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Bioresorbable responsive materials systems for ultrasonic monitoring

Yima He,[1,2,6] Jiaqi Liu,[1,6] and John A. Rogers[1,2,3,4,5,*]
[1]Querrey Simpson Institute for Bioelectronics, Northwestern University, Evanston, IL 60208, USA
[2]Department of Materials Science and Engineering, Northwestern University, Evanston, IL 60208, USA
[3]Department of Mechanical Engineering, Northwestern University, Evanston, IL 60208, USA
[4]Department of Biomedical Engineering, Northwestern University, Evanston, IL 60208, USA
[5]Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA
[6]These authors contributed equally
*Correspondence: jrogers@northwestern.edu
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The ability to monitor physiological parameters in deep anatomical regions can be essential for many aspects of patient care. Emerging methods combine small implantable structures formed in soft, shape-responsive materials with ultrasound imaging to address this need. The results allow for accurate long-term or transient local measurements of biophysical or biochemical characteristics.

Physiological parameters such as core body temperature, blood pressure, extracellular fluid pH, glucose level, and tissue oximetry are essential for stable function at the cellular, tissue, and organ scales. As a result, accurate longitudinal measurements of these characteristics can provide important pathophysiological insights for early detection and treatment of disease. Over recent years, the development of bio-integrated electronic and microfluidic devices[1,2] has created opportunities for real-time, noninvasive monitoring, with the potential to revolutionize personalized diagnosis and therapy. Engineering approaches for sensing and remote assessments span optical, radio frequency, and thermal modalities but with limitations in measurements at locations deep within the body due to attenuation in biological tissues. Challenges thus remain for tracking of chemically or physically specific physiological parameters in deep anatomical regions.

In this context, ultrasound is of growing interest due to its ability to penetrate through significant depths (10 cm or more) of tissues with high spatial (micron-scale range) and temporal (submillisecond) resolution. Ultrasound imaging is extensively used as a routine diagnostic tool in clinical practice, where contrast associated with anatomical structures of internal organs follows from variations in acoustic impedance. Advanced methods use Doppler shifts to capture flow velocities of blood in vessels with suitable sizes. Recent advances in functional ultrasound imaging enable measurements of microbiological dynamics and activities in living systems.[3] Moreover, the emergence of wearable and conformable ultrasound patches allows for noninvasive and continuous imaging and monitoring of central blood pressure and flow.[4] Nevertheless, techniques for monitoring of biophysical and especially biochemical signals such as pH, glucose concentration, temperature, mechanical strain, and pressure remain largely unexplored.

Responsive soft materials such as hydrogels, shape memory polymers, and liquid crystal elastomers, of historical interest for various biomedical applications, may have relevance in this context. These materials respond to external stimuli such as pH, light, magnetic and electric fields, ionic strength, glucose, and enzymes through volumetric changes, shape transformations, or modulations of mechanical properties. Such responses can be exploited as the basis of biosensors. Specifically, shape memory polymers memorize temporary shapes and recover their permanent shapes upon exposure to external stimuli. Liquid crystal elastomers possess intrinsic molecular anisotropy, enabling reversible and anisotropic changes in volumes or mechanical properties depending on the molecular designs.

Among these categories of responsive soft materials, hydrogels (Figures 1A and 1B) offer attractive properties for biosensing and other related healthcare applications due to their aqueous nature and tissue-like soft mechanical properties.[5] These characteristics, together with their intrinsic biochemical compatibility, allow for seamless integration with target tissues for physiological monitoring with minimal damage. Their responsiveness to variations in pH (Figure 1A) has relevance to various pathophysiological conditions such as leakage from the gastrointestinal fluids, acidity of the tumor microenvironment, and infection of wounds. Specifically, suitable hydrogels respond to changes in pH in the surrounding physiological environment through volumetric expansion or contraction, depending on the anionic or cationic nature of functional groups in the hydrogel network. Protonation or deprotonation of these functional groups transforms the network from hydrophobic to hydrophilic when pH deviates from the acid dissociation constant (pK_a). Subsequent changes in osmotic pressure due to electrostatic repulsion cause volumetric swelling or deswelling of the hydrogel. Other extensively studied hydrogels respond to changes in temperature (Figure 1B), with relevance to local variations in blood flow and metabolic activity. The underlying mechanism in these systems follows from temperature-induced shifts in the

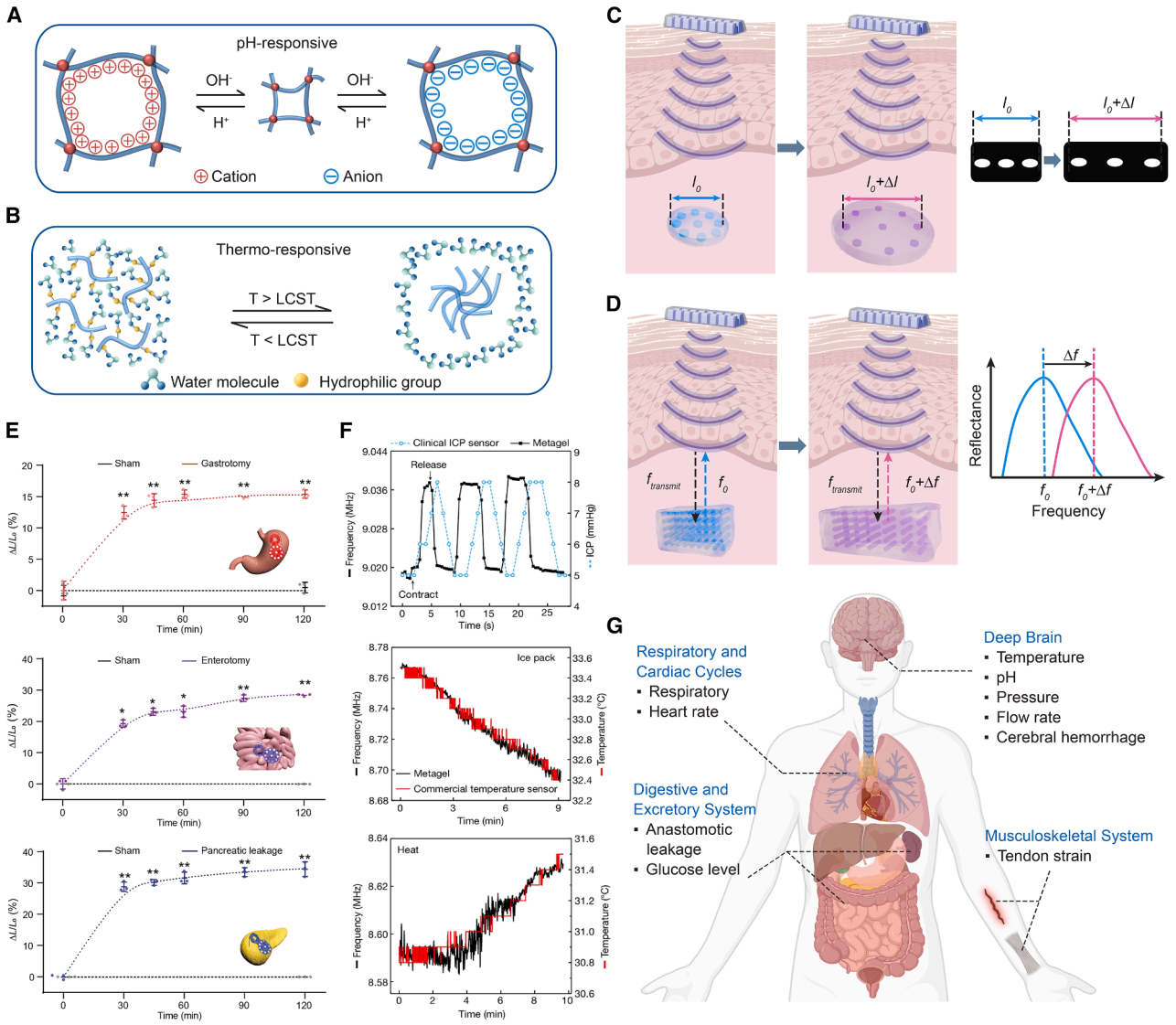

Figure 1. Bioresorbable responsive materials systems for ultrasonic monitoring

(A) Schematic illustration of volumetric changes in bioresorbable pH-responsive hydrogels.
(B) Schematic illustration of volumetric changes in bioresorbable thermo-responsive hydrogels with a lower critical solution temperature (LCST).
(C) Schematic illustration of dimensional changes of features in ultrasound images for monitoring biophysical and biochemical signals in deep tissues.
(D) Schematic illustration of frequency shifts in reflected ultrasound waves for monitoring biophysical and biochemical signals in deep tissues.
(E) Ultrasonic monitoring of pH homeostasis and detection of anastomotic leakage from dimensional changes of features in ultrasound images. Adapted from Liu et al.[6] with permission from *Science*.
(F) Ultrasonic monitoring of intracranial pressure (ICP) and temperature from reflected ultrasound waves using hydrogels with periodically aligned air columns. Adapted from Tang et al.[7] with permission from *Nature*.
(G) Schematic illustration of the potential to address various needs in clinical medicine via the combined use of bioresorbable responsive materials systems and ultrasonic monitoring.

solubility in aqueous solutions, often correlated with the critical solution temperature that results in the phase transition and volumetric change of the network. For commonly used thermo-responsive hydrogels with a lower critical solution temperature (LCST), the network experiences a transition from a hydrated, expanded state to a dehydrated, collapsed state when the temperature increases above the LCST, resulting in deswelling of the hydrogel. Other examples of responsive hydrogels that can be exploited in biosensors include glucose-responsive systems that incorporate phenylboronic acid or glucose oxidase as an enzyme for sensing. Ionic responsive hydrogels respond to changes in the ionic strength via variations of ionic conductivity, mechanical stiffness, or volume, offering potential applications in wound healing and sweat sensing. Rational choices and designs of materials chemistry and compositions in the hydrogel networks even allow

for bioresorbable responsive materials. The resulting systems can serve as the basis for temporary implantable sensors of interest because they eliminate the need for an additional surgical extraction following a clinically relevant operational lifetime.

As described recently, the combined use of bioresorbable responsive materials systems and advanced ultrasound technologies enables real-time, noninvasive monitoring of relevant biophysical and biochemical signals in deep tissues. In particular, dimensional changes of features in ultrasound images[6] (Figure 1C) or frequency shifts in reflected ultrasound waves[7,8] (Figure 1D) serve as a mechanism for transducing volumetric changes of these responsive materials into measurable signals that precisely define variations in physiological properties of the surrounding tissue environment at individual or multiple targeted regions within soft tissues.

In the case of millimeter-scale, bioresorbable, shape-adaptive materials structures[6] (Figure 1C), symmetrically distributed metal discs generate strong contrast in ultrasound images when embedded within a soft, pH-responsive hydrogel matrix for measurements of local pH. The hydrogel undergoes well-defined dimensional changes upon pH perturbations in the surrounding environment, thereby altering the spacings between the discs, quantified by analysis of ultrasound images. The symmetric layout of these discs and the mechanical flexibility of the materials structures enable angle-independent detection within a curvilinear tissue environment. Suitable choices of material chemistry of the responsive matrix support operation across a range of pH values relevant to the gastrointestinal system for early assessments of anastomotic leaks that can occur following gastrointestinal surgeries (Figure 1E). This capability addresses an unmet clinical need in postsurgical patient monitoring, where bioresorption after a recovery period bypasses the need for surgical extraction. Miniaturized versions of these materials structures allow for deployment by surgical implantation or syringe injection, compatible with modern minimally invasive procedures. Demonstrations in small and large animal models illustrate capabilities in monitoring leaks from the stomach, the small intestine, and the pancreas.

A complementary strategy[7,8] (Figure 1D) uses periodically aligned air columns within a hydrogel to allow for continuous and wireless monitoring of intracranial signals and mechanical strains. Here, the air columns form structures that reflect ultrasonic waves at specific frequencies, depending on the spacing. Changes in the resultant reflection spectra follow from the active responses of the hydrogels to changes in local pH and temperature, or from passive deformation due to pressure, flow rate, or strain. Demonstrations include monitoring in regions of the deep brain, tracking of respiratory and cardiac cycles, and measurements of tendon strains during bending motions (Figure 1F). The millimeter-scale dimensions of these structures enable implantation using a puncture needle, and bioresorption over timescales of several weeks eliminates the necessity for surgical extraction to minimize risks of infection.

These examples illustrate the power of combining advanced ultrasound technologies with responsive materials systems for unique capabilities in biophysical and biochemical sensing in deep tissues without the need for complex electronic or photonic devices, wireless communication hardware, power supplies, or signal processing strategies. The chemical biocompatibility; the soft, tissue-like mechanical properties; and the miniaturized device dimensions are additional attractive features of these approaches for minimally invasive implantation procedures and reduced patient burden. Tailored materials compositions furthermore support the natural processes of bioresorption to address temporary needs in patient monitoring without requiring subsequent surgical extraction.

These and related approaches have the immediate potential to address various needs in clinical medicine (Figure 1G), ranging from maintaining normothermia intraoperatively via measurements of core body temperature to assessments of tumor growth via monitoring of the acidic tumor microenvironment. Additional likely possibilities are in monitoring of glucose levels and internal bleeding through hydrogels designed to be responsive to glucose and hemoglobin, respectively. Improvements in the sensitivity and spatiotemporal resolution may follow from tailored chemistries that minimize hysteresis and increase the volumetric responsiveness. Additional routes to enhanced capabilities will be enabled by advanced ultrasound imaging systems and signal analysis methods. Further synergies lie in developments in neurovascular functional ultrasound imaging,[9] ultrasound localization microscopy,[10] biomolecular ultrasound,[3] and wearable ultrasound patches.[4] These and other trends may allow for tracking of cellular functions in living organisms and for long-term monitoring in closed-loop systems that offer therapeutic benefits. In all cases, advances in materials chemistry will play an essential role.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Kim, D.-H., Ghaffari, R., Lu, N., and Rogers, J. A. (2012). Flexible and stretchable electronics for biointegrated devices. Annu. Rev. Biomed. Eng. *14*, 113–128. https://doi.org/10.1146/annurev-bioeng-071811-150018.
2. Li, Y., Li, N., De Oliveira, N., and Wang, S. (2021). Implantable bioelectronics toward long-term stability and sustainability. Matter *4*, 1125–1141. https://doi.org/10.1016/j.matt.2021.02.001.
3. Bourdeau, R.W., Lee-Gosselin, A., Lakshmanan, A., Farhadi, A., Kumar, S.R., Nety, S. P., and Shapiro, M.G. (2018). Acoustic reporter genes for noninvasive imaging of microorganisms in mammalian hosts. Nature *553*, 86–90. https://doi.org/10.1038/nature25021.
4. Lin, M., Zhang, Z., Gao, X., Bian, Y., Wu, R.S., Park, G., Lou, Z., Zhang, Z., Xu, X., Chen, X., et al. (2024). A fully integrated wearable ultrasound system to monitor deep tissues in moving subjects. Nat. Biotechnol. *42*, 448–457. https://doi.org/10.1038/s41587-023-01800-0.
5. Fang, Y., Yang, X., Lin, Y., Shi, J., Prominski, A., Clayton, C., Ostroff, E., and Tian, B. (2022). Dissecting biological and synthetic soft–hard interfaces for tissue-like systems. Chem. Rev. *122*, 5233–5276. https://doi.org/10.1021/acs.chemrev.1c00365.

6. Liu, J., Liu, N., Xu, Y., Wu, M., Zhang, H., Wang, Y., Yan, Y., Hill, A., Song, R., Xu, Z., et al. (2024). Bioresorbable shape-adaptive structures for ultrasonic monitoring of deep-tissue homeostasis. Science *383*, 1096–1103. https://doi.org/10.1126/science.adk9880.

7. Tang, H., Yang, Y., Liu, Z., Li, W., Zhang, Y., Huang, Y., Kang, T., Yu, Y., Li, N., Tian, Y., et al. (2024). Injectable ultrasonic sensor for wireless monitoring of intracranial signals. Nature *630*, 84–90. https://doi.org/10.1038/s41586-024-07334-y.

8. Tian, Y., Yang, Y., Tang, H., Wang, J., Li, N., Cheng, Y., Kang, T., Tang, J., Zhou, M., Chen, W., et al. (2025). An implantable hydrogel-based phononic crystal for continuous and wireless monitoring of internal tissue strains. Published online April 14, 2025. Nat. Biomed. Eng. https://doi.org/10.1038/s41551-025-01374-z.

9. Macé, E., Montaldo, G., Cohen, I., Baulac, M., Fink, M., and Tanter, M. (2011). Functional ultrasound imaging of the brain. Nat. Methods *8*, 662–664. https://doi.org/10.1038/nmeth.1641.

10. Errico, C., Pierre, J., Pezet, S., Desailly, Y., Lenkei, Z., Couture, O., and Tanter, M. (2015). Ultrafast ultrasound localization microscopy for deep super-resolution vascular imaging. Nature *527*, 499–502. https://doi.org/10.1038/nature16066.