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A 0.5 cm³ Ingestible Capsule Sensor with Synchronized Sensing and Tracking for Active Gastrointestinal Event Identification and Localization

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Abstract

Characterizing natural gastrointestinal (GI) biochemical and physiological processes at specific anatomical sites and matched time points is a long-sought goal in research on digestive mechanisms and related disorders, which requires capabilities that conventional research modalities cannot provide: non-invasive, real-time sensing and monitoring with precise spatial localization. Here, by leveraging the ionic conductivity of biological tissues to enable intra-body coupled communication and precise spatial localization, we overcome the size and power bottlenecks inherent to conventional ingestible sensors based on resonant antennas and discrete positioning modules. We demonstrate a fully functional ingestible platform integrating centimeter-scale localization, multimodal sensing, onboard computation, and high-speed wireless transmission within a swallow-safe 0.5 cm³ frame-supported membrane architecture. This ultra-miniaturized integrated system enabled long-term, real-time monitoring of key GI biomarkers, such as temperature, peristaltic rhythm, bleeding, and gas distribution, while synchronously tracking their dynamic spatial coordinates throughout GI transit, thereby realizing spatial and temporal mapping of multi-modal GI biomarkers. We demonstrated complete functional validation in freely moving animal models, maintaining full functionality from ingestion to excretion, and established a foundation for spatially resolved GI health monitoring, mapping of dynamic gut microenvironments, and precision therapeutic interventions.

Introduction

The gastrointestinal (GI) tract exhibits spatiotemporal heterogeneity in its physiological and biochemical properties throughout digestive cycles. Decoding this site-specific, time-varying physiobiochemical property is a prerequisite for understanding GI physiology, disease pathogenesis, and therapeutic response. However, invasive modalities such as endoscopy and biopsy only enable discrete, single-point sampling under anesthesia, which disrupts native GI function and fails to capture continuous dynamic processes^{1, 2}. Ingestible sensors offer a promising tool to overcome this limitation³⁻⁵. Driven by advances in microelectronics, functional materials, and sensing technologies, current capsule sensors have evolved beyond single-modal imaging that solely visualizes established lesions, and now enable multimodal physiobiochemical monitoring^{6, 7}. These devices are suited to measure parameters highly susceptible to interference from anesthesia or invasive sampling, delivering unprecedented value for early detection of prepathological changes and investigation of gastrointestinal disorders⁸⁻¹¹. Nevertheless, the potential of ingestible sensors remains constrained by a pervasive limitation: the lack of precise correlation between detected events and their corresponding locations, which severely compromises the interpretability and medical value of the acquired data. When equipped with synchronized high-resolution sensing and precise localization, ingestible capsules will transcend their current role as time-series monitoring tools and evolve into versatile platforms for spatially resolved gastrointestinal research. Such capabilities would enable autonomous, targeted medical interventions including precise lesion localization¹², in-situ sampling⁹, and precision drug delivery¹³, opening a new view for next-generation GI diagnostics and therapeutics.

To overcome this limitation, researchers have conventionally paired ingestible sensors with external tracking modalities, including X-ray imaging¹⁴, ultrasonography¹⁵, and magnetic field localization systems¹⁶. However, the integration of such external apparatus fundamentally undermines the core advantage of ingestible sensing: the ability to monitor gastrointestinal function under unperturbed freely moving conditions. Stationary tracking systems confine subjects to controlled laboratory environments, precluding continuous, long-duration monitoring across the entire digestive transit, and may introduce measurement artifacts due to physical restraint, sedation, or radiation exposure¹⁷. Even advanced gradient encoded magnetic localization systems still depend on precisely configured external coil array^{18, 19}, limiting their flexibility and cost effectiveness for clinical use. Eliminating dependence on bulky external equipment therefore necessitates integrating all core functions, including sensing, signal processing, communication, and localization, into a single, safely swallowable miniaturized device. Clinical data from osmotic controlled release oral delivery systems (OROS) indicate that ingestible sensors can safely cover full gastrointestinal tract studies if they achieve full

functionality for over 72 hours within a volume of less than 0.9 cm³²⁰. To date, very few swallowable microsystems meet this criterion. Even clinically approved capsule endoscopes have considerable risk of prolonged retention, especially in patients with pre-existing GI disorder^{21, 22}.

Among all required functional modules in ingestible sensors, communication and localization typically account for the largest share of device volume and power consumption⁴. Conventional wireless communication faces inherent challenges from absorption by body tissues and the Wheeler-Chu limit for antenna size. While received signal strength indication (RSSI) or phase measurements can be leveraged to perform triangulation based localization^{23, 24}, this approach enforces unavoidable tradeoffs among device size, power consumption, communication range, and localization accuracy^{25, 26}. Furthermore, dynamic variations in GI composition and dielectric properties exacerbate these challenges by disrupting antenna impedance matching and degrading positioning reliability²⁷⁻²⁹. Intra-body coupled communication (IBCC), a modality that leverages the ionic conductivity of biological tissue as the signal transmission medium offers a path to overcoming this compromise³⁰. By establishing a signal loop between on-board coupling electrodes and external receivers via endogenous tissue ions, IBCC enables low-power, short-range data transmission and energy transfer using compact coupling antenna³¹⁻³⁴, making it uniquely suited for ultra-miniaturized ingestible devices with extended operational endurance^{35, 36}. With minimal energy leakage outside the body, IBCC also provides physical-layer privacy protection for sensitive medical data^{37, 38}. Most critically, the dipole electric field distribution generated within biological tissues provides a natural geometric basis for source localization. This allows communication and localization functions to share a single hardware module, holding the potential to achieve high-precision spatiotemporally synchronized measurement without external bulky equipment.

Here, we report a universal ingestible sensor platform based on body-coupled communication, termed Pill-Scanner. This platform performs physiological and biochemical measurements within the digestive tract while reporting its real-time spatial coordinates, enabling dynamic, location-specific GI mapping of multimodal indicators. All functional modules have been integrated into a frame-supported membrane architecture with a total volume of 0.5 cm³, offering superior mechanical stability and information interaction capability. The platform achieved a communication baud rate of at least 0.1 Mbps over a 10 cm transmission range *in vivo*, while providing centimeter-level positioning with orientation information and maintaining over 10 days of operational endurance, ensuring long-term real-time sensing and monitoring throughout the entire GI tract. Safety and functionality were validated in a series of animal experiments, with the platform monitoring contractions throughout the GI tract and investigating the impacts of food, pharmaceuticals, and pathological conditions. To enable non-invasive, high-resolution GI biomarker screening, we integrated

optical detection with recognition algorithms, demonstrating its potential in detecting gastrointestinal bleeding, tracking whole-tract oxygen distribution, and locating active lesions. Overall, the Pill-Scanner platform introduces a previously unavailable measurement capability: the ability to assign every sensor reading to its exact anatomical location within the dynamic GI tract. This transforms ingestible sensing from simple timeline recording into a true spatiotemporal physiological mapping tool.

Results

Miniaturization Design of the Pill-Scanner

The Pill-Scanner shown in Fig. 1a establishes a new performance benchmark for next-generation ingestible sensors. Beyond merely capturing what physiological events occur and when, it synchronizes every detected event with its precise anatomical coordinates to resolve the long-standing question of where the event originates. This capability fundamentally elevates the interpretability of GI monitoring data, and unlocks entirely new research modalities including site-specific gastrointestinal investigations and active anomaly localization. Notably, these enhanced functionalities are achieved without trading off endurance or size, thanks to a complete restructuring of the communication, localization, and structural design paradigms. The entire system is enclosed within one of the most stringent swallow-safe size constraints reported to date, while retaining sufficient lifetime to support full gastrointestinal transit from oral ingestion to safe excretion.

The detailed design of the Pill-Scanner is shown in Fig. 1b. Instead of conventional rigid shell encapsulation, the Pill-Scanner employs a more space-efficient frame supported membrane structure, consisting of a 3D printed frame and a medical grade LDPE heat shrink membrane. Beyond its structural confinement role, the LDPE heat-shrink membrane also acts as the dielectric layer for the conformal coupling antennas, establishing effective capacitive coupling with the surrounding body tissues. A differential on-off keying (OOK) modulation with a 6 MHz carrier frequency is applied to this special antenna (Fig. 1c), enabling energy transmission to the body tissues through the formed capacitance. This special OOK signal is achieved by differential phase modulation, where the in-phase state represents 0 and the inverse phase state represents 1. This differential signal can elevate the transmission amplitude to twice the supply voltage. By eliminating the high-frequency resonant antennas, the Pill-Scanner avoids the large peak currents inherent to conventional wireless communication schemes. As shown in Fig. 1d, the average current during a single operating cycle is only about 600 μA , roughly one order of magnitude lower than that of conventional designs^{45, 46}. This significantly relaxes the power supply requirements and enables the use of miniature batteries with low peak current ratings. Typically, at a transmission frequency of 10 Hz, a 10 mAh miniature battery

delivers over one week of continuous operational endurance which is unattainable with conventional wireless technologies such as Bluetooth Low Energy (BLE) or Sub-G.

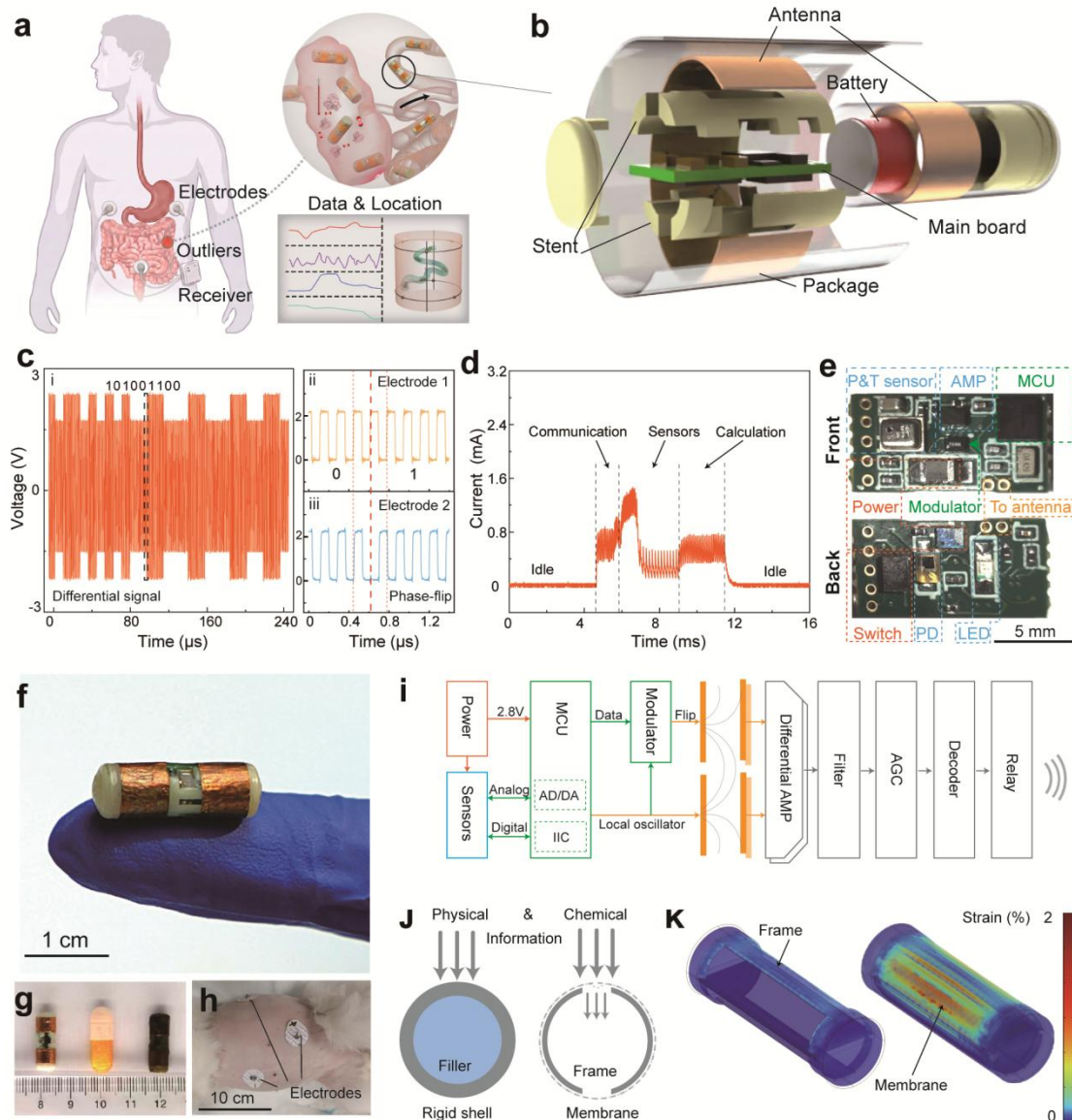


Fig. 1 Structural and Electrical Design of the Pill-Scanner. (a) Concept of monitoring, identifying, and positioning active lesions by an ingestible sensor. (b) Main structure and composition. (c) Waveform of the transmitted signal, differential OOK modulation is achieved by flipping the phase. (i) Summation of signals from electrode 1 and electrode 2. The waveform of electrode 1 (ii) and 2 (iii). (d) Power consumption profile of the Pill-Scanner over a typical operational cycle. (e) PCB design and component layout within a space of 5.8×11 mm². (f) The image of the Pill-Scanner. (g) Size comparison (left to right): a newly assembled Pill-Scanner, a #2 oral capsule and a Pill-Scanner safely excreted from the digestive tract. (h) Receiver electrodes employed for communication and localization. (i) Composition structure of the entire system, including the entire process from signal generation to transmission and reception. (j) Comparison diagram of rigid shell structure and frame supported membrane structure. (k) FEA simulation results of the frame supported membrane structure under 0.1 MPa pressure.

Figure 1e presents the detail hardware design, which integrates pressure, temperature, and optical sensing functions. The on-board microcontroller unit (MCU) digitizes all measured signals and transmits them wirelessly via the IBCC link. All components are enclosed within a $\varnothing 6 \times 18$ mm cylindrical package, corresponding approximately to a 2#capsule (Figs. 1f and 1g). To receive this unique IBCC signal, electrodes are arranged in a defined spatial configuration across the abdominal region (Fig. 1h). These electrodes capture the weak body surface potential difference induced by the transmitted signal, while simultaneously providing the spatial coordinate references required for synchronized localization. Fig. 1i demonstrates the detail structure of transmitting and receiving system, showing the complete signal flow from modulation and transmission to body surface reception.

Compared with rigid shell and filling structures (Fig. 1j), the frame supported membrane structure further expands the interaction capabilities of temperature, pressure, light, and gas multi-modal physical or chemical information. Without the need for additional cavities, connecting chambers, or sealing designs, it provides a unified environmental interface for multi-modal ingestible sensors. In this architecture, the support frame maintains the overall device geometry under compressive stress, while most structural strain is distributed across the membrane (Fig. 1k). Finite element analysis (FEA) confirms that this configuration can withstand the mechanical forces generated by gastrointestinal peristalsis. The above-mentioned features enable long-term, spatiotemporal synchronized, and multimodal sensor profiling in the gastrointestinal tract within a 0.5 cm³ ingestible sensor platform.

Long-range Low Power Wireless Communication of the Pill-Scanner

Unlike other superficial implants, ingestible sensors that move passively *in vivo* are usually covered by a few inches of body tissue. These body tissues are typically lossy dispersive media for electromagnetic waves and significantly reduce the communication distance³⁹. Fig. 2a shows the variations of the electrical conductivity, relative permittivity, and attenuation of the muscle with frequency⁴⁰. As the frequency increases, the attenuation of the signal becomes more remarkable, and a higher transmission power is required to counteract this path loss. This trend becomes more pronounced when the carrier frequency exceeds 100 MHz. That is the main reason why the battery life and size of the ingestible sensor could hardly be further optimized. However, to deploy an ideal ingestible GI monitoring, a compact, low power consumption, long range, and high-speed communication is an essential requirement.

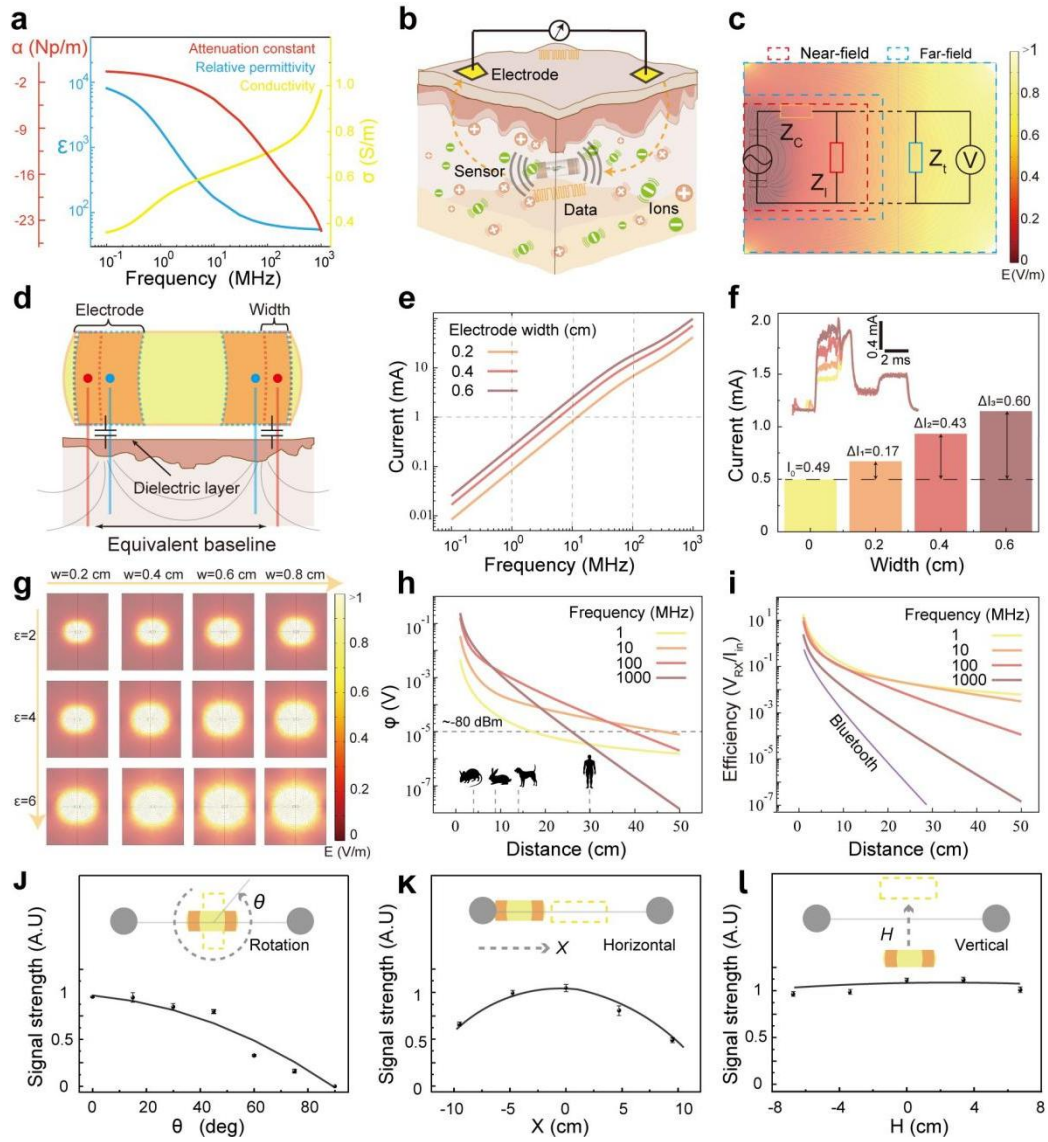


Fig. 2 Intra-body coupled communication model and in vitro verification. (a) Utilizing the ionic conductance of body tissues to transmit electrical signals for long-range high efficiency communication. (b) The electrical conductivity (yellow), relative permittivity (blue), and electromagnetic field loss factor α (red) of muscle. (c) The energy coupling interface, where the electrode width affects the area of the coupling capacitor plate and the dipole moment (equivalent baseline), and the dielectric layer (encapsulation) influences the permittivity. (d) A simplified signal transmission model, Z_c , Z_i , Z_t represent the coupling impedance, tissue loss, and transmission impedance, respectively. (e) The influence of electrode width and carrier frequency on power consumption. (f) Actual measurement results of communication power consumption under different electrode widths. (g) The influence of electrode width and encapsulation material on signal transmission. (h) Estimation of *in vivo* communication distance at carrier frequencies ranging from 1 MHz to 1000 MHz. The receiver sensitivity limit is set at 10 μ V, approximately -80 dBm in standard digital wireless receiver. The silhouette represents the approximate abdominal radius of common laboratory animals and the human. (i) Energy utilization efficiency is calculated by the ratio of the received signal strength to the transmission current. (j-l) Received signal strength measurement in *ex vivo* pork tissue under different movement paths: Rotation (j), Horizontal (k), Vertical (l), indicates a pronounced signal directionality.

Due to the large quantity of free ions within body tissues, it is possible to directly establish an electrical loop between the sensor and the receiver (Fig. 2b). To conduct a quantitative analysis of key parameters such as power consumption, communication distance and efficiency, a simple equivalent circuit of body coupling communication was constructed in Fig. 2c. The calculation was carried out in two steps (Supplementary Note 1). Firstly, the energy coupled to the tissue was estimated through the near-field circuit, while the far-field transmission was estimated based on the potential distribution of an infinitesimal electrical dipole in an infinitely large medium. In the near-field coupling circuit, the tissue load impedance Z_l is considered to be uniform, and its conductance and dielectric constant are only related to the carrier frequency. The main variables come from the coupling impedance Z_c , as shown in Fig. 2d, which can be regarded as a series plate capacitor composed of the coupling electrodes and the dielectric material of the encapsulation layer. Obviously, the larger the capacitor is, the smaller the coupling impedance will be, and more energy will be coupled into the body tissue. The most direct impact comes from the electrode width which is proportional to the coupling capacitance, and also slightly affects the baseline length. Fig. 2e shows the calculation results of the total output current varying with the carrier frequency under different electrode widths. Since both the coupling impedance Z_c and the load impedance Z_l decrease with frequency, the total coupling current increases rapidly as the frequency rises. Meanwhile, the coupling energy increases proportionally with the electrode width. We conducted actual power consumption measurements with different electrode configurations in pork tissue to verify the calculated results (@ 6 MHz). The 0 antenna width (yellow) in Fig. 2f represents the current of one working cycle when the coupling electrode was not installed. This base current was from the rest of the system, including the MCU and sensors, and the increased part was the transmission energy coupled to the pork tissue. The actual measured results were very close to the theoretical values (the actual transmission current was approximately half of the calculated value under OOK modulation), which indicated that the assumptions of the near-field circuit were valid. Other factors affecting the coupling energy also include the dielectric properties of the encapsulation layer. As shown in Fig. 2g, under the same carrier frequency, the more coupling energy there is, the greater the communication distance will be.

Fig. 2h shows the estimation results of communication distance with the following configuration: 0.6 cm electrode width, 100 μm thickness encapsulation layer with a dielectric constant of 2. All the calculations assumed that the sensor was located at the center of the symmetrical receiving electrodes, which results in a worst-case scenario with the largest attenuation. The results show that the coupling performance, together with the attenuation characteristics, affected the final communication distance. Under a 1 MHz carrier frequency, the coupling impedance is high. Although the attenuation is slightly lower than that of the carrier at 10 MHz, the transmission distance is still short. However, when the frequency exceeds

100 MHz, due to the rapid increase in attenuation, the communication distance drops sharply. Thus, for small experimental animals, a lower carrier frequency should be used first based on efficiency considerations, while, for humans, the optimal carrier frequency should be selected around the 10 MHz band. We defined an efficiency factor to better illustrate this transmission characteristic, which is the received voltage divided by the current at the transmitting side. As shown in Fig. 2i, the larger the efficiency factor is, the higher the energy utilization for transmission. According to our coupling communication model, the optimal carrier frequency range for ingestible sensors is approximately several megahertz, which can take into account both the coupling impedance design and the attenuation characteristics of the body tissue.

To verify the actual communication quality, a piece of pork ($20 \times 10 \times 6 \text{ cm}^3$) was used as a simulation of the abdominal tissues, and the received signal strength when the Pill-Scanner moved inside (Fig. 2j-l) was measured. When the receiving electrode and the Pill-Scanner were in a straight line, the signal had a maximum value, while when the two were perpendicular, the signal could hardly be received. The beam shape is determined by the position and attitude of the Pill-Scanner, implying that this communication mode can be regarded as a measurement of the potential distribution of a dipole that could be tracked.

For the design of a compact ingestible sensor system, our method requires approximately only hundreds of micro-watts peak power for data transmission which is 1-2 orders of magnitude lower than BLE (Supplementary Table 1) technology. This feature can greatly reduce the instantaneous discharge requirement of the energy storage unit, which is usually directly related to its package size. In addition to ingestible applications, this method is also effective for other implantable microsystems and can be used for linking multiple devices. Moreover, this technology can ensure that the signal is only distributed within the body and can hardly be intercepted by external devices, unlike conventional RF technologies like Bluetooth, which is extremely important for wirelessly transmitting sensitive medical data and protecting user privacy.

Pill-Scanner Coordinate Tracking Strategy via Quasi-Static Electric Field Geometric Features

Since the surface potential distribution is determined by the Pill-Scanner's position, the positioning could be realized by solving the inverse problem of the surface potential distribution. For solving this inverse problem, we rely on the nonlinear mapping ability of a Multi-Layer Perceptron (MLP) to achieve the prediction of all 5 degrees of freedom (DoF) data, including position coordinates, pitch, and yaw angles. The execution flow of the positioning algorithm is illustrated in Fig. 3a. First, an abdominal electric field FEA model (details are shown in Supplementary Note 2.) was built to obtain the training set, which included about 10000 sets of random dipole positions, orientations, and their electric field distribution. Then, the surface electric potential difference between the reference electrodes and the observation electrodes

was calculated. The distribution of electrodes is shown in Fig. 3a, which includes two reference points and two equilateral triangular observation planes. All the electric field distribution data were input into the MLP to learn its features. The training details are shown in Supplementary Fig. 7. The error function is defined as the sum of the mean square errors between the output coordinates and the input coordinates. After the MLP was fully trained, the input FEA calculated potential differences will be replaced with the actual signal amplitudes received by the real receiver between different electrodes, to obtain the actual positioning coordinates and orientation.

Fig. 3b-f demonstrates the validation set error for each DoF. The horizontal axis represents the practical parameters, while the vertical axis shows the predicted results obtained by solving the inverse problem using the electric potential distribution. The MLP model effectively learned the characteristics of the dipole electric field distribution, resulting in data points clustering closely around the theoretical values. It is worth noting that the dispersion of data varies across different DoF, which may be attributed to the influence of electrode distribution characteristics on model performance. Based on the test set performance, this strategy achieves a positioning accuracy within ± 5 mm and an orientation accuracy within $\pm 10^\circ$ under ideal conditions. Overall, as shown in Fig. 3g, the errors of most coordinate points are within one centimeter, indicating that the prediction accuracy is acceptable and sufficient for doctors to determine the anatomical location of the Pill-Scanner.

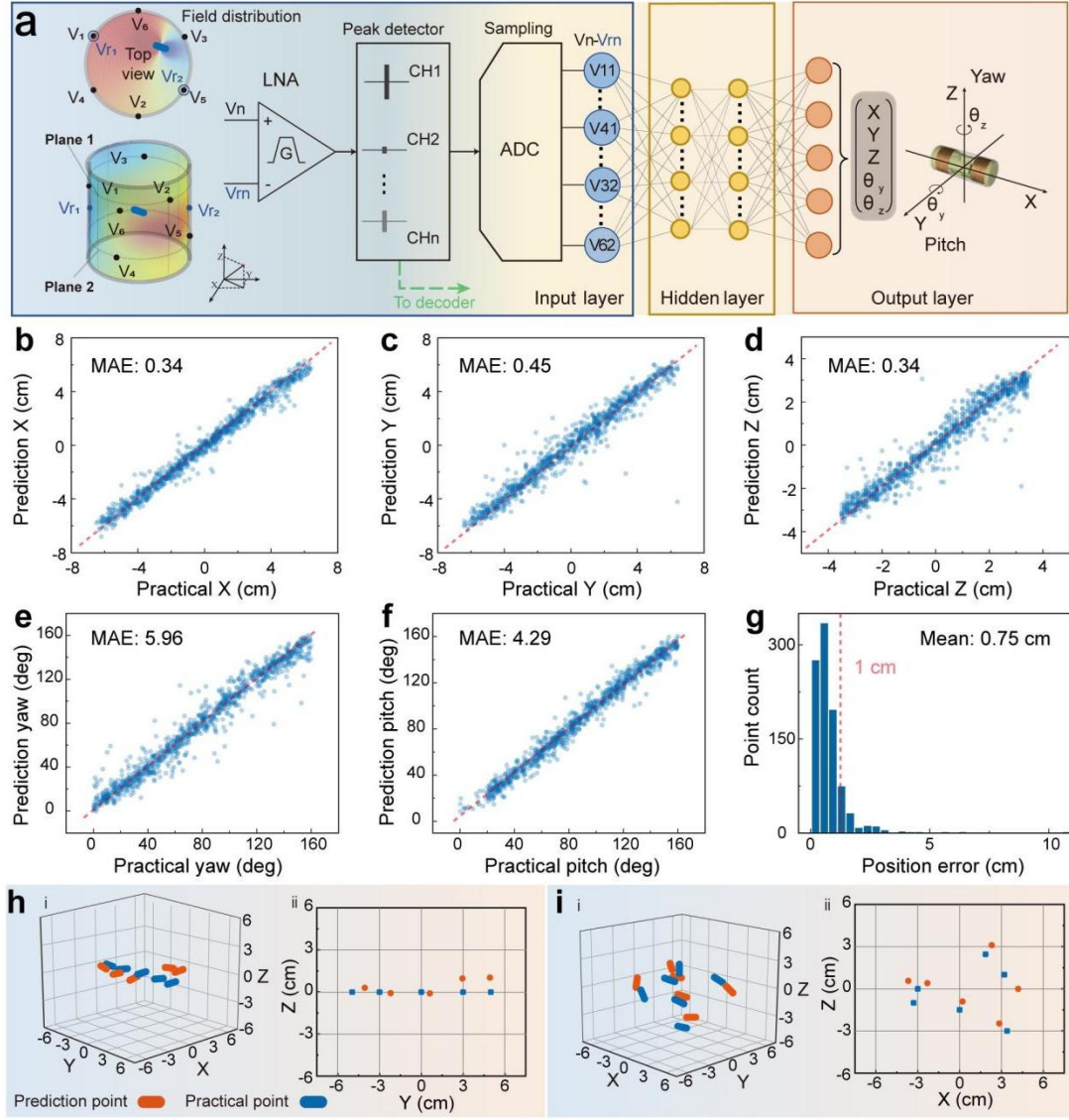


Fig. 3 Electric Dipole-based Positioning Algorithm. (a) Electric dipole positioning concept. The error of the model at (b) X-axis, (c) Y-axis, (d) Z-axis, (e) yaw, and (f) pitch on the test set, calculated in terms of mean absolute error (MAE). (g) The distribution of coordinate errors. (h-i) Comparison between the predicted coordinates by the algorithm and the actual position for targets distributed along a straight line (h) and distributed randomly (i), respectively.

We also verified the applicability of this localization algorithm in a cylindrical water tank. The experimental setup is shown in Supplementary Fig. 8. Fig. 3h, i present the results of locating a randomly rotated Pill-Scanner in different positions. The detailed coordinates can be found in Supplementary Table 2. The results obtained by the model agree with the actual position and posture, with an error of about 1 cm. In general, this special communication mode can solve the contradiction between size and power consumption and provide precise positioning without additional components support. Compared with other magnetic positioning technologies, this strategy establishes a localization coordinate system relative to the worn

electrodes and the body itself. This approach allows subjects or experimental animals to move freely without relying on external absolute reference coordinates. Compared with imaging and interventional examinations, it can provide a non-invasive device with high resolution at an extremely low cost for both doctors and patients. When combined with real-time sensor data, it can improve diagnostic accuracy, making it sufficient to serve as a critical bridge connecting non-invasive screening and further definitive diagnosis. Also, it can provide reliable and synchronous coordinates for each data transmission, which makes it a reliable tool for carrying out medical tasks, such as precise drug delivery, lesion identification and localization. Compared to 3 DoF positioning, the additional posture information can also be used for directional wireless power transmission, for in-body treatment or intervention⁴¹.

Comprehensive In Vivo Functional Validation of Pill-Scanner in Freely Moving Rabbits

Freely moving rabbit models were employed to validate the safety, communication quality, and system's capacity for *in vivo* long-term real-time monitoring. Fig. 4a illustrates the experimental setup. First, an electrode array for measuring potential differences was placed on the rabbit's abdomen, and a wearable receiver was connected to this electrode array. After that, the Pill-Scanner was orally administered into the rabbit's GI tract. The OOK modulated dipole electric field was then demodulated by the receiver into digital signals, which were subsequently transmitted to a host computer for further data processing, visualization, and storage. (The testing process can be viewed in the Supplementary Video 1-5.) Fig. 4b presents 10 minutes of raw received data. With the support of the novel communication design, the system achieved real-time data transmission from the GI tract at a frequency of 240 times per minute. Even at such high communication rates, it maintained stable transmission performance and extended operational endurance. Benefiting from the high sampling rate enabled by the communication module and the high sensitivity ensured by the structural design, the pressure data, which precisely captures detailed GI motility, can even clearly distinguish respiratory signals as low as 100 pascals.

Following comprehensive validation of its functionality, two representative medical studies were conducted, including feeding experiments and pharmacological experiments (Fig. 4c). During all experiments (~4 hours), the capsule was confirmed to remain in the stomach, and the average retention time in the rabbits' GI tract was approximately two days. After that, all the Pill-Scanners were safely excreted and still function normally (Supplementary Video 5 and Supplementary Fig. 9). As shown in Fig. 4c, in addition to precise gastrointestinal motility data, the Pill-Scanner measured the variation in core temperature with an exceptionally high resolution of 0.01°C. These data not only clearly recorded the real-time effects of feeding, drinking, and drug injections on core temperature, but also recorded the precise timing of these physiological events.

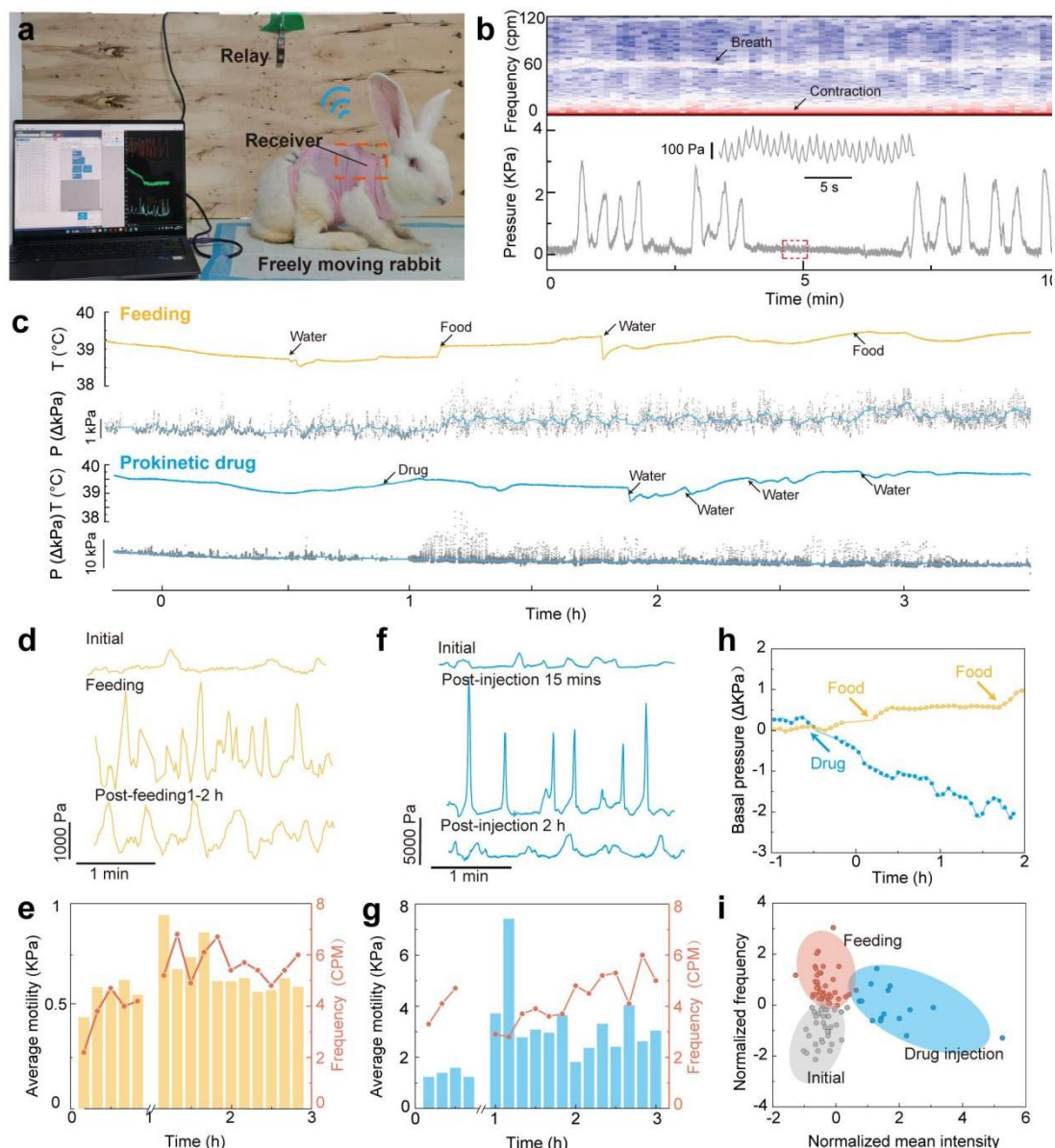


Fig. 4 Peristalsis Monitoring in Freely Moving Rabbits. (a) Typical experimental setup. (b) Raw pressure data, acquired by the high-sensitivity sensor. (c) Long-term gastrointestinal physiological monitoring data, including core temperature and pressure measurements. Variation in (d) contraction waveform and (e) statistical comparisons before and after feeding. Variation in (f) contraction waveform and (g) statistical comparisons before and after drug injection. (h) Temporal trend of intragastric basal pressure. (i) Cluster analysis of motility patterns, each point represents 3 minutes of statistical results of motility data.

In the feeding experiment, the waveform (Fig. 4d) revealed a slow, weak, and irregular gastric contraction during the fasting state (initial). During the feeding process, both the contraction frequency and amplitude increased significantly and exhibited pronounced periodicity. We developed a program for real-time peak identification and annotation to calculate the average contraction count and amplitude within a defined interval (Supplementary Fig. 10-11). Fig. 4e summarizes the statistical results. Gastric contraction frequency increased

from 3-4 contractions per minute (CPM) during fasting to approximately 5 CPM after feeding. In the pharmacological experiment, metoclopramide was administered intramuscularly. Fig. 4f and 4g display representative contraction waveforms and their statistical results, respectively. Approximately 15 minutes post-injection, metoclopramide markedly enhanced contraction force, elevating pressure from 1000 Pa to over 7000 Pa. Contraction amplitude remained above 2000 Pa for the next two hours, then gradually subsided and ultimately returned to baseline. These data align with previously reported pharmacodynamics results⁴¹.

Utilizing an absolute pressure sensor enabled the simultaneous acquisition of dynamic contraction data and static basal pressure. As shown in Fig. 4h, this basal pressure contains information on gastric volume. Food intake and retention progressively distended the stomach, increasing basal pressure. Metoclopramide injection significantly accelerated gastric emptying, evidenced by a gradual decline in basal pressure. This demonstrates the sensor's utility for measuring both feeding and gastric emptying processes. Cluster analysis (Fig. 4i) reveals a distinct separation between the effects of feeding and metoclopramide. Feeding primarily induced greater changes in contraction frequency, whereas metoclopramide predominantly enhanced contraction amplitude. It confirmed that the rhythm and strength of gastrointestinal peristalsis have independent control mechanisms at the level of nerve innervation and drug action⁴². These results verified that the system enables long-term, real-time monitoring of natural gastrointestinal physiology without anesthesia or invasive procedures. Furthermore, for medical and drug research, this technology can obtain the most realistic biomedical indicators without affecting the behavior of small animals. Furthermore, it can significantly reduce the number of experimental animals and improve animal welfare by replacing the terminal measurements with long-term and continuous data.

In Vivo Validation of Site-Specific Gastrointestinal Scanning

To further demonstrate the advantages of our platform in screening for GI diseases, two new approaches were validated, referred to as passive scanning and active scanning, respectively. In the passive scanning protocol, the region of interest (ROI) is pre-labeled via oral administration or injection and is subsequently detected by the ingestible sensor as it passes through or temporarily resides in the area. The active scanning protocol, on the other hand, utilizes targeted photoluminescent probes integrated within the sensor to generate a spatial-temporal mapping of specific biomarkers while traversing the GI tract.

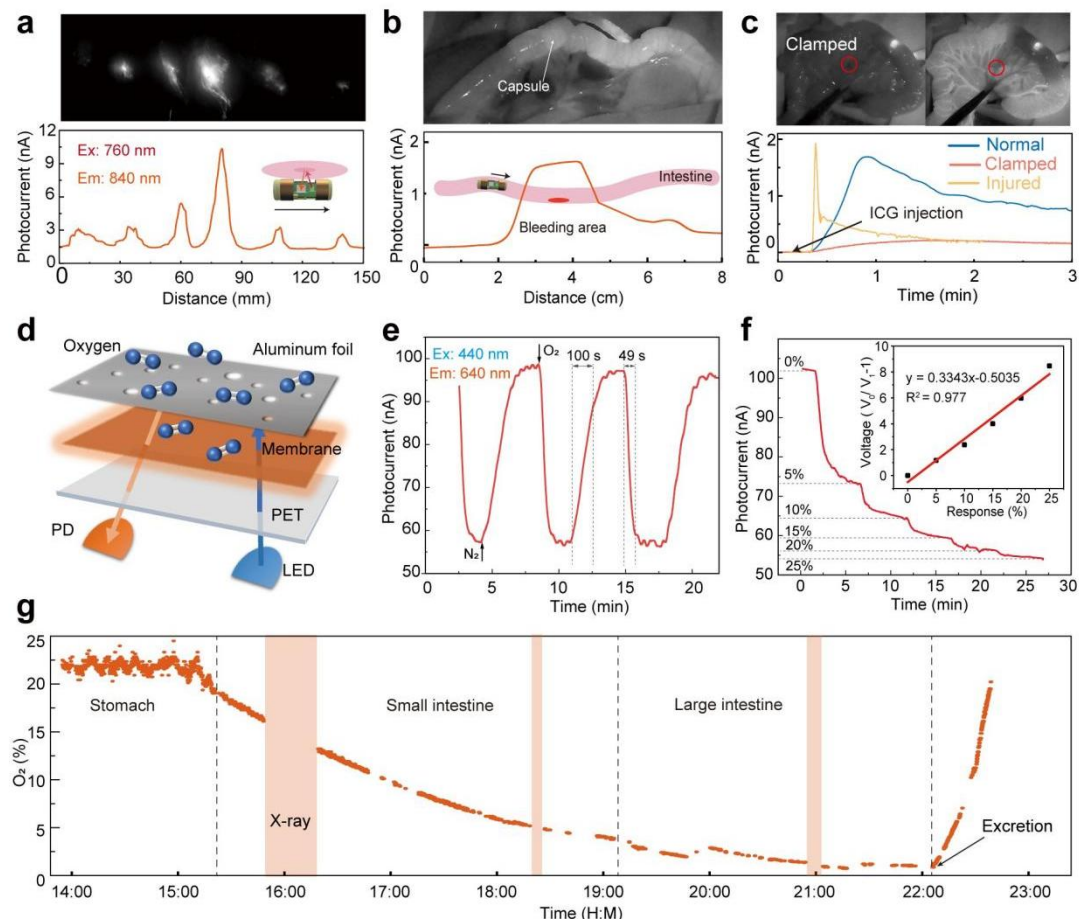


Fig. 5 Spatially Resolved Photoluminescence Measurement of Gastrointestinal Bleeding and Gas Distribution (a) ICG fluorescence detection in *ex vivo* chicken tissue. Correspondence between fluorescence camera imaging and sensor readings (b) *In vivo* fluorescence detection of intestinal bleeding sites. (c) Blood perfusion monitoring in different conditions. (d) Structural design of the optical oxygen sensor. (e) Dynamic response and (f) linear calibration of the oxygen sensor. (g) Spatial mapping of oxygen distribution in the rabbit gastrointestinal tract under freely moving conditions.

A clinically widely used vascular and tumor marker, indocyanine green (ICG), was employed to demonstrate the feasibility of the passive scanning protocol. Fig. 5a demonstrates the detection of locally injected ICG in *in-vitro* chicken tissue. As the Pill-Scanner traversed the tissue, it measured regional fluorescence intensity simultaneously. Recorded photocurrent was consistent with fluorescence camera imaging. Further validation involved *in vivo* measurements of bleeding sites (Fig. 5b) and blood perfusion (Fig. 5c) in rabbit small intestine. In the bleeding localization experiment, a hemorrhagic point was surgically created within the intestine. Intravenously administered ICG extravasated with blood and accumulated at the bleeding site. Extravasated ICG is trapped in the interstitial space and thus escapes hepatobiliary clearance, so approximately 30 minutes after the ICG injection, a significant increase in photocurrent was detected immediately upon the Pill-Scanner passing the bleeding site. Supplementary Fig. 12 shows the location of the bleeding points within the body. The positioning coordinates and the 3D reconstruction position were highly consistent with the

results of imaging examinations. For the perfusion experiment, ischemia was induced by clamping the mesenteric arteries. Photocurrent data distinctly differentiated perfused from ischemic zones. Dynamic data revealed intricate perfusion details: although major vessels remained intact, prolonged clamping disrupted local microcirculation, causing incomplete perfusion and transient fluorescence responses. In this approach, the Pill-Scanner's position was synchronized in real time, thus enabling the marking process to be completed before its approach to the ROI, and even allowing for real-time perfusion assessment. This sensing-positioning synchronization capability enables ingestible optical sensors to overcome penetration depth limitations and measure the luminescence in situ, so as to localize active lesions or the spatiotemporal mapping of interested biomarkers, thereby promoting photoluminescence detection as a low-cost and non-invasive screening method for gastrointestinal diseases.

To demonstrate the active scanning protocol, a phosphorescence oxygen-sensitive membrane was integrated inside the Pill-Scanner (Fig. 5d). The porous aluminum foil provides the reflective layer and the breathable base. The ground-state oxygen molecules can cause a decrease in the lifetime of phosphorescence and a temporary decline in intensity. This membrane had quick oxygen desorption and adsorption times of approximately 100 s and 49 s, respectively (Fig. 5e), which helps to obtain reliable results in dynamic tests. Fig. 5f shows the linear calibration of the photocurrent response. It conformed to the Stern-Volmer equation and had a wide detection range covering from 21% in air to 0% in an oxygen-free environment. After all the calibrations were completed, the Pill-Scanner was fed into a rabbit to monitor the variation of oxygen concentration in the digestive tract (Fig. 5g). In the upper digestive tract, there was no significant decrease in oxygen content. At approximately 15:00, the oxygen concentration decreased continuously and slowly. The positioning coordinates indicated that the Pill-Scanner had begun moving toward the deeper regions of the digestive tract. The X-ray image also confirmed that the capsule had left the stomach and entered the intestine. In the small intestine, this concentration decrease was almost uniform until it dropped below 5%. The fermentation action of microorganisms gradually consumed the oxygen in the intestinal contents. As the path extends, the oxygen content decreased and reached an almost anaerobic environment in the colon and rectum. This variation data aligns with and mutually validates the previously reported results of *in vivo* redox potential measurements in the digestive tract⁹.

Real-time Precise Active Identification and Localization of GI Dysfunction Regions

Complications such as intestinal dysmotility and obstruction may occur after digestive tract surgery, thus requiring periodic passive postoperative evaluation of the recovery of gastrointestinal function⁴³. To reduce the healthcare burden, including the occupancy of personnel and large equipment, we envisioned and validated a novel approach for active, precise, safe, and continuous postoperative gastrointestinal monitoring leveraging spatio-

temporal gastrointestinal scanning technology. As shown in Fig. 6a, three experimental paths were designed. In the normal path experiment, the Pill-Scanner was administered orally to the rabbit and passed through the entire GI tract to obtain reference baseline data. In the ileus path experiment, the Pill-Scanner was implanted directly into the duodenal lumen via an abdominal surgery to simulate the effects of anesthesia and laparotomy on GI function. For the obstruction path experiment, besides sensor implantation, an obstruction model was created at the jejunum, and the obstruction site was marked by a barium impregnated thread. The objective of this experiment is to leverage the real-time sensing and localization functions to validate the sensor's ability to actively identify dysfunctional regions and report their status.

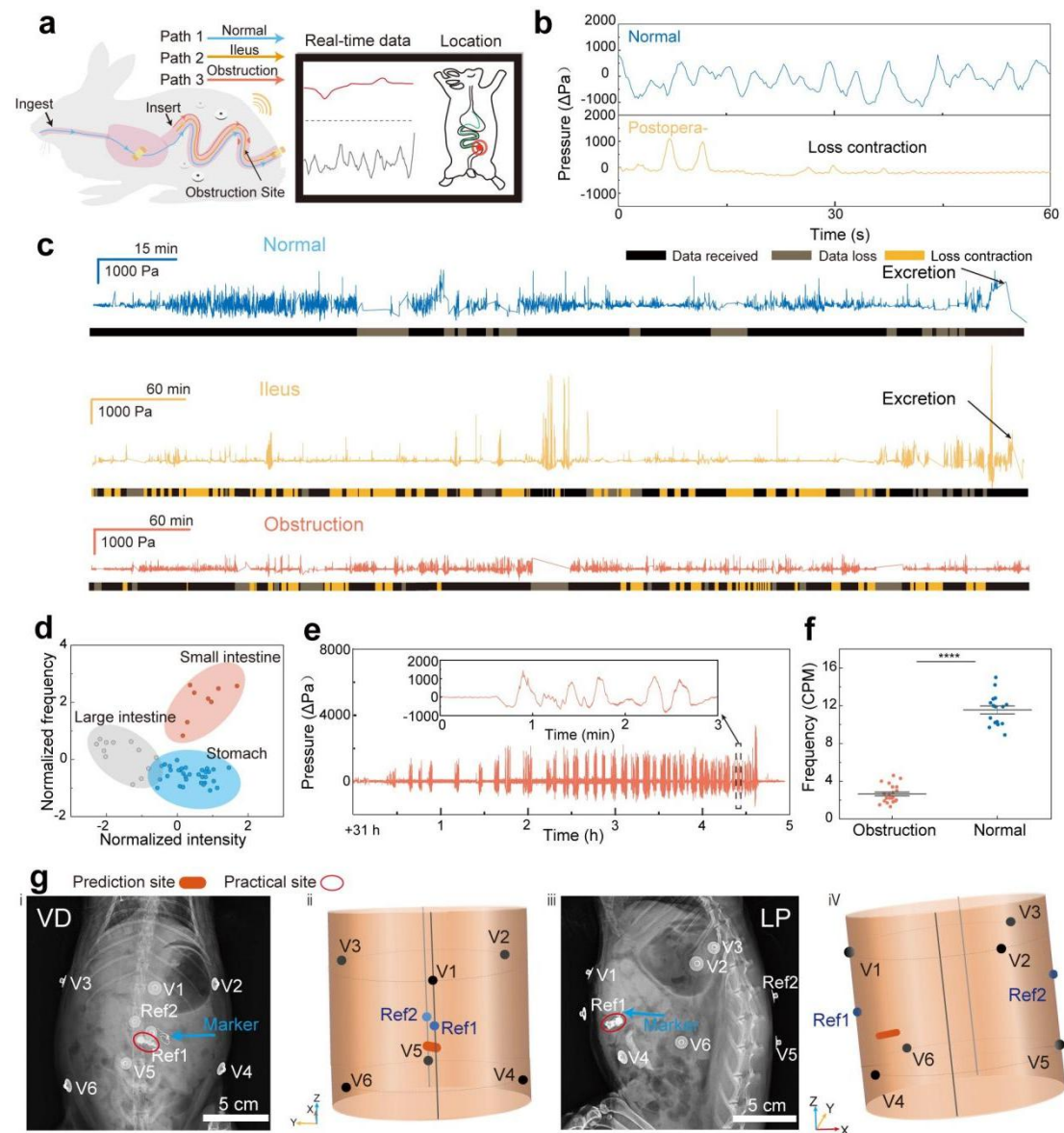


Fig. 6 Real-time Monitoring of Postoperative Gastrointestinal Dysfunction (POGD) and Obstruction Localization. (a) Conceptual and experimental design for POGD monitoring. (b) Waveform comparison of normal GI motility and postoperative GI motility. (c) Primary experimental data across all three paths. (d) Region-specific clustering analysis of normal contraction. (e) Abnormal

contraction waveforms near the obstruction site. (f) Frequency analysis of abnormal contraction waveforms revealed significantly lower rates compared to normal states ($p < 0.0001$). (g) Localization of the abnormal region and corresponding X-ray imaging, including ventral dorsal (VD) position and lateral position (LP) views.

Fig. 6b shows the difference between the normal and postoperative intestinal contraction waveform. Under normal physiological conditions, it is continuous and regular, while the postoperative waveform exhibits random interruptions and strength reduction due to anesthesia and surgical trauma⁴⁴. This prolonged stagnation represents the primary sign of Postoperative Gastrointestinal Dysfunction (POGD). Fig. 6c shows partial long-term data from all experiments. In the normal path experiment, intestinal contraction never ceased. In contrast, initial contractions in both the ileus and obstruction paths exhibited random pauses and a decrease in intensity. The difference was that the stagnation ratios of the ileus path decreased gradually. Normal contractions resumed after approximately 7 hours, followed by spontaneous excretion of the sensor from the rabbit 1.5 hours later. But the contraction in the obstruction path never recovered to normal throughout the observation period. Analysis of normal contraction across the rabbit digestive tract revealed its regional characteristics (Fig. 6d, Supplementary Fig. 13 and Supplementary Video 6). These data served as reference values for the normal state. Once a prolonged deviation was observed in the corresponding region, it implied that a lesion had occurred in that region. Thirty-one hours postoperatively, intestinal contractions in the obstruction model remained abnormal. Fig. 6e shows the unique waveform alternating between stagnation and contractions with progressively shortening cycles. Presumably mediated by compensatory mechanisms at the obstruction site, contraction intensity increased significantly from approximately 1000 Pa to over 2000 Pa. Localization coordinates showed that the sensor had stopped moving, with recorded contraction frequency around 3 CPM which is significantly lower than the normal state of 12 CPM (Fig. 6f). All data suggested the capsule had reached the modeled obstruction site. The X-ray image in Fig. 6g confirmed the sensor's retention at the marked site. The localization coordinate and its 3D reconstruction position show good agreement with the actual image. Compared to traditional postoperative monitoring based on clinical scales and physician experience, the Pill-Scanner significantly reduces operational and usage costs, and, by safely providing precise and quantifiable data, can be administered postoperatively or even implanted directly during surgery, thus enabling long-term continuous monitoring of GI recovery processes, identification and localization of abnormal areas, and optimization of postoperative care workflows. Moreover, these results further demonstrate the possibility of our technology to carry out complex medical tasks safely and achieve integrated gastrointestinal disease monitoring, identification, and localization.

Discussion

For the first time, we demonstrate that an ingestible capsule sensor can fully integrate critical functionalities, including wireless communication, real-time coordinate tracking, and multi-modal biochemical and physiological sensing, within the safety-constrained volume of 0.5 cm³ without compromising either device size or operating lifetime. The comprehensively optimized low-power body coupled communication reduces power consumption by an order of magnitude compared to previous devices, and the reduction in size does not compromise performance or operating time. This not only minimizes interference with the gastrointestinal physiological state, but also improves data accuracy while ensuring safety. The frame-supported membrane design optimizes spatial utilization and mechanical robustness, while facilitating biochemical and physiological sensing, including optical, chemical, and mechanical signals. These advances enable us to achieve high-resolution spatiotemporal GI healthy monitoring of multi-modal parameters from ingestion to excretion.

These advancements eliminate the long-standing retention risk inherent to ingestible sensors and provide a novel tool for screening and locating of GI diseases. Moreover, our system can provide precise data closest to the natural state, offering an effective and objective evaluation method for studying gastrointestinal micro-ecology and diseases with complex mechanisms or stress-related conditions, such as irritable bowel syndrome, while significantly improving the welfare of experimental subjects. Furthermore, the methods and technologies proposed in this study possess universality and transferability to other applications. The proposed high-precision dipole positioning technology can also be used for intelligent drug delivery, in situ sampling, and micro-robot navigation. The developed low-power coupled communication technology can also be used for high-speed, low-probability-of-intercept secure data transmission across in-body and on-body scenarios, whether the targets are statically implanted or freely moving, enabling a unified link protocol for interventional, wearable, and implantable sensors to advance the implementation of the "body area network" concept for *in vivo* medical sensors.

Methods

Electronics Design

The detailed circuit diagram can be found in Supplementary Fig. 14. A four-layer FR4 PCB measuring 5.8×11 mm² was manufactured by Shenzhen JLC Technology Group. A Texas Instruments low power microcontroller MSP430FR2433 was used as the master controller. For gastrointestinal motility monitoring, a Bosch BMP280 was used as the temperature and pressure sensor. For the fluorescence test, an Osram SFH2704 photodiode with a filter was used. The transimpedance amplifier was built by Analog device MAX44265. A Texas Instruments

SN74AUP1G57 was used as the communication modulator. Two series $\varnothing 4.8 \times 2.15 \text{ mm}^3$ silver oxide batteries (Seizaiken, SR421SW) were installed. The main power supply of 2.8V was generated by a Texas Instruments TPS63901. The power supply signal was generated by a tunnel magneto-resistive sensor, TMR1366G, made by Multi Dimension. The assembled electronic capsule can be stored in the magnetic field for a long time ($\sim 200 \text{ nA}$ shutdown current), once the capsule leaves the storage field, the whole system starts to power up (Supplementary Video 3).

Device Assembly

The detailed assembly process can be found in Supplementary Fig. 15. First, two silver oxide batteries (SR421SW) were soldered to the main board with silver paste and copper wires. All functions were checked by an oscilloscope subsequently. Then, the main board was assembled in the cavity structure, which was combined with two pieces of a 3D printed capsule stent. Before packaging, two copper foil coupling electrodes (3M $30 \mu\text{m}$) were attached to the surface of the stent. These two electrodes will form an energy transfer capacitor with the body tissue to transmit communication signals. After completing assembly, above mentioned combination is covered in a medical heat-shrinkable tube (G·APEX MT2-0064). The strength of the package is from the pyrocondensation of the heat-shrinkable tube. To enhance the sensitivity of the pressure sensor, the internal cavity of the device used in the gastrointestinal motility measurement experiment was filled with silicone oil (DOWCORNING 360). Due to the incompressibility of the liquid and the semi-rigid structural design, this process improved the external-to-internal pressure transmission ratio significantly (Supplementary Fig. 16). Finally, the finished product was stored under a vertical magnetic field (45 mT).

Communication Characterization and Power Consumption Testing

Fresh skin-on pork ($20 \times 10 \times 6 \text{ cm}^3$) was used to simulate the human abdominal tissue. To investigate the power consumption and capsule displacement impact on communication signals, the bottom surface of the pork was incised transversely, and a capsule was put into the center of this incision. Two receiving electrodes were positioned on the long sides of the pork to measure the signal strength. The orientation and position of the capsule were adjusted manually, and the variation of the received signal and attenuation characteristics were recorded. The details of the experiment can be found in Supplementary Fig. 17. Capsules with varying electrode widths (0.2, 0.4, 0.6 cm) were fabricated to evaluate the power consumption of body-coupled communication. A 100Ω resistor was placed into the main power supply circuit in series, and the partial voltage was monitored by an oscilloscope to calculate the power consumption of the capsule during operation. The power consumption baseline (beside communication power transmission) was confirmed by using a configuration with no electrode (zero-width electrodes).

Localization Model and Calibration of the Capsule Sensor

The positioning algorithm was designed based on solving the inverse problem of the spatial potential distribution of electric dipoles using neural networks. The algorithm was developed in Python. It used a Multi-Layer Perceptron (MLP), consisting of 7 fully connected layers, and was implemented using the TensorFlow and Keras libraries. The data of the training set (positive problems) was generated by COMSOL, specifying six measurement points and two reference points. By changing the five degrees of freedom of coordinates and attitudes, the model randomly calculated and generated 10000 sets of data, with 12 potential differences (between each measurement point and the reference point) in each set. Among them, 80% of the data was used as the training set and 20% as the test set. Details can be found in Supplementary Fig. 7.

The *in vitro* experiment used a $\varnothing 15$ cm transparent acrylic cylindrical bucket with a 12 cm height of pure water. The distribution of electrodes was strictly consistent with the COMSOL model's configuration. Detail experimental setup can be found in Supplementary Fig. 8. First, the electrical conductivity was adjusted by sodium chloride to be approximately 0.6 S/m, which is similar to that of body tissue. Then, the capsule was suspended in solution using insulated nylon cable ties, with its coordinates and orientation manually adjusted through visual measurement. Finally, the received signal amplitudes (potential difference) were recorded and input into the trained model to calculate the predicted coordinates.

Photoluminescence Sensor Design

Customized excitation light sources, photodiodes, and optical filters were used to target-specific detection of diverse probes. The spectral data of these probes, light sources, and filters can be found in Supplementary Fig. 18. 760 nm (for ICG detection) and 440 nm (for oxygen detection) wavelength LEDs with 100 μ A peak current were used as excitation sources. The excitation light was pulse-modulated to reduce the average power consumption. The transimpedance amplifier's gain was set at 110 M Ω to detect nA-level photocurrents. A series of filter lens sets (purchased from Beijing YongXing Perception) were used for the detection of specific signals. In ICG detection, a band-pass filter with a central wavelength of 750 nm and a bandwidth of 50 nm was used to limit the excitation light wavelength. An 830 nm long-pass filter was used to filter out other wavelengths of light. In oxygen detection, a band-pass filter with a central wavelength of 650 nm and a bandwidth of 100 nm was used. The oxygen-sensitive membrane was fabricated based on previous research¹⁹. A 2 mL mixture of acetone and 1,2-dichloroethane (1:3 volume) was prepared. Subsequently, 0.3 g of polymethyl methacrylate was added to the mixture and put in a magnetic stirrer at room temperature until fully dissolved. After that, 6.05 mg platinum-octaethylporphyrin (PtOEP) was added and stirred for 30 minutes. Afterward, 10.54 mg of c545T was added, and the entire solution was stirred for another 30 minutes. For membrane fabrication, the prepared solution was drop-cast on a porous aluminum foil and cured at room temperature for 24 h. All the chemicals were bought

from Shanghai Aladdin Biochemical Technology and used without further purification.

In Vivo Testing

All animal experiments were approved by Kelian Rabbit Specialized Cooperative, Yuhang, Hangzhou, China. (KL2024-10-16-09) and conducted in accordance with standard ethical guidelines. New Zealand rabbits (weight 3.5 ± 1 kg) were used in all experiments. Prior to actual testing, a 3D-printed patency capsule was used to validate the transit safety (Supplementary Fig. 19). Three rabbits were orally administered the patency capsules, and all of them were excreted with feces within 3 days. In the gastric experiment, all rabbits were fasted overnight. All rabbits were fed capsules orally and resumed feeding after establishing stable communication. The pharmacological model experiment was performed by injecting 0.3 mL of metoclopramide.

Experiments for intestinal bleeding and perfusion detection were performed in a fully anesthetized rabbit. ICG was administered at 0.5 mg/kg via the auricular marginal vein, and bleeding sites were induced by needle-prick injury. All experiments were carried out within the field-of-view of a fluorescence camera to validate the accuracy of sensor responses. Afterwards, the Pill-Scanner and the measured intestinal segment were placed back into the rabbit's abdominal cavity, and localization coordinates were acquired after the abdominal cavity sutured. Prior to X-ray examination, the anesthetized rabbit was secured using a V-shaped sponge support. The animal was carefully repositioned to minimize unintended sensor displacement. ventral dorsal position and lateral position X-ray images were captured to determine the localization error. Gas distribution measurements within the GI tract were performed in a freely moving rabbit. Measurement regions within the gastrointestinal tract were defined using the localization coordinates obtained from the sensor. X-ray examinations were performed every 2.5 h to verify the actual position of the Pill-Scanner.

The postoperative gastrointestinal dysfunction model was constructed through general abdominal surgery, considering both the effects of anesthesia and mechanical injury. Anesthesia was induced by an intravenous injection of disopropofol and maintained by isoflurane via a ventilator. A 10 cm incision was made along the midline of the abdominal wall, and a 1 cm incision was created at the junction of the pylorus and duodenum to insert the sterilized Pill-Scanner. In the ileus experiment, the pathological model was constructed by creating mechanical damage to the jejunum of a rabbit. An X-ray detectable suture was used to mark the site (Supplementary Fig. 20). The incision of the abdominal wall was finally sutured, and the wounds were covered and fixed with bandages. Antibiotics and pain relievers were given to all rabbits after surgery.

Digital Signal Processing

All motility data analysis processes were conducted in MATLAB R2024a. First, a second-

order Butterworth bandpass filter with a pass band of 0.005–1 Hz was applied to remove baseline drift, high-frequency noise, and respiratory interference. After that, initial contraction waves were extracted through baseline correction via median filtering and identified based on adaptive thresholds and minimum peak spacing. Then, false contractions induced by rabbit or capsule movement were eliminated based on the identification criteria of temporal proximity and amplitude similarity between adjacent contraction waves. The algorithm-automated annotation results of gastrointestinal motility are presented in Supplementary Fig. 10-12. Finally, reference data collected from 5 normal rabbits (summary 22 hours in the gastric, 20 hours in the intestinal) were analyzed. Each segment was classified by intensity level based on defined thresholds. Physiological metrics, including mean contraction intensity, contraction frequency, and static pressure, were calculated. Cluster analysis was used to differentiate motility patterns by physiological state and location.

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