Responsive Gels

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Local Switching of Chemical Patterns through Light-Triggered Unfolding of Creased Hydrogel Surfaces**

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Elastic surface instabilities that allow for reversible generation of micrometer-scale topographical features hold significant promise for designing responsive materials.[1–4] For example, the wrinkling of a thin stiff plate on a soft foundation has been harnessed to modulate adhesive,[1] optical,[2] and wetting[3] properties. Recently, our group has described an approach to switchable chemical patterns based on the surface creasing instability of surface-attached hydrogel layers.[4] In this case, the instability corresponds to a direct transition from a smooth surface to a sharply folded state, allowing chemical functionalities to be efficiently masked by self-contact of the surface.[4] To date, reversible formation of creases on hydrogel surfaces has been demonstrated by using changes in temperature,[4,5] osmotic stress,[6,7] and salt concentration,[7] but, in light of the diversity of responsive hydrogels that have been developed[8] it should be possible to generalize this strategy to a wide range of switching stimuli.

Light represents a particularly attractive stimulus, because it enables rapid changes with high spatial resolution, and does not require making physical contact to the material.[9–11] To render hydrogels sensitive to light, two general approaches have been followed. The first is the incorporation of chromophores into the gel that undergo reversible photochemical processes[9–11] thereby altering the polarity or concentration of counterions within the gel, and leading to a change in the degree of hydration. While effective, these methods are generally hampered by one or more limitations, including the acid environment ($pH \approx 3$) and slow ring-opening kinetics for spirobenzopyran,[10] modest swelling changes for azobenzene,[11] or the use of ultraviolet light,[9] which may have harmful effects on biomolecules or living cells.

The second approach relies on light-induced heating to trigger swelling changes of a temperature-responsive hydrogel matrix, typically by including a light-absorbing material in the gel.[12–15] For example, poly(*N*-isopropylacrylamide) (PNIPAM) gels containing gold nanoparticles have been shown to provide reversible light-triggered volumetric changes, permitting controlled release[13] and remote actuation of microfluidic valves.[14] While large changes in swelling have been achieved under otherwise ambient conditions, these materials have required high intensity laser sources for switching, limiting somewhat their applicability.

Here, we describe visible light-induced switching of surface chemical patterns based on hybrid gels of PNIPAM containing iron oxide nanoparticles (NPs). Due to the superparamagnetic properties of these NPs, similar composites undergo reversible swelling changes when heated using an ac magnetic field.[15] Here, we instead rely on their strong light absorbance to generate heat and thereby achieve reversible deswelling of gel layers using a modest intensity light source, i.e., a mercury lamp for fluorescence microscopy. Furthermore, we show how the use of localized illumination allows for selective switching of individual elements within a dynamic chemical pattern. We note that photothermal properties of iron oxide nanoparticles have recently been used to induce an order–disorder transition in lyotropic liquid crystals.[16]

Our approach to light-responsive chemical patterns is illustrated in Figure 1a. An aqueous ferrofluid (average particle diameter 7.4 nm) is mixed with a pregel solution containing NIPAM, sodium acrylate, and *N*,*N*-methylenebisacrylamide crosslinker in molar ratios of 94.5:5:0.5, which after polymerization yields a temperature-responsive hydrogel matrix[17] containing physically entrapped NPs. Gelation is conducted within a gap of thickness 170 μm, and the bottom glass substrate is treated with [3-(methacryloxy)propyl]trimethoxysilane to anchor the gel film. Following polymerization and removal of the top coverslip, the resulting surface-attached gel layer is immersed in aqueous solution, resulting in compressive in-plane stresses due to unidirectional swelling, and driving formation of creases on the free surface beyond a critical level of hydration.[7,18] We patterned rigid topographic features on the substrate,[19] thereby templating creases exclusively above the raised regions.[4] Chemical patterning of the surface is achieved by first depositing a "blocking layer" (tagged with fluorescein) while the surface is folded, and subsequently back-filling the remaining areas that were previously folded through a second deposition step in the unfolded state. Here, we use tetramethyl rhodamine as the patterned "functionality", though we have previously shown how peptides, enzymes, and biomolecular ligands can be patterned in similar fashion.[4]

Actuation of surface patterns with visible light is demonstrated for a pattern of parallel stripes in Figure 1b. At room temperature and under ambient light, the gel is swelled such that the functionalized areas of the surface are entirely hidden within folds, as shown by both epifluorescence images and

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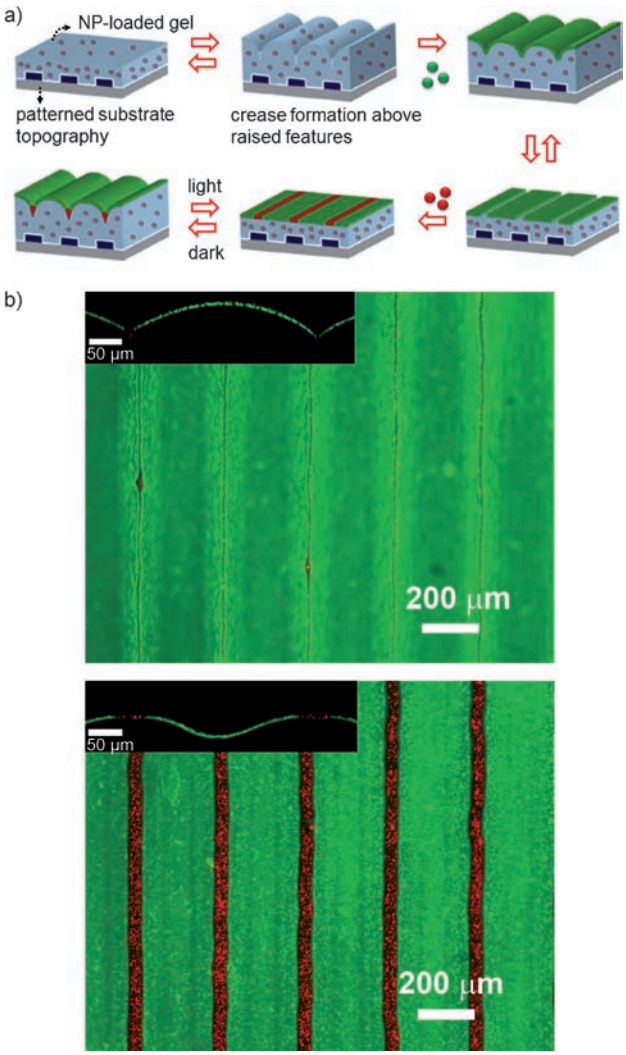

Figure 1. a) A schematic diagram showing the reversible actuation of striped chemical patterns induced by exposure of PNIPAM hydrogels loaded with iron oxide nanoparticles to visible light. b) Epifluorescence images at room temperature and under ambient light (top) and under flood illumination with blue light (bottom), with cross-sections (insets) from confocal fluorescence microscopy.

cross-sections obtained by laser scanning confocal fluorescence microscopy (LSCM). Upon flood exposure with blue light for 3 min (illumination by a Hg vapor lamp through a 450–490 nm band-pass excitation filter), the gel deswells, causing creases to unfold, and red fluorescent regions to be fully exposed on the gel surface. After turning off the blue light, reswelling of the hydrogel over ca. 3 min returns the surface to its initial folded state with functionalities sequestered, indicating that the switching behavior is fully reversible. As creasing is an elastic phenomenon and hence highly reversible, this process can be repeated multiple times with no change in either the degree or speed of unfolding, consistent with our previous report.[4]

To establish that the absorption of light by iron oxide NPs, and the resulting heating of the composite NIPAM gel, are responsible for the light-induced switching, we performed several control experiments. First, we measured the optical absorption spectrum of the NPs (Supporting Information, Figure S3) to show that they absorb strongly in the blue region of the spectrum, with a smooth decrease in absorption at longer wavelengths. Next, we determined that an aqueous dispersion of particles with the same concentration as the gel layers increases from 20 °C to 38 °C over ca. 1.5 min under illumination with blue light, while pure water under the same conditions increases only to 22 °C (Figure S4). To confirm that this light-induced temperature increase induces volumetric shrinkage of pNIPAM copolymer gels, we next considered the linear swelling ratio λ_f, for unconstrained gel disks relative to their size at the time of polymerization. Starting with a fully swelled disk at room temperature ($\lambda_f = 1.42$), irradiation with blue light causes shrinkage to $\lambda_f = 1.27$ in 3 min (Figure 2),

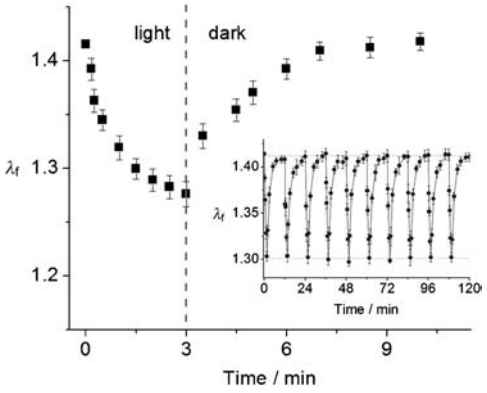

Figure 2. Linear swelling ratio for freely swelling poly(*N*-isopropylacrylamide-*co*-sodium acrylate) gels containing 2.0 wt% iron oxide nanoparticles exposed to blue light during the first 3 min. Inset: Illumination-induced change in swelling ratio which was found to be highly repeatable over multiple cycles.

which is a sufficient to switch the surface-attached gels from creased to unfolded.[4,7] This light-induced deswelling is fully reversible and can be repeated multiple times without significant changes. Notably, the system reaches steady-state for both light and dark conditions within 3–4 min, which is slower than the temperature change, but is consistent with the poroelastic time-scale for gels of this thickness,[20] indicating that mass transport of water into and out of the gel limits the switching speed. When the experiment is repeated for non-responsive poly(acrylamide) hydrogels containing iron oxide NPs, even 10 min of exposure to blue light results in negligible changes to the swelling ratio (Figure S5), further confirming that this effect arises from the coupling of photothermal conversion by iron oxide NPs to the temperature-responsive PNIPAM copolymer gel. A greater loading of ferrofluid and higher intensity of light each induce a larger reduction in volume under otherwise identical conditions (Figure S6).

One of the most attractive features of photo-responsive dynamic patterns is the possibility for local switching by irradiating only selected regions. To demonstrate this point, we consider the behavior of surfaces patterned with a hexagonal array of functionalized rings, as shown in Figure 3. Under ambient light (Figure 3 a) the composite gel film is in the creased state, sequestering the patterned surface func-

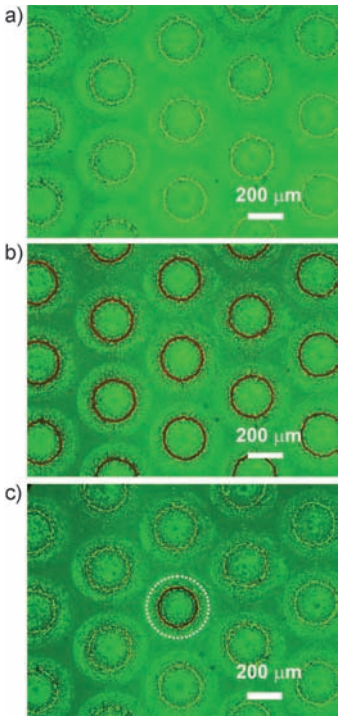

Figure 3. Epifluorescence images demonstrating the local switching of an individual feature within an array of patterned circular rings. a) At room temperature under ambient light, the composited gel film is in the creased state and all features are closed. b) Upon flood illumination with blue light, all rings switch to the open state, while c) local illumination within the region indicated by the dotted circle leads to unfolding of only a single ring.

tionalities, while flood illumination with blue light (Figure 3b) switches all rings to the open state. However, upon irradiation through an aperture (300 μm diameter; dotted line in Figure 3c) only slightly larger than a single ring, we find that only the illuminated feature unfolds, with neighboring rings remaining essentially unperturbed. Importantly, the confining substrate in this experiment is a silicon wafer, which has much greater thermal conductivity than the gel and surrounding aqueous solution, and at steady state the temperature increase will therefore be limited to only the illuminated area and a surrounding region of order the gel thickness in lateral dimension. Since the characteristic pattern dimensions are also of order the gel thickness,[7] this suggests that the strategy of locally switchable surface folds by illumination of photothermally active gel composites should hold even for much smaller scale features.

In conclusion, we have demonstrated that composite hydrogels consisting of iron oxide NPs embedded within a thermally responsive polymer matrix provide an efficient means to trigger changes in volumetric swelling using visible light. This system allows for the design of optically switchable chemical patterns based on the creasing instability of surface-attached gel layers, wherein individually folded features can be independently actuated through localized illumination. Having previously established that creased surfaces actuated by global temperature changes can be used to culture and reversibly encapsulate cells,[4] we anticipate that the current approach, coupled with structured illumination to enable independent control over individual elements within patterned arrays of chemical functionalities, will provide a valuable platform for applications in cell biology.

Experimental Section

Gel preparation on patterned substrate: Composite pre-gel solutions were formed by mixing 30 μL of an aqueous ferrofluid with 170 μL of a monomer solution containing 853 mM *N*-isopropylacrylamide (NIPAM), 45 mM sodium acrylate (NaAc), and 4.5 mM *N,N′*-methylenebis(acrylamide) (BisAA). The ferrofluid was prepared from $FeCl_2$ and $FeCl_3$ with ammonium hydroxide as described in a previous report.[21] Free radical polymerization was initiated by adding 0.3 μL of *N,N,N′,N′*-tetramethylethylenediamine (Fluka) and 1.0 μL of a 10 wt% aqueous ammonium persulfate (Sigma) solution to 200 μL of the composite solution. The desired topographic substrate features was fabricated by photolithography using SU-8 photoresist (MicroChem) and NOA81 (Norland Optical Adhesive 81, Norland Products) as described in the Supporting information. NP-containing pre-gel solutions were loaded into a capillary channel formed by the silane-treated patterned substrate and a bare coverslip, separated by spacers to define the gel thickness (170 μm, no. 1 glass coverslips). To anchor gels to substrates, patterned substrates were treated with the adhesion promoter [3-(methacryloxy)propyl]trimethoxysilane, such that the gel formed covalent attachments to the substrate during polymerization. Gelation, carried out in a sealed chamber under positive pressure of nitrogen, was allowed to proceed for 30 min before separating the release coverslip from the gel. After polymerization, coverslip and spacers were removed, then hydrogel on patterned substrate was immersed in phosphate buffered saline (PBS; 137 mM NaCl) swelling medium. To extract unreacted components, the swelling medium was changed at least three times over a period of 3 h. All reagents were obtained from Aldrich, except where otherwise noted, and were used as received.

Fabrication of dynamic chemical patterns: To generate chemical patterns, a blocking layer was first deposited by mixing 30 μL of a suspension containing 2 wt% amine-coated 100 nm diameter green fluorescent beads (Aldrich, USA), 1 μL of 1M hydrochloric acid to adjust the pH, and 70 μL of phosphate buffered saline (PBS) solution at 4 times the typical salt concentration (548 mM), and placing this mixture on the gel surface at room temperature. After 30 min, the gel surface was rinsed several times with PBS (137 mM NaCl). This deposition process was repeated three times to saturate the accessible surface area. Next, the sample was immersed into a more concentrated PBS solution (1.37 M NaCl) to induce deswelling and expose the uncoated areas of the surface. A second deposition solution, obtained by mixing 10 μL of 2.7 wt% amine-terminated 200 nm diameter red fluorescent beads (Invitrogen, USA), 1 μL of 1M HCl, and 50 μL of PBS (1.37 M NaCl), was next placed on the scaffold at room temperature for 5 s, followed by several washing steps with PBS (1.37 M NaCl).

Characterization of composite gels and light-responsive patterns: To measure unconstrained swelling ratios, freestanding disks of 170 μm initial thickness were prepared, and the positions of a collection of at least 10 embedded fluorescent beads were tracked as a function of irradiation time, as described previously.[20] Reported values represent the average of linear expansion determined for each bead, with uncertainties as the standard deviation.

Blue light irradiation was provided by exposing samples to light from a high pressure mercury short arc lamp (X-Cite 120, Lumen Dynamics) through a blue excitation filter (450–490 nm, Carl Zeiss), which yielded an intensity of 38 $mW\,cm^{-2}$, as measured by an X-Cite XR2100 Power Meter (Lumen Dynamics). Swelled hydrogel films were imaged using an epi-fluorescence microscope (Zeiss Axiovert

200, 10x objective) or a laser scanning confocal microscope (LSCM) (Zeiss LSM 510 META, 25× objective).

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