 2nd ed, Vol. *PM136*(Ed: Y. B. Cohen), SPIE Press Monograph, Bellingham, WA **2004**, pp. 123–136.
[129] T. Shiga, T. Kurauchi, *J. Appl. Polym. Sci.* **1990**, *39*, 2305.
[130] T. Shiga, Y. Hirose, A. Okada, T. Kurauchi, *J. Appl. Polym. Sci.* **1992**, *44*, 249.
[131] T. Shiga, Y. Hirose, A. Okada, T. Kurauchi, *J. Appl. Polym. Sci.* **1992**, *46*, 635.
[132] T. Shiga, Y. Hirose, A. Okada, T. Kurauchi, *J. Intell. Mater. Syst. Struct.* **1993**, *4*, 553.
[133] T. Shiga, Y. Hirose, A. Okada, T. Kurauchi, *J. Mater. Sci.* **1994**, *29*, 5715.
[134] T. Shiga, *Adv. Polym. Sci.* **1997**, *134*, 131.
[135] L. Yeghiazarian, S. Mahajan, C. Montemagno, C. Cohen, U. Wiesner, *Adv. Mater.* **2005**, *17*, 1869.
[136] Y. K. Yew, T. Y. Ng, H. Li, K. Y. Lam, *Biomed. Microdevices* **2007**, *9*, 487.
[137] R. A. Paxton, A. M. Al-Jumaily, *Polymer* **2006**, *47*, 5997.
[138] D. Brock, W. Lee, D. Segalman, W. Witkowski, *J. Intell. Mater. Syst. Struct.* **1994**, *5*, 764.
[139] S. A. V. Swanson, in *The Mechanical Properties of Biological Materials*, Vol. *34*(Ed: J. F. V. Vincent, J. D. Currey), Cambridge University Press, Cambridge **1980**, pp. 377–395.
[140] D. T. Kaneko, T. Tada Kurokawa, J. P. Gong, Y. Osada, *Adv. Mater.* **2005**, *17*, 535.
[141] G. Ateshian, H. Wang, W. Lai, *J. Tribol. Trans. ASME* **1998**, *120*, 241.
[142] Y. Pan, D. Xiong, R. Ma, *Wear* **2007**, *262*, 1021.
[143] C. Azuma, K. Yasuda, Y. Tanabe, H. Taniguro, F. Kanaya, A. Nakayama, Y. M. Chen, J. P. Gong, Y. Osada, *J. Biomed. Mater. Res. A* **2007**, *81A*, 373.
[144] B. Pepin-Donat, A. Viallat, *Macromol. Symp.* **2003**, *200*, 55.
[145] B. C. Kim, G. Spinks, C. O. Too, G. G. Wallace, Y. H. Bae, *React. Funct. Polym.* **2000**, *44*, 31.
[146] S. Siddhanta, R. Gangopadhyay, *Polymer* **2005**, *46*, 2993.
[147] K. Checkiewicz, G. Zukowska, W. Wieczorek, *Chem. Mater.* **2001**, *13*, 379.
[148] C.-C. Lin, A. T. Metters, *Adv. Drug Delivery Rev.* **2006**, *58*, 1379.
[149] H. Marchais, G. Cayzeele, J.-Y. Legendre, M. Skiba, P. Arnaud, *Eur. J. Pharm. Sci.* **2003**, *19*, 129.
[150] G. S. Banker, C. T. Rhodes, *Modern Pharmaceutics*, 3rd ed, Marcel Dekker, Inc, Monticello, NY **1996**.
[151] L. A. Felton, N. H. Shah, G. Zhang, M. H. Infeld, A. W. Malick, J. W. McGinity, *Int. J. Pharm.* **1996**, *127*, 203.
[152] H. J. Bae, D. S. Cha, W. S. Whiteside, H. J. Park, *Food Chem.* **2008**, *106*, 96.
[153] V. D. Vilivalam, L. Illum, K. Iqbal, *Pharm. Sci. Technol. Today* **2000**, *3*, 64.
[154] J. M. Newsam, D. King-Smith, A. Jain, P. Karande, I. Feygin, J. Burbaum, T. R. Gowrishankar, M. Sergeeva, S. Mitragotri, *J. Mater. Chem.* **2005**, *15*, 3061.
[155] M. D. Blanco, M. V. Bernardo, C. Teijón, R. L. Sastre, J. M. Teijón, *Int. J. Pharm.* **2003**, *255*, 99.
[156] E. Jarrat-Binstock, A. Bentolila, N. Kumar, H. Harel, A. J. Domb, *Polym. Adv. Technol.* **2007**, *18*, 720.
[157] O. Ben-Zion, M. Karpasas, A. Nussinovitch, *J. Appl. Polym. Sci.* **2003**, *87*, 2130.
[158] M. J. D. Nugent, C. L. Higginbotham, *Eur. J. Pharm. Biopharm.* **2007**, *67*, 377.
[159] Y. Onuki, M. Hoshi, H. Okabe, M. Fujikawa, M. Morishita, K. Takayama, *J. Controlled Release* **2005**, *108*, 331.
[160] E.-S. Khafagy, M. Morishita, Y. Onuki, K. Takayama, *Adv. Drug Delivery Rev.* **2007**, *59*, 1521.
[161] K. R. Meckstroth, P. D. Darney, *Obstetrics Gynecol. Clin. North Am.* **2000**, *27*, 781.
[162] A. M. Zalfen, D. Nizet, C. Jérôme, R. Jérôme, F. Frankenne, J. M. Foidart, V. Maquet, F. Lecomte, P. Hubert, B. Evrard, *Acta Biomater.* **2008**, *4*, 1788.
[163] J. A. Hubbell, *J. Controlled Release* **1996**, *39*, 305.
[164] A. J. DeFaila, C. R. Chub, N. Izzo, K. G. Marra, *Biomaterials* **2006**, *27*, 1579.
[165] T. Holland, Y. Tabata, A. Mikos, *J Controlled Release* **2005**, *101*, 111.
[166] K. Y. Lee, S. H. Yuk, *Prog. Polym. Sci.* **2007**, *32*, 669.
[167] S. Varghese, J. H. Elisseeff, *Adv. Polym. Sci.* **2006**, *203*, 95.
[168] D. Kim, D. Beebe, *Lab chip* **2007**, *7*, 193.
[169] D. J. Beebe, J. S. Moore, J. M. Bauer, Q. Yu, R. H. Liu, C. Devadoss, B.-H. Jo, *Nature* **2000**, *404*, 588.
[170] M. Bassetti, A. Chatterjee, N. Aluru, D. Beebe, *J. Microelectromech. Syst.* **2005**, *14*, 1198.
[171] T. Shibuya, H. Yasunaga, H. Kurosu, I. Ando, *Macromolecules* **1995**, *28*, 4377.
[172] E. A. Moschou, S. F. Peteu, L. G. Bachas, M. J. Madou, S. Daunert, *Chem. Mater.* **2004**, *16*, 2499.
[173] K. Arndt, A. Richter, S. Ludwig, J. Zimmermann, J. Kressler, D. Kuckling, H. Adler, *Acta Polym.* **1999**, *50*, 383.
[174] A. Kakugo, K. Shikinaka, J. P. Gong, Y. Osada, *Polymer* **2005**, *46*, 7759.
[175] E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem. Int. Ed.* **2007**, *46*, 72.
[176] J. Holtz, S. Asher, *Nature* **1997**, *389*, 829.
[177] J. H. Holtz, J. S. W. Holtz, C. H. Munro, S. A. Asher, *Anal. Chem* **1998**, *70*, 780.
[178] K. W. Kimble, J. P. Walker, D. N. Finegold, S. A. Asher, *Anal. Bioanal. Chem.* **2006**, *385*, 678.
[179] X. Zhao, X. Ding, Z. Deng, Z. Zheng, Y. Peng, X. Long, *Macromol. Rapid Commun.* **2005**, *26*, 1784.
[180] L. W. Norton, H. E. Koschwanez, N. A. Wisniewski, B. Klitzman, W. M. Reichert, *J. Biomed. Mater. Res. Part A* **2007**, *81A*, 858.
[181] K. Rasmussen, K. Østgaard, *Water Res.* **2003**, *37*, 519.
[182] J. Kopecek, J. Yang, *Polym. Int.* **2007**, *56*, 1078.
[183] M. Taya, W. J. Kim, K. Ono, *Mech. Mater.* **1998**, *28*, 53.
[184] X. Wang, D. D. L. Chung, *Sens. Actuators A: Phys.* **1998**, *71*, 208.
[185] B. Lavine, N. Kaval, D. Westover, L. Oxenford, *Anal. Lett.* **2006**, *39*, 1773.
[186] T. Watanabe, M. Akiyama, K. Totani, S. Kuebler, F. Stellacci, W. Wenseleers, K. Braun, S. Marder, J. Perry, *Adv. Funct. Mater.* **2002**, *12*, 611.
[187] H. Tsutsui, M. Mikami, R. Akashi, *Adv. Mater.* **2004**, *16*, 1925.
[188] S. Sershen, G. Mensing, M. Ng, N. Halas, D. Beebe, J. West, *Adv. Mater.* **2005**, *17*, 1366.
[189] P. D. Calvert, *Polymer* **1994**, *35*, 4484.
[190] Z. Liu, P. Calvert, *Adv. Mater.* **2000**, *12*, 288.
[191] Y. Yoshioka, *MS Thesis*, University Arizona (U.S.A.) **2001**.
[192] A. Sahoo, K. R. T. Ramasubramani, M. Jassal, A. K. Agrawal, *Eur. Polym. J.* **2007**, *43*, 1065.
[193] M. Doi, M. Matsumoto, Y. Hirose, *Macromolecules* **1992**, *25*, 5504.