MATERIALS SCIENCE

Monitoring homeostasis with ultrasound

An implant could allow at-home monitoring of deep-tissue changes after surgery

By **Shonit Nair Sharma**[1,2] *and* **Yuhan Lee**[1,3]

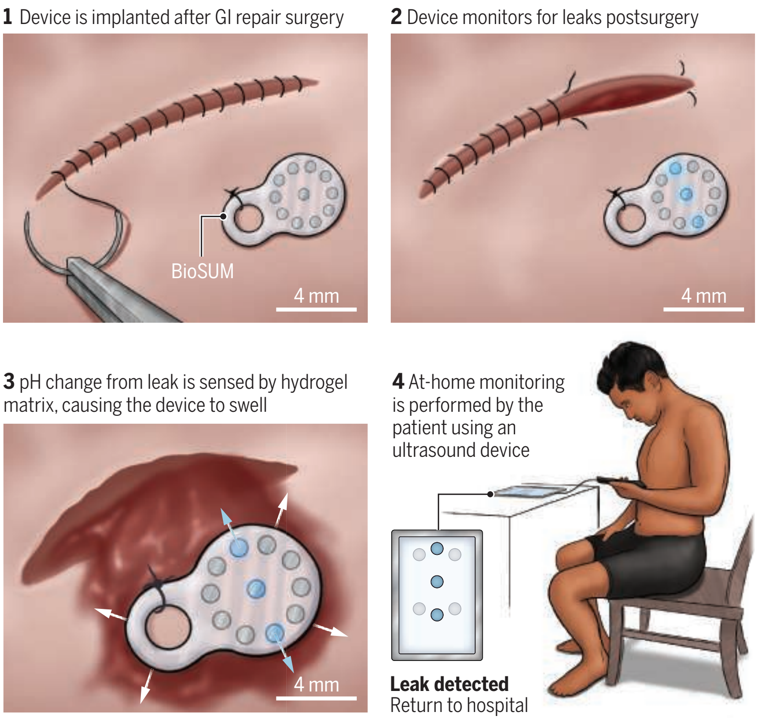
The ubiquity of phrases such as "high blood pressure" or "low blood sugar" not only indicates their integration into our personal perception of health but also underscores the societal importance of the medical technologies that enable their measurement. In modern medicine, devices that can monitor biological changes in cells and organs are essential to understanding, diagnosing, and managing disease. However, many limitations exist in current monitoring devices, particularly in those that aim to detect changes deep within tissues (*1*). For example, high cost, invasiveness, and lack of real-time feedback need to be overcome to enable earlier detection and treatment of disease (*2*). On page 1096 of this issue, Liu *et al.* (*3*) report an innovative approach to monitoring using an implant called a bioresorbable, shape-adaptive, ultrasound-readable materials structure (BioSUM). This device could allow at-home monitoring of deep-tissue changes after surgery.

BioSUM is a millimeter-scale monitoring device. It is simple in form but complex in function. Composed of small metal discs embedded within a pH-responsive hydrogel matrix, the device is implanted into the body with the intended purpose of monitoring homeostasis in deep tissues. The thin and flexible nature of BioSUM confers shape adaptivity, allowing it to be rolled into a tube and shunted through a trocar during laparoscopic surgery, sutured to tissue, or placed directly on a surface of interest using an adhesive. The metal discs serve as visual indicators that can be readily detected on ultrasound, and their symmetric circular distribution allows for identification regardless of how the device is oriented when implanted. Unlike many medical implants that require an additional procedure to remove the device when its purpose is fulfilled, the metal discs and hydrogel matrix of BioSUM are bioresorbable, eliminating the need to retrieve the device or any residuals of the device.

Gastrointestinal leaks can occur as a complication of anastomosis surgeries (which involve connecting tubular structures), resulting in fluid spreading through the peritoneal cavity and causing organ damage. When BioSUM senses a pH change—such as in the case of a gastrointestinal leak—the chemical composition of the hydrogel matrix allows the device to swell. Polymers making up BioSUM were fine-tuned to respond to different pH changes by using the protonation behavior of tertiary amine and carboxylic acid. This causes the metal discs in BioSUM to predictably spread apart, which can be continuously monitored through conventional ultrasound.

Transforming postsurgical care

Bioresorbable, shape-adaptive, ultrasound-readable materials structure (BioSUM) is an implantable device composed of small metal discs within a pH-responsive hydrogel. The device could allow recovery at home after surgery and rapid detection of postoperative complications. For example, when carrying out gastrointestinal (GI) anastomosis surgeries, BioSUM can be implanted. During recovery at home, the distance between the metal discs is measured by ultrasound. If a leak occurs, the hydrogel swells, so the metal discs are further apart. This early detection would prompt a return to the hospital before substantial organ damage arises.



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Liu *et al.* surgically sutured BioSUM on the gastrointestinal organs of rats and pigs for 14 days, demonstrating its stability. Then, a gastrointestinal leak was induced, and they could detect changes in the geometry of the metal discs within 10 mins in rats and 30 mins in pigs. The information gathered from ultrasound imaging reveals the presence and magnitude of the leak, and thus the authors contend that the device would be of use in postsurgical monitoring. The surgeon could simply place BioSUM on the tissue during the wound-closure procedure and send the patient home for recovery with confidence. Handheld ultrasound devices are accessible to the general public (*4*), enabling the patient to monitor the implanted BioSUM at home. By incorporating ultrasound image processing software in the workflow, perhaps with automated feature detection or artificial intelligence (*5*), the patient could easily detect postoperative complications and return to the hospital (see the figure).

Although postsurgical monitoring is a practical application for its use—and indeed may be how the technology is initially

[1]Department of Anesthesiology, Perioperative and Pain Medicine, Center for Accelerated Medical Innovation, and Center for Nanomedicine, Brigham and Women's Hospital, Boston, MA, USA. [2]Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA. [3]Harvard Medical School, Boston, MA, USA. Email: shonit@mit.edu; ylee21@bwh.harvard.edu

implemented—BioSUM is an important platform technology. The hydrogel matrix that enables it to swell in response to pH change can be tuned for different ranges of pH. Thus, three versions of BioSUM were created, demonstrating the ability to operate in three different environments: One version operates and detects leaks within the pH range of the stomach, another detects leaks in that of the gut, and another detects leaks from the pancreas. And although it has only been shown to detect leaks, BioSUM seems well-suited for other monitoring scenarios, such as for inflammation or flare-ups in the bowels of people with irritable bowel syndrome (*6*), or for sepsis, provided that the technology is adapted for such purposes.

Suppose the hydrogel matrix is swapped for an entirely different stimulus-responsive polymer. In this way, the device could respond to other cues, such as biomolecules (for example, drug metabolites or antibody accumulation) or pathogens (for example, bacteria or viruses). As a biosensor, the device could monitor the body's response to a drug, eliminating the need for multiple invasive blood draws (*7*), or it could track the onset of infection while in resource-limited settings. Given the numerous possibilities for device applications, a deeper investigation into the need for continuous at-home health monitoring may identify the application with the most promising potential for accelerated translation (*8*).

Monitoring technologies that meet societal demands for precise, personalized, and convenient health care are on the rise (*9*, *10*). BioSUM, in its current iteration, introduces a platform technology that yields the potential to fit within a repertoire of emerging monitoring tools, such as capsule-based diagnostics (*11*) and ophthalmic imaging techniques (*12*), that enhance the way that disease can be understood, diagnosed, and managed. ■

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Vocal-respiratory coupling is essential for proper calling, such as by this red deer (*Cervus elaphus*) during the rut.

NEUROSCIENCE

Breathing control of vocalization

A crucial brainstem circuit for vocal-respiratory coordination of the larynx is revealed

By **Steffen R. Hage**[1,2]

Vocalizations play a pivotal role in communication across species. Although the complexity of articulation varies, the basic process of sound production for the tonal component in mammals involves narrowing of the larynx (vocal cord adduction)—located between the trachea and pharynx—and exhalation. There is an intricate interplay between phonation and respiration to ensure that breathing is not affected. As a result, vocal utterances are properly aligned and embedded within respiratory cycles, usually during expiration; otherwise, a lack of coordination could result in vocal cord dysfunction or breathing problems (*1*, *2*). The mechanisms of vocal generation and respiratory pattern generation in the hindbrain are well studied (*3*, *4*). However, the interplay between these two behaviors and the underlying neural circuits that coordinate them remain unclear. On page 1074 of this issue, Park *et al.* (*5*) investigated the underlying neural substrate involved in vocal pattern generation and breathing in mice, revealing a laryngeal premotor circuit that is critical for respiratory-vocal coupling.

Understanding the neural mechanisms that orchestrate vocalization and respiratory coordination is crucial to unravelling the complexities of communication in general. The nucleus retroambiguus (RAm) in the ventrolateral pontine brainstem is involved in controlling the laryngeal motoneurons in the nucleus ambiguous as well as expiratory motoneurons in the spinal cord during vocal output (*6*), making it a potential interface between respiration and vocalization. However, this has not yet been experimentally demonstrated.

Park *et al.* used a combination of genetic tools, viral tracing, immunohistochemistry, optogenetic manipulation, and behavioral measurements in mice to investigate the brainstem circuit involved in vocalization and its coordination with respiration, with a focus on the RAm. They confirmed that the RAm is part of the vocal pattern–generating network, which includes the premotor neurons that innervate the laryngeal muscles. Excitatory RAm input is both necessary and sufficient to drive vocal cord adduction and to evoke vocal output in mice. Silencing the RAm inhibited vocal fold adduction, which

[1]Neurobiology of Social Communication, Department of Otolaryngology-Head and Neck Surgery, Hearing Research Centre, University of Tübingen, Medical Center, Tübingen, Germany. [2]Werner Reichardt Centre for Integrative Neuroscience, University of Tübingen, Tübingen, Germany. Email: steffen.hage@uni-tuebingen.de