

Conductive, Physiologically Responsive Hydrogels

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Coupling molecular sensing with electrical conductivity may provide an important and valuable resource in assessing disease pathology. Here, we introduce pH-responsive hydrogels with homogeneously synthesized gold (Au) nanoparticles that reversibly alter conductivity through pH-induced volumetric swelling. These intelligent hybrid materials respond to physiological pH shifts (pH 7.4 to 5.5) that can (1) alter the conductivity of the gel or (2) create conductive conduits via micropatterned arrays.

Electrical conductivity may be used to sense physiological changes related to disease pathology. Several diseases are associated with acidosis of the blood, such as diabetic ketoacidosis,¹ tumors,² respiratory distress,³ and ischemia.⁴ The lack of sensitivity to small changes in pH has limited the use of hydrogels in drug delivery to areas of large pH changes, such as the gastrointestinal system.⁵ pH-responsive gels have also been employed in devices for use as valves and pumps, which requires the ability to be molded in proximity to a microchannel that is then obstructed or reversibly actuated given a wide nonphysiological pH range.⁶ Recently, we have reported that pH-sensitive nanoparticles composed of poly(*N,N*-dimethylaminoethyl methacrylate) (DMAEMA) and 2-hydroxyethyl methacrylate (HEMA) trigger the release of drugs⁷ and DNA⁸ based on physiologically relevant pH changes. These pH-sensitive gels serve as a platform technology that can be coupled with electrical conductivity. Such bioresponsive gels may react to biological cues through volumetric expansion, which in turn facilitates the transduction of a signal by either increasing diffusion^{9,10} or altering the volume fraction¹¹ within the matrix. We synthesized a series of pH-responsive gels with homogeneously dispersed gold (Au) nanoparticles that reversibly alter conductivity through pH-induced volumetric expansion. These intelligent hybrid materials respond to a narrow physiological pH shift (pH 7.4 to 5.5) that may be used to create conductive conduits via micropatterned arrays.

Hydrogels typically have acted as electrical insulators.¹² Biocompatible conductive polymers (i.e., polypyrrole and polyaniline)

have been used to fabricate polymer/filler mixtures.^{13,14} However, these polymers are rigid and opaque. Polypyrrole¹⁵ and polyaniline¹⁶ particles incorporated into hybrid gels were heterogeneous in size. Our goal was to prepare hybrid gels that were responsive within a physiological pH range, conductive, easily molded, and mechanically flexible.

In this letter, we synthesized a series of hybrid gels that couple a physiologically relevant (pH 7.4–5.5), pH-responsive polymer network with homogeneously dispersed, biologically inert, highly conductive Au nanoparticles. We demonstrated that Au-impregnated pH-responsive gels altered their conductivity via reversible, pH-induced volumetric changes. Au nanoparticles are bioinert and good conductors of electricity (4.1×10^7 S/m).¹⁷ Volumetric swelling, induced by a pH change of greater than 0.2, alters the interparticle spacing of the network, affecting both the volume fraction of Au and conductivity. Au particles are strongly bound within the nondegradable matrix and are not secreted within the biological milieu.

Nanoparticles of controlled size were prepared using a polymeric templating technique. Inorganic nanoparticles have been prepared using a variety of templating techniques (i.e., porous silica,¹⁸ block copolymers,¹⁹ dendrimers,²⁰ lyotropic liquid crystals,²¹ and nonaqueous polymer resins²² and gels²³). For biomedical applications, alternative approaches that are compatible with biological molecules, cells, and tissues have been explored. These systems utilized surfactant/polyelectrolyte gel complexes,²⁴ gels with varying cross-linking density,²⁵ gels with chemical functionality,²⁶ or mechanical dispersion. Forming dispersions

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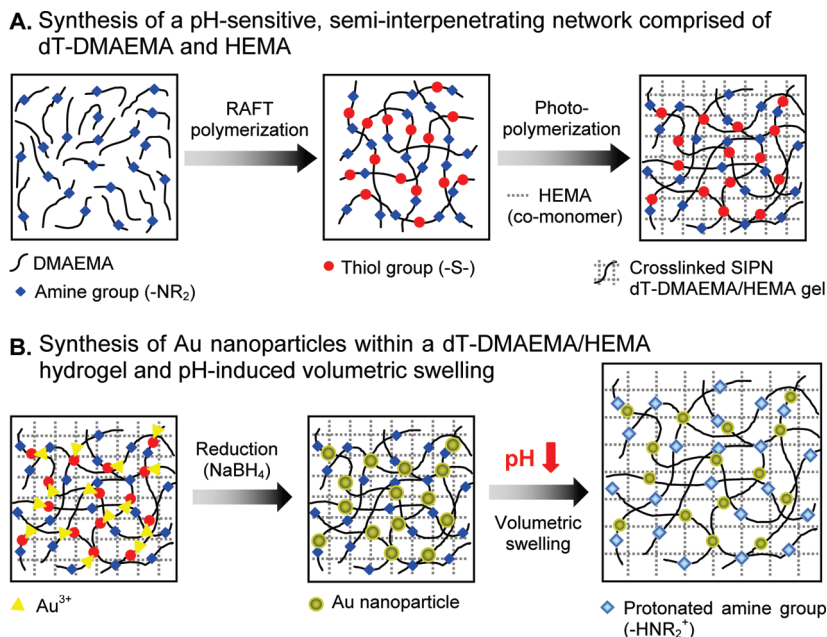


Figure 1. Schematic illustration of (A) the synthesis of a pH-sensitive semi-interpenetrating network composed of dT-DMAEMA and HEMA and (B) the synthesis of Au nanoparticles within dT-DMAEMA/HEMA hydrogels. pH-induced, volumetric swelling is also illustrated.

of nanoparticles in gels has employed the preparation of gels and particles separately, followed by subsequent mixing of the two phases,²⁷ mixing preformed particles with a hydrogel precursor prior to gelation,²⁸ or synthesizing particles after gel formation.²⁶ In situ synthesis created a homogeneous dispersion of narrow-sized particles whereas other methods often resulted in particle aggregation and/or distribution heterogeneity.

Hydrogels, composed of an oxidized dithiolated-poly(*N,N*-dimethylaminoethyl methacrylate) (dT-DMAEMA) network and a tetraethyleneglycol dimethacrylate (TEGDMA) cross-linked HEMA network, were prepared as described in Figure 1. dT-DMAEMA was synthesized by reversible addition–fragmentation chain-transfer (RAFT) polymerization using difunctional chain-transfer agent 1,4-bis(2-(thiobenzoylthio)prop-2-yl) benzene.²⁹ dT-DMAEMA was mixed with HEMA at varying molar ratios and cross linked by TEGDMA to form a pH-sensitive semi-interpenetrating network (SIPN). The thiol groups of dT-DMAEMA have affinity for itself and both colloidal Au and Au^{3+} ions. Au colloids were synthesized by immersion in an aqueous potassium tetrachloroaurate ($KAuCl_4$) solution, followed by the addition of a reductant, sodium borohydride ($NaBH_4$).

Au nanoparticles (2–5 nm) were homogeneously distributed in dT-DMAEMA/HEMA hydrogels as confirmed by transmission electron microscopy (TEM) (Figure 2A,B). The size and distribution were dependent on the thiol concentration. Hydrogels with 10, 30, and 50 mol % dT-DMAEMA produced particles with average diameters of 4.5 ± 0.9 , 3.8 ± 0.8 , and 2.6 ± 0.7 nm, respectively (Figure 2C). A higher density of particles was achieved at 50 mol % dT-DMAEMA content because of the greater number of thiol groups. Higher dT-DMAEMA content resulted in a greater number of particles that were smaller and more uniform in size.

Au nanoparticles altered the optical appearance of the gel (Figure 2D).²⁶ UV–vis spectroscopy (Figure 2E) revealed markedly different absorption spectra as a function of increasing Au nanoparticle size. The UV–vis traces had an absorption maximum near 525 nm, characteristic of the surface plasmon resonance of well-spaced Au nanoparticles.^{30,31} However, no peak is shown at 50 mol % dT-DMAEMA because the average particle size was less than 3 nm, which is consistent with other findings.³² The low absorption above 600 nm revealed that the Au nanoparticles had a low tendency to aggregate.²⁶ Thermogravimetric analysis showed that Au nanoparticles varied between 1.1 ± 0.03 and $3.9 \pm 0.2\%$ (w/w) for 10/90 and 50/50 (mol/mol) dT-DMAEMA/HEMA gels, respectively (Table 1).

DMAEMA was studied because of its use in various biomedical applications^{7,33} and its ability to respond to changes in pH because of its tertiary amine, $pK_a \approx 7.5$.³⁴ We measured the swelling ratio as a function of the molar ratio of dT-DMAEMA to HEMA, TEGDMA content, and the pH of the medium (Figure 3A–C). The swelling ratios for 10/90 and 50/50 (mol/mol) dT-DMAEMA/HEMA were 1.4 ± 0.2 and 2.0 ± 0.2 after 4 h at pH 5.5, respectively. Higher dT-DMAEMA content hydrogels had higher swelling ratios because of the increase in protonated amine groups. In contrast, raising the TEGDMA concentration increased the cross-linking density of the hydrogel network, which made the gels more rigid and less susceptible to swelling. The swelling ratios after 4 h at pH 5.5 were 2.0 ± 0.2 , 1.7 ± 0.2 , and 1.3 ± 0.1 for dT-DMAEMA/HEMA hydrogels (50/50 mol/mol) with 3, 6, and 9 mol % TEGDMA, respectively. Maximum swelling was observed at the lowest pH tested, pH 5.5. In summary,

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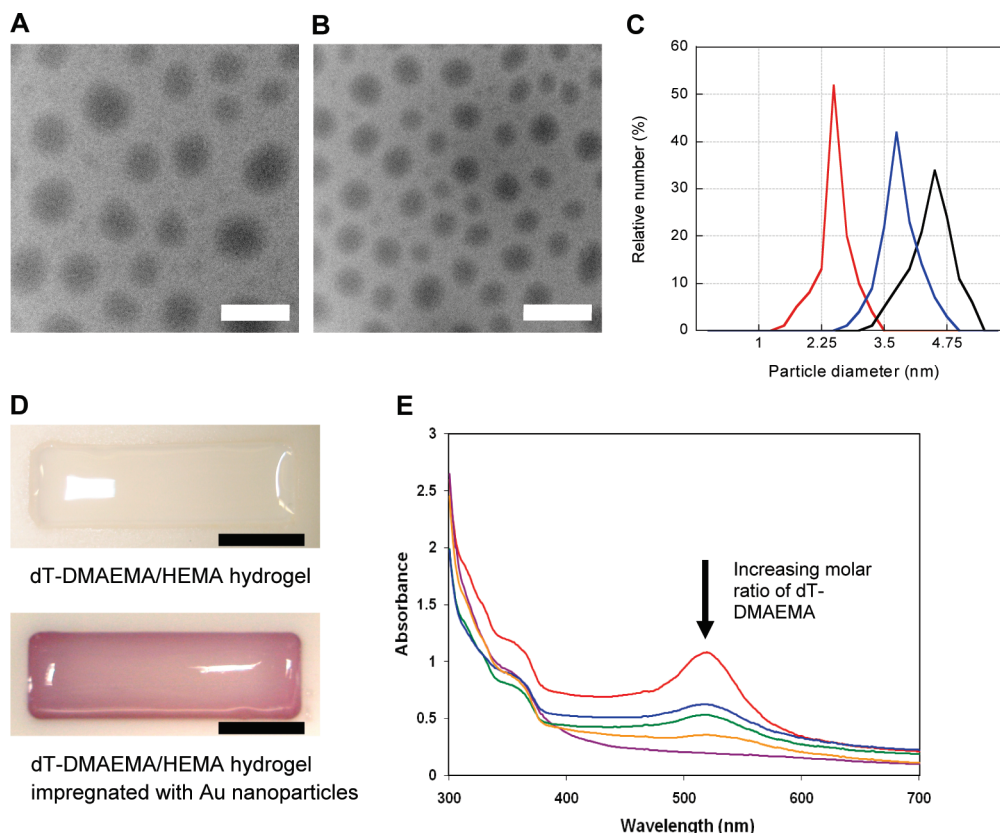


Figure 2. Characterization of Au synthesis within dT-DMAEMA/HEMA hydrogels. TEM images of Au nanoparticles within (A) 10/90 and (B) 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogels cross linked with 3 mol % TEGDMA. Scale bar = 5 nm. (C) Au nanoparticle size distribution for different molar ratios of 10/90 (black), 30/70 (blue), and 50/50 (red) (mol/mol) dT-DMAEMA/HEMA hydrogels. (D) Optical images of a 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogel and a Au-impregnated 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogel. Scale bar = 10 mm. (E) UV-vis spectra of Au-impregnated dT-DMAEMA/HEMA hydrogels in deionized water with different molar ratios {10/90 (red), 20/80 (blue), 30/70 (green), 40/60 (orange), and 50/50 (purple)} of dT-DMAEMA/HEMA.

high swelling ratios were achieved with a high content of dT-DMAEMA, low cross-linking density, and low pH.

The conductivity of Au-impregnated pH-responsive gels was regulated by volumetric changes (Figure 3D–F). A constant concentration of dT-DMAEMA was used to maintain the Au nanoparticle size and density. We observed changes in conductivity as a function of swelling ratio (i.e., interparticle distance) by increasing the amount of DMAEMA. Increasing the DMAEMA content, decreasing the cross-linking density, or reducing the pH maximized swelling, which resulted in a decrease in conductivity. The conductivity of Au-embedded DMAEMA/dT-DMAEMA/HEMA (10/20/70 mol/mol/mol) gels cross linked with 3, 6, and 9 mol % TEGDMA at pH 5.5 was 43.1 ± 4.5 , 54.6 ± 5.8 , and 67.2 ± 6.1 mS/cm, respectively. In contrast, the conductivity of DMAEMA/HEMA (30/70 mol/mol) gels cross-linked with 3 mol % TEGDMA at pH 5.5 without homogeneously distributed Au nanoparticles was ~ 10 mS/cm. These gels had no dT-DMAEMA but were subjected to the process of gold synthesis. We have demonstrated a sensitive swelling mechanism that alters conductivity by up to 7-fold (relative to nonconductive DMAEMA/HEMA gels) with changes of ~ 2 pH units in the environment.

Conductive polymer/filler mixtures typically exhibit a sudden jump to a higher conductivity at a specific concentration, known as the percolation concentration. Statistical percolation models have described this phenomenon.^{35,36} Despite the acceptance that statistical percolation models have received, there have been

several experimental indications that demonstrate that these models are not applicable to mixtures where the conductive filler particles are of colloidal size.³⁷ Interactions between the conductive fillers and polymer materials, processing of the mixtures, wettability, initial viscosity, and crystallinity have been suggested to play a role in the overall conductivity of the system.^{38,39}

The effect of Au nanoparticle synthesis on the Young's modulus was examined. Five molar ratios of dT-DMAEMA/HEMA (10/90, 20/80, 30/70, 40/60, and 50/50 mol/mol) and three concentrations of TEGDMA (3, 6, and 9 mol %) (Figure 4A,B) were tested with and without Au nanoparticle synthesis. In summary, the Young's modulus for hydrogels with Au-embedded nanoparticles was lower than that for hydrogels without particles. This suggests that a disulfide bridge is stronger than the thiol–Au interaction. The Young's modulus increased with decreasing dT-DMAEMA content and increasing cross-linker concentration. The mechanical properties of the pH-sensitive composite gels can be tuned between approximately 0.4 and 3.1 MPa by altering the Au density, cross-linking density, and dT-DMAEMA/HEMA molar ratio.

To demonstrate the electrochemical properties of the nanocomposite hydrogel, we designed a microscale device with a square and diamond blueprint using a silicon wafer (Figure 5A–E). The silicon wafer was used to cast a mold from PDMS. dT-DMAEMA/HEMA

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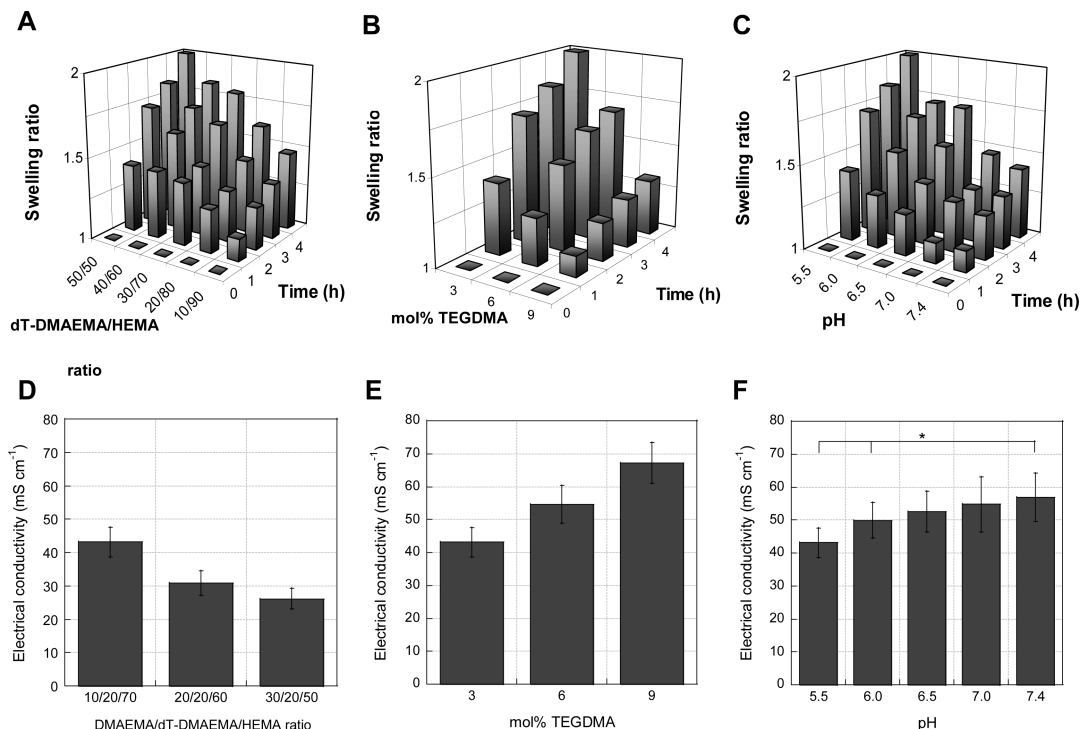


Figure 3. Mass swelling ratios of (A) Au-impregnated dT-DMAEMA/HEMA hydrogels at different molar ratios. Hydrogels were cross-linked with 3 mol % TEGDMA and swollen in pH 5.5 buffer. (B) Au-impregnated 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogels cross-linked with 3, 6, and 9 mol % TEGDMA in pH 5.5 buffer. (C) Au-impregnated 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogels cross-linked with 3 mol % TEGDMA at pH 5.5, 6.0, 6.5, 7.0, and 7.4. All data were obtained in triplicate. Electrical conductivity of (D) Au-impregnated 10/20/70, 20/20/60, and 30/20/50 (mol/mol/mol) DMAEMA/dT-DMAEMA/HEMA hydrogels cross-linked with 3 mol % TEGDMA at pH 5.5. (E) Au-impregnated 10/20/70 (mol/mol/mol) DMAEMA/dT-DMAEMA/HEMA hydrogels cross-linked with 3, 6, and 9 mol % TEGDMA at pH 5.5. (F) Au-impregnated 10/20/70 (mol/mol/mol) DMAEMA/dT-DMAEMA/HEMA hydrogels cross-linked with 3 mol % TEGDMA at pH 5.5, 6.0, 6.5, 7.0, and 7.4. The error is the standard deviation of the mean, where $n = 3$. *The statistical significance is calculated relative to pH 7.4, $p < 0.05$.

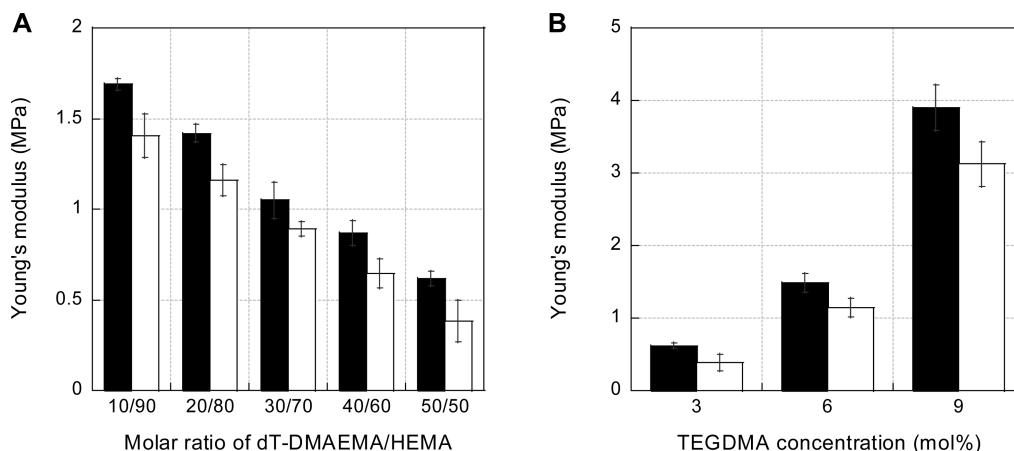


Figure 4. Young's moduli of dT-DMAEMA/HEMA and Au-impregnated dT-DMAEMA/HEMA hydrogels. (A) Different molar ratios of dT-DMAEMA/HEMA (black) and Au-impregnated dT-DMAEMA/HEMA (white) cross linked with 3 mol % TEGDMA were measured. (B) Increasing TEGDMA content was investigated for 50/50 (mol/mol) dT-DMAEMA/HEMA (black) and Au-impregnated 50/50 (mol/mol) dT-DMAEMA/HEMA (white). The error is the standard deviation of the mean, where $n = 5$.

gels were fabricated with a nonconducting HEMA gel backing and impregnated with Au colloids as described.

Microfabricated hydrogels, composed of 50/50 (mol/mol) dT-DMAEMA/HEMA cross linked with 3 mol % TEGDMA, were observed by optical microscopy before and after swelling (Figure 5B, C, diamond; Figure 5D,E, square). Diamond-shaped hydrogels ($400 \times 400 \mu\text{m}^2$) formed two conductive lanes after 4 h. Square-shaped hydrogels ($400 \times 400 \mu\text{m}^2$) swelled until all lanes merged at 6 h. The hydrogel formulation determined the extent of swelling

(swelling ratio), the volume fraction of Au particles, and the conductivity. We measured the time to contact as a function of gel formulation and pH.

Square hydrogels were unable to conduct electricity prior to swelling and the formation of gel–gel contacts. After swelling of the composite hydrogel, the conductivity steeply increased and leveled off at a maximum value (Figure 5F–H). The conductivity increased with greater dT-DMAEMA content; the highest conductivity (204 mS/cm) was obtained at 50/50 (mol/mol)

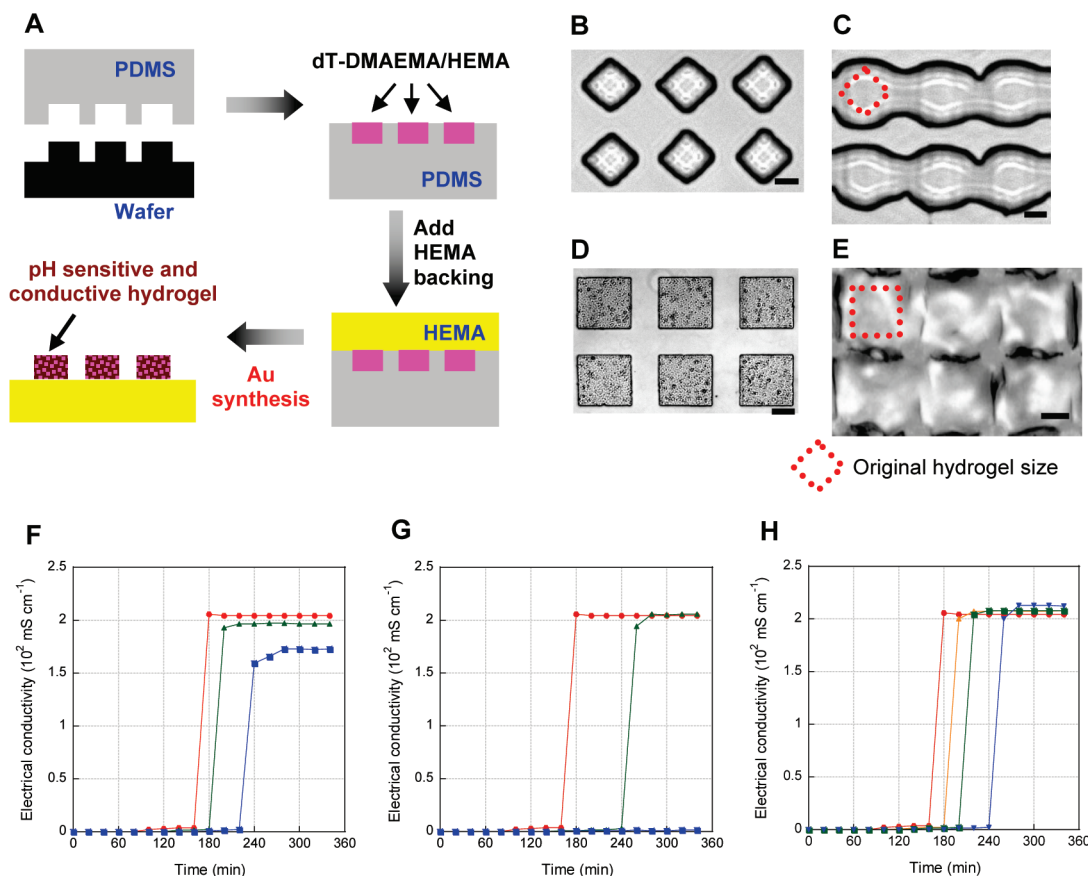


Figure 5. Preparation of microfabricated, conductive, physiologically responsive hydrogels and electrical conductivity resulting from pH-induced swelling. (A) Schematic representation of hydrogel fabrication via soft lithography. (B) Optical microscope image of six diamond-shaped hydrogels prepared from Au-impregnated 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogels cross linked with 3 mol % TEGDMA on a 100% HEMA hydrogel base. (C) Optical microscope image of swollen, diamond-shaped hydrogels in pH 5.5 buffer after 4 h. (D) Optical microscope image of six square-shaped hydrogels fabricated from 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogels cross linked with 3 mol % TEGDMA on a 100% HEMA hydrogel base. (E) Optical microscope image of swollen, square-shaped hydrogels in pH 5.5 buffer after 6 h. Scale bar = 200 μm . Conductivity measurements vs swelling time for (F) square-shaped, microfabricated, Au-impregnated 10/90 (blue), 30/70 (green), or 50/50 (red) (mol/mol) dT-DMAEMA/HEMA hydrogels. (G) Au-impregnated 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogels cross linked with 3 (red), 6 (green), or 9 (blue) mol % TEGDMA. (H) Au-impregnated 50/50 (mol/mol) dT-DMAEMA/HEMA hydrogels cross linked with 3 mol % TEGDMA at pH 5.5 (red), 6.0 (orange), 6.5 (green), and 7.0 (blue).

Table 1. Thermogravimetric Analysis of Au-Impregnated dT-DMAEMA/HEMA Gels Cross Linked with 3 mol % TEGDMA at Different Molar Ratios

sample ^a	wt %
10/90	1.14 \pm 0.03
20/80	1.82 \pm 0.03
30/70	2.38 \pm 0.08
40/60	3.26 \pm 0.12
50/50	3.85 \pm 0.17

^a dT-DMAEMA/HEMA ratio (mol/mol).

dT-DMAEMA/HEMA cross linked with 3 mol % TEGDMA. Thus, a high density of small (2.6 nm) Au nanoparticles had a higher conductivity than a lower density of larger (4.5 nm) Au nanoparticles.

Swelling of the 50/50 (mol/mol) dT-DMAEMA/HEMA gel occurred quickly. Increasing the cross-linking density inhibited swelling and extended the swelling time. At 9 mol % TEGDMA, gel–gel contact was not achieved. The rate of swelling increased with decreasing pH. The conductivity was also measured in the presence of 10% fetal bovine serum in Dulbecco's modified Eagle's

medium at pH 5.5 to measure the effects of fouling; however, no change was observed. Conductivity measurements were dependent on the gel dimensions.⁴⁰

Au nanoparticles have been integrated into a variety of biomedical devices because of their physical properties and ease of synthesis. In most cases, they have been used to modulate drug release photothermally.⁴¹ They have also been used as effective gene carriers.⁴² Conductive composites based on Au particles have been demonstrated in temperature-sensitive systems;⁴³ however, these systems are not useful in detecting disease pathogenesis and require an external excitation source.⁴⁴

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Cells may be cultured on or in the presence of Au-impregnated pH-sensitive gels. For cardiac,^{45,46} neuronal,⁴⁷ and muscle cells,⁴⁸ environments that stimulate electrical activity are highly desirable. Coupling conductive environments to a physiological signal (e.g., pH) may allow the sensing of molecular changes within a system or facilitate the excitation of cells. For example, sensors placed in the vicinity of tumorigenic cancers may monitor pH to signal recurrent tumor growth.⁴⁹ The tunable mechanical, electrical, and pH-sensitive properties of these hybrid SIPN hydrogels are well suited for an array of biological applications.

In summary, we have introduced a reversible electrochemical system based on Au colloids embedded within a pH-sensitive SIPN hydrogel that was responsive within a narrow physiological pH range. The matrix conductivity may be tailored by altering the particle size, particle density, and swelling ratio of the matrix. High swelling ratios were achieved at high dT-DMAEMA content,

low cross-linking density, and low pH. The conductive and pH-sensitive properties of composite SIPN hydrogels may be useful in pH-sensitive actuators, biosensors, diagnostics, microfluidic devices, cell assays, and drug delivery devices.

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Supporting Information Available: Details of experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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