BIOELECTRONIC DEVICES

Sensing gastrointestinal motility

Flexible piezoelectric sensors can detect mechanical deformations in the gastrointestinal tract of ambulating pigs and simultaneously harvest energy from it.

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Annually, 60 to 70 million individuals in the United States suffer from gastrointestinal (GI) disorders[1] — such as irritable bowel syndrome and chronic constipation. Efficient monitoring of the GI environment and its corresponding biomarkers could play a vital role in the diagnosis and treatment of some of these disorders. In recent years, numerous efforts have been directed towards the development of ingestible medical devices that could ultimately be less invasive than gastric electrical-stimulation devices and other implantable electronics[2]. Ingestible devices can in principle also be used in biosensing[3], health monitoring[4] and in other medical interventions[5,6]. However, primarily because of the rigidity and relatively large dimensions of current ingestible electronics, their application has raised concerns regarding tissue perforation, retention of the device and obstruction of the GI tract[2,7]. Also, the lack of efficient means for powering the devices in prolonged applications may adversely impact their functionalities[7]. Reporting in *Nature Biomedical Engineering*, Canan Dagdeviren, Giovanni Traverso and colleagues now demonstrate a flexible piezoelectric sensor that detects mechanical deformations in the GI cavity and that can operate as a self-powered unit[8]. The work represents a step towards the development of autonomous, flexible and ingestible electronics.

Dagdeviren and co-authors' sensor consists of 12 serially connected modules, each comprising 10 lead zirconate titanate (PZT) ribbons with parallel connections, with the individual PZT ribbons sandwiched between two electrodes on a polyimide substrate (Fig. 1a). The final device is encapsulated to shield the components from the GI environment. The authors evaluated the device for stability, biocompatibility and functionality. The device's mechanical and electrical stability was confirmed by showing that the sensor's output voltage did not exhibit significant changes over the course of applying over 10,000 cycles of bending, both with and without placing a piece of stomach tissue on top of the device.

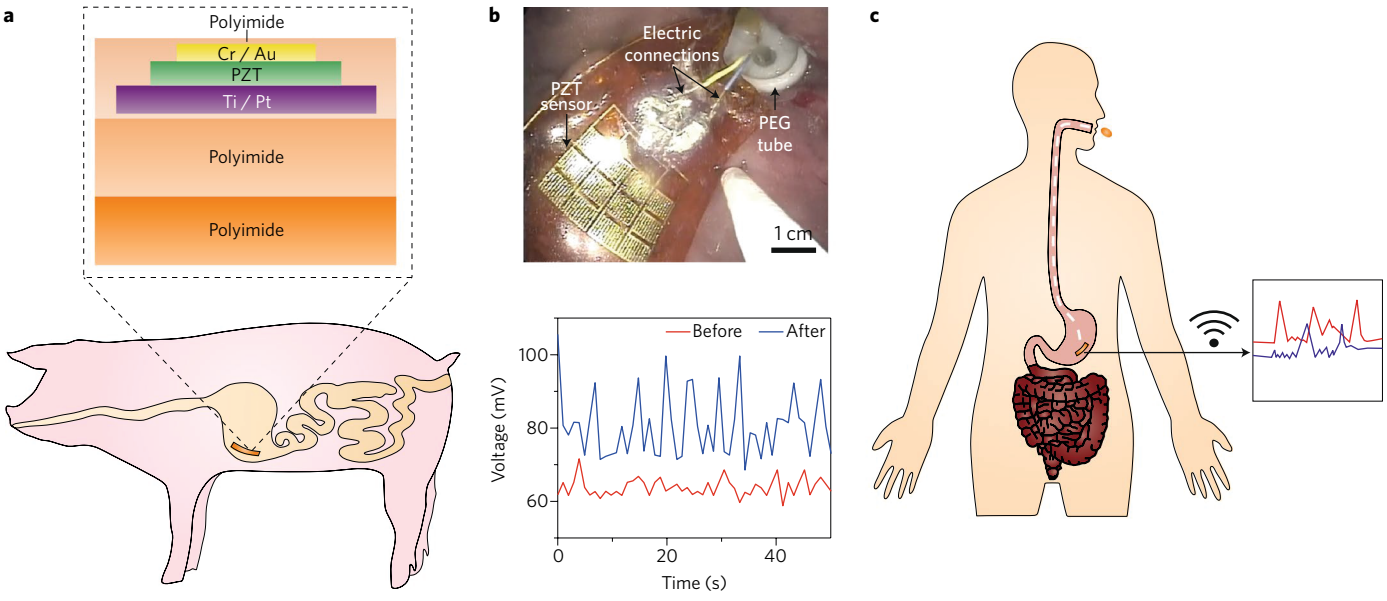

Fig. 1 | Gastrointestinal motility sensing via a flexible piezoelectric sensor. a, Schematic of a device embedded in the gastric cavity of a swine. The inset shows the cross-section of an individual PZT ribbon (500 nm in thickness) sandwiched between layers of Ti/Pt (20 nm/300 nm) and Cr/Au (10 nm/200 nm) as electrodes, and mounted on a polyimide substrate (bottom layer, 75 μm). The two other polyimide layers are used for device encapsulation[8]. **b**, In vivo demonstration of the application of the device and of its conformal settlement on the lining of the stomach of a swine (top), and corresponding output voltage before and after milk ingestion (bottom)[8]. PEG, percutaneous endoscopic gastrostomy. **c**, Schematic of perceived improvements for the proposed device, such as the incorporation of wireless sensing and the modification of the device for biodegradation and oral delivery in clinical applications. Figure adapted from: **a**, ref. [16], under a Creative Commons licence CC BY 4.0; **b**, ref. [8], Macmillan Publishers Ltd.

To evaluate the stability of the sensor in the GI environment, the authors immersed the device in simulated gastric and intestinal fluids, and in solutions with variable pH values to account for potential variations in the GI environment due to diet or GI-disease conditions. Following 48 hours of immersion, the lack of defects in the device encapsulation layer (as evidenced by scanning electron microscopy), and the lack of significant changes in the sensor's output voltage during bending cycles, confirmed the stability of the device for prolonged performance. To validate the sensor's biocompatibility, the authors assessed the growth and adhesion of GI-model cells on the surface of the device, as well as their viability when exposed to compounds released from the device immersed in the simulated gastric fluid.

The functionality of the device as a GI sensor was studied by performing a set of in vitro, ex vivo and in vivo experiments. In the in vitro experiments, the stomach was mimicked by a latex balloon in a set-up comprising a flow inlet, a flow outlet, a pressure gauge and a check valve. This set-up simulated fluid ingestion in the stomach by allowing for the infusion of unidirectional water flow into the balloon. The authors conducted in vitro experiments for two cases: a floating device inside the balloon, and a device affixed to the balloon's inner wall. In each case, 200 ml of water were introduced into the balloon in 50-ml increments. The output voltage of the device showed four consecutive peaks, corresponding to each water infusion increment for both cases. In addition, output voltages followed an increasing trend until a maximum value was achieved due to water accumulation and pressure build-up inside the balloon. The device generated higher output voltage in the case of the wall-affixed device because of the larger effective in-plane strains induced from the geometric constraint. In the ex vivo experiments, the balloon was replaced by a stomach from a swine and was infused with the same amount of water in four incremental steps. The authors observed a similar trend of increasing output voltage with pressure.

Before the in vivo experiments, Dagdeviren and co-authors rolled the devices and encapsulated them in a dissolvable gelatin layer. They then inserted the devices laparoscopically into the gastric cavity of a sedated swine. Following insertion, the gelatin dissolved in the GI fluid, leading to the unfolding and placement of the device on the gastric lining (Fig. 1b). The swine stomach was then inflated and deflated with air to mimic gastric expansion and to evaluate the potential applicability of the device in the diagnosis and treatment of GI diseases that are caused by, for example, aerophagia, or that result in increased levels of gas in the GI environment (as occurs for small-intestine bacterial overgrowth, disacharidase deficiency and lactose intolerance). The observed output voltage from the device exhibited a sudden increase from ~10 mV to ~60 mV at the instant of inflation, reached a plateau of ~40 mV after stabilization, and dropped back to ~10 mV on deflation. The same test was repeated by injecting water to demonstrate the capability of the device to sense fluids and foods, which could potentially be used for the treatment of obesity or eating disorders.

Moreover, Dagdeviren and co-authors evaluated the capability of the device to harvest energy from GI motility, and thus its potential to function as a self-powered sensor. For this purpose, the authors simulated the walking motion of an ambulating swine by applying lateral movement and abdominal palpation on the stomach of the sedated animal. Changes in the output voltage were observed as a result of the mechanical stimulations (~10 mV during palpation). Importantly, the authors also examined the capability of the device for GI motility and ingestion sensing in an ambulating swine by placing the device into the animal's stomach and establishing external electric connections via a percutaneous endoscopic gastrostomy tube (Fig. 1b). Monitoring the response from the device twice a day over the course of two days confirmed the increase in the output voltage level following ingestion (Fig. 1b).

Dagdeviren and colleagues' work has implications for the diagnosis and treatment of GI motility disorders and for bariatric purposes. To this end, various aspects of the device could be improved to extend its applicability and efficacy. For instance, from a commercialization perspective, integration of a wireless sensing network into the device to yield an untethered system would facilitate disease monitoring[9,10]. In addition, the flexibility of the device could be exploited for further miniaturization of its form factor, and consequently for using oral delivery as the primary method of device implementation instead of laparoscopic insertion (Fig. 1c). Incorporation of biodegradable materials, minerals[2], and possibly lead-free piezoelectric systems[11] as the constituents of the device would bolster its potential for clinical applications. Moreover, the integration of functional materials into 3D-printing processes would enable flexible devices and wearable electronics with intricate architectures and geometries[12,13]. And the incorporation of advanced smart materials and systems — such as pH-responsive polymer gels for device encapsulation[14] or programmable-release capsules[15] — may uncover new application areas for ingestible devices, such as targeted drug delivery with spatiotemporal control. ❐

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