Ingestible electronics for diagnostics and therapy

*Christoph Steiger[1,2], Alex Abramson[1], Phillip Nadeau[3,4], Anantha P. Chandrakasan[3], Robert Langer[1,5] and Giovanni Traverso[1,2,5]**

Abstract | The gastrointestinal (GI) tract offers the opportunity to detect physiological and pathophysiological signals from the human body. Ingestible electronics can gain close proximity to major organs through the GI tract and therefore can serve as clinical tools for diagnostics and therapy. In this Review, we summarize the physiological and anatomical characteristics of the GI tract, which present both challenges and opportunities for the development of ingestible devices. We describe recent breakthroughs in materials science, electrical engineering and data science that have permitted the exploration of technologies for sensing and therapy via the GI tract. Novel sensing opportunities include electrochemical, electromagnetic, optical and acoustic protocols, which have the capacity to sense luminal or extra-luminal analytes in the GI tract. We review therapeutic interventions, such as anatomical targeting for drug delivery, delivery of macromolecules and electrical signals. Finally, we investigate major challenges associated with ingestible electronics, including safety, communication, powering, steering and tissue interactions. Ingestible electronics are an exciting area of scientific innovation and they may pave the way for a new era in medicine, enabling patients to receive remote, electronically assisted health care.

[1]*Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA.*

[2]*Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.*

[3]*Microsystem Technology Laboratories, Massachusetts Institute of Technology, Cambridge, MA, USA.*

[4]*Analog Devices, Inc, Boston, MA, USA.*

[5]*Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA.*

**e-mail: ctraverso@bwh.harvard.edu; cgt20@mit.edu*

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In the 1950s, the first generation of ingestible electronics was developed, and clinical proof-of-concept studies demonstrated that they could be used to measure pressure, temperature and pH in the gastrointestinal (GI) tract[1–4]. In the late 1980s and early 1990s, the first commercially available ingestible temperature sensors underwent clinical testing[5–7] (FIG. 1). Breakthroughs in camera technology set the stage for the PillCam, which was introduced in 2000 and later became the first widely used ingestible electronic device[8]. It took the US Food and Drug Administration (FDA) only one more year[9] to approve this capsule endoscopy system. The PillCam offered the ability to more readily evaluate the small intestine, which would otherwise require complex endoscopic procedures, such as double balloon enteroscopy[10]. Widespread acceptance of this technology by physicians inspired scientists to develop complex ingestible electronics with the capacity to provide rich data sets about human health[11].

Breakthroughs in materials science[12–16], electrical engineering[17–20] and data science[21], as well as developments in mobile computing and decentralized medicine, have fostered aspirations for new ingestible surgical and diagnostic devices. Ingestible sensors can be exposed to a broad array of signals to monitor disease and health, including GI-related signals, such as local biomarkers that can be linked to GI inflammation, and signals that can be used to evaluate the function of adjacent organs, such as heart or respiratory sounds[22] (TABLE 1).

In this Review, we provide an overview of the anatomy, physiology and pathophysiology of the GI tract in the context of possible sensing and therapeutic applications. We discuss electrochemical, electromagnetic, optical and acoustic sensing concepts and provide an overview of biodegradable materials and fabrication methods[12,23]. Finally, we discuss challenges related to the clinical application of ingestible electronics and highlight how materials science can help to overcome these limitations.

The gastrointestinal tract

The GI tract is involved in the physiology of every organ. The main function of the GI tract is to digest, metabolize and absorb nutrients; however, the GI tract also trains the immune system[24], possesses a nervous system, communicates with the central nervous system (CNS)[25] and hosts the GI microbiome[26].

The GI tract is a tubular organ with an inner lumen. It is compartmentalized into several functionally different areas (FIG. 2). The GI wall consists of multiple tissue layers. The innermost (luminal) layer is formed by organized epithelial cells, which maintain the appropriate

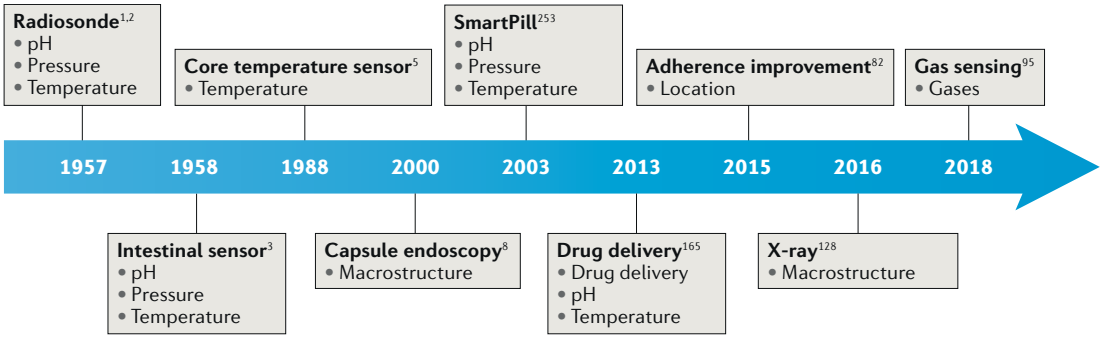


Fig. 1 | **Major milestones of ingestible electronic devices.**

environment by absorbing and secreting nutrients, enzymes, mucus, protons and multiple other molecules. The luminal mucosal layer also regulates the permeation of essential molecules, such as glucose and amino acids, and limits the diffusion of toxins into and out of the lumen. Loose connective tissue underneath this layer maintains structural integrity and provides protection against pathogens by hosting a variety of immune cells. Two muscular layers surround the connective tissue and enable passage of food through peristaltic movements. The enteric nervous system orchestrates all these processes and helps to maintain a highly complex homeostasis[27].

Although we refer to each segment of the GI tract as one, there are substantial differences between local geographic areas. For example, the proximal oesophagus has striated muscle, whereas the distal portion consists of smooth muscle. In the stomach, there are differences with respect to cellular components. For example, parietal cells that secrete hydrochloric acid are located in the proximal stomach[28]. Similar complexity and variation are being elucidated for the small intestine and colon at the cellular level. These local tissue properties provide unique opportunities for targeted sensing and therapy[29,30]. Pathologies of the GI tract can be broadly classified according to their anatomical location[29].

Oesophagus

Following initial ingestion, food reaches the oesophagus and is transported to the stomach through peristaltic contractions. Important pathologies that can affect the oesophagus include cancer, motility disorders, infection, tissue irritation caused by refluxing gastric fluid and abnormally dilated venous vessels. These conditions can be assessed using endoscopic procedures and thus are amenable to capsule endoscopy evaluation[31].

Stomach

The stomach is involved in the mechanical, enzymatic and acid-mediated digestion of food. In the stomach, food is exposed to gastric fluid, which contains hydrochloric acid and gastric enzymes, such as pepsin and gastric lipase. Secretion of mucin and hydrogen carbonate at the gastric wall establishes a zone of fine-tuned homeostasis. This zone shields epithelial cells from the degradative gastric fluid. *Helicobacter pylori*, a Gram-negative bacterial pathogen that can colonize the gastric mucosa, can create an imbalance in the gastric homeostasis by producing ammonia, proteases, vacuolating cytotoxin A and phospholipase[32]. *H. pylori* infection is associated with gastric diseases such as gastritis, gastric ulcers and stomach cancers[33]. Diagnosis of these sequelae generally requires both gastroscopy and biopsy to rule out malignant neoplasms[34]. Gastroparesis, which is a medical condition associated with impaired motility of the stomach and occurring in many patients with diabetes mellitus[35], requires scintigraphic measurement of gastric emptying time for formal diagnosis.

In a healthy stomach, a thick acidic liquid, which is called chyme, is generated through muscular contractions that mix solid and liquid meals with gastric fluid to facilitate mechanic, enzymatic and acid-mediated digestion. The chyme contains partly digested food particles, which are small enough to pass through the pyloric sphincter into the small intestine. This size dependency[36] can be exploited by ingestible devices and dosage forms for long-term sensing[37] and drug delivery[16].

Small intestine

In the duodenum, which is the first segment of the small intestine (FIG. 2), the acidic chyme is exposed to bicarbonate-containing biliary and pancreatic secretions. In the small intestine, enzymes and bile acids support further digestion and absorption of proteins, lipids and carbohydrates[38]. Mucin and bicarbonate-secreting glands protect the intestinal wall from auto-degradation[39]. Homeostatic imbalance of this environment is associated with a variety of pathophysiologic states, including peptic ulcers and cancer[40]. In addition to an array of membrane-based transporters, two levels of finger-like evaginations increase the surface area of the small intestine, facilitating nutrient absorption[41]. The first level contains villi, which are finger-like evaginations that cover the innermost epithelial tissue layer. The villi have finger-like projections called microvilli, which form the second layer of evaginations. Pathophysiological breakdown of these villi, called villous atrophy, is commonly associated with coeliac disease[42].

Nutrient exposure and absorption are controlled by a highly regulated immunocompetent control system and its concentric oriented lymphoid follicles[43]. Imbalances in the homeostasis of exposure, absorption, microbiota

Table 1 | **Analytical design space of ingestible electronics**

Signal	Examples	Diagnostic value	Refs
Biomarker	Gas; small molecules; DNA; RNA; proteins	GI infection; IBD	91–97
Location	Localization and orientation of capsule endoscopes and other ingestible electronics	Monitoring of medication adherence; targeted drug delivery; disease localization for surgery	84–86,128, 158,159,165
Structure	Tissue-specific architecture, such as epidermal, gastric, intestinal or colonic tissue	IBD; peptic ulcer disease; coeliac disease; cancer	68,204,258
Motion	Peristalsis of the oesophagus, stomach, small intestine or colon	Motility disorders of the stomach, small intestine and colon, including gastroparesis, postoperative ileus and constipation	35,87,88
Temperature	Temperature within the GI tract	Core body temperature evaluation	6,7,259
Sound	Sounds associated with GI motility; heart sounds; respiratory sounds	Intestinal obstruction; cardiac and vascular pathologies; pulmonary pathology	22,260
Microbiota	Bacteria; fungi; viruses	Dysbiosis; IBD; GI infections	24,261,262
pH	Gastric, intestinal or colonic fluid	Hyperchlorhydria and achlorhydria; inflammation	258,263,264
Pressure	GI pressure	Motility disorders; hydration states	4,212,265–267
Electrophysiology	Gastric electrical activity	Motility disorders; enteric plexus activity; cardiac monitoring	163,164
Food	Food	Luminal content monitoring for nutritional status monitoring	268

GI, gastrointestinal; IBD, inflammatory bowel disease.

and immune response can also cause pathologies in the small intestine[44,45], including conditions associated with impaired absorption, such as lactose intolerance[46], and autoimmune diseases, such as Crohn's disease[47]. Moreover, motility disorders often affect the small intestine in the form of postoperative ileus[48]. Capsule endoscopy is used for the diagnosis and monitoring of diseases that affect the small intestine, because techniques such as gastroscopy can reach only a limited area of the small intestine[49] and double balloon enteroscopy, which can be applied to evaluate greater portions of the small intestine, requires specific expertise and infrastructure.

Colon

The vast majority of nutrients are taken up by the body before the chyme reaches the colon[50]. In the colon, microorganisms continue to degrade the aqueous suspension, leftover materials agglomerate and water is absorbed. The microbiota interact with the CNS and enteric nervous system (gut–brain axis)[51] and regulate the peripheral immune response, and changes in the microbiome may be associated with systemic inflammatory diseases[44,52]; for example, microbiota changes have been associated with nervous pathologies, including multiple sclerosis[53] or Parkinson disease[54]. Therefore, signals or surrogates, such as microbial distribution or calprotectin levels, have been suggested as diagnostic markers for systemic and local GI pathologies[55–60]. Other common diseases in the colon include infections (for example, *Clostridium difficile*), diverticulitis, vascular insufficiency and colon cancer[29].

Clinical applications

Ingestible electronics can be applied to systemically monitor GI health and disease by detecting signals in the different compartments of the GI tract (TABLE 1).

Capsule endoscopy

Capsule endoscopy was first approved for the evaluation of occult GI bleeding and, subsequently, for the evaluation of inflammatory bowel disease[61–66]. Conventional capsule endoscopes contain high-resolution cameras, silver oxide batteries, microcontrollers, antennas and light-emitting diodes (LEDs). These devices can transmit videos of the GI tract for up to 12 hours to a wearable receiver[67] (FIG. 3a). The video is then evaluated by a gastroenterologist in a 40–120-minute viewing session[68]. Commercially available capsule endoscopes largely share characteristics such as size or form factors required to record and transmit high-quality videos, but they are also associated with a risk of intestinal obstruction (BOX 1). Extensive data sets on safety and efficacy from clinical trials, collected over two decades, in combination with the possibility to visualize the small intestine, provide evidence of the risks and benefits of capsule endoscopes[63,69]. For example, a high level of evidence is available for the diagnosis of occult GI haemorrhage[61–63]. This condition is typically first evaluated by conventional upper GI endoscopy and colonoscopy. If the diagnostic procedures suggest small bowel bleeding, capsule endoscopy is applied to collect further information. Small intestine capsule endoscopy is also recommended in patients with suspected Crohn's disease after negative ileoscopy[63,70,71]. Evidence for colon capsule endoscopy, for example, in the detection of polyps, is low to moderate[64–66,72] and largely based on a series of comparative studies between capsule endoscopy and colonoscopy[73–75].

Current challenges that may impair broader use of these systems include the inability to steer the device or to perform histological examination and the risk of triggering GI obstructions[76,77] (BOX 1). Moreover, conventional endoscopy allows for additional environmental and directional manipulation (for example,

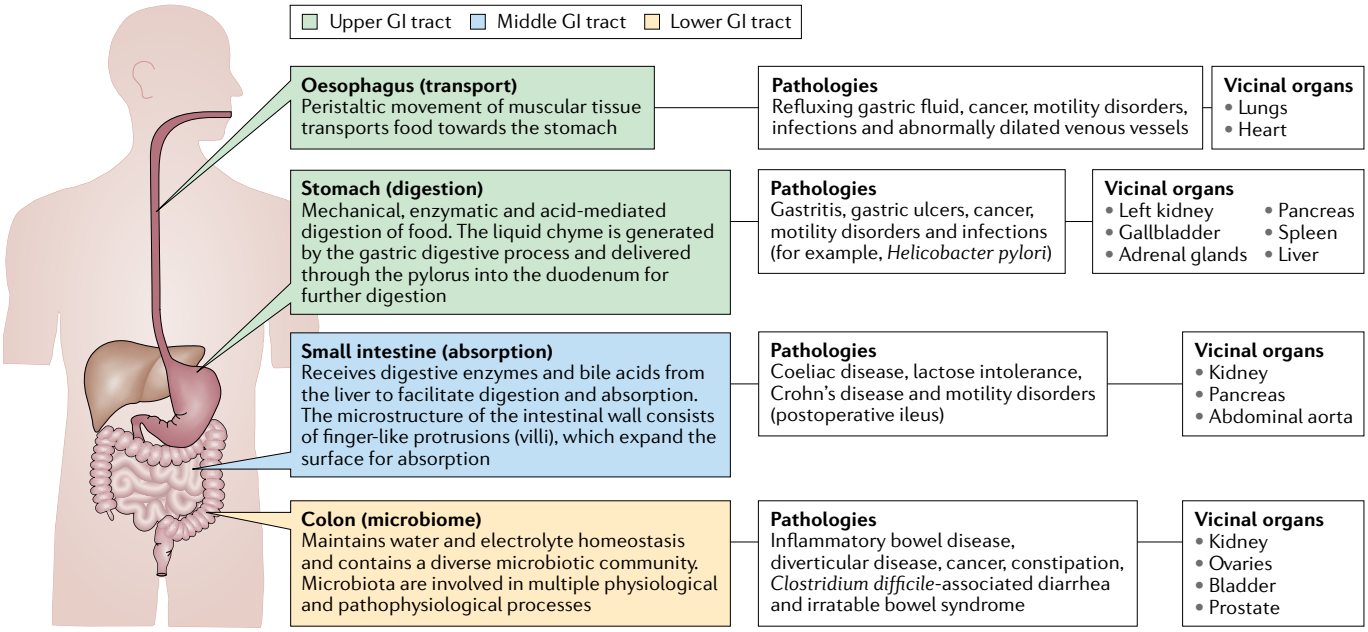


Fig. 2 | **Gastrointestinal anatomy, physiology and pathophysiology.** The main organs of the gastrointestinal (GI) tract and vicinal organs are described to demonstrate the potential of ingestible electronics to monitor signals in the GI tract and extra-GI signals.

flushing, suction, injection and biopsy), which cannot be performed by current capsule endoscopes. Although several autonomously moving ingestible devices have been developed and evaluated in preclinical settings[78–81], research is needed for the clinical translation of these devices. In particular, safety challenges need to be addressed, such as the risk of obstruction or perforation caused by legs or arms used for locomotion or manipulation[81].

Digital compliance management

Ingestible electronic devices can be included in conventional medication to address medication non-adherence[82,83] (FIG. 3b). Among the US population, approximately 20–50% are non-adherent to chronic drug treatment plans, which is estimated to translate into a preventable annual burden of $100 billion for the US healthcare system alone[83]. To address this challenge, an oral drug product can be tagged with a radio-frequency identification (RFID) chip, for example, Proteus Discover, which monitors a patient's compliance to a specific treatment plan[84]. After ingestion and upon contact with gastric fluid, the Proteus Discover system is powered by a galvanic couple and communicates its identification code to a receiver patch, which is worn by the patient (FIG. 3b). Proof-of-concept studies assessing the transmitting efficacy have been performed by attaching the chips to inert tablets, which were co-administered with tuberculosis medications[84]. Subsequent studies to assess the impact on medical adherence were performed with kidney transplant recipients receiving mycophenolate therapy[85]. The patients were followed over a mean of 9.2 weeks; the intake observed by medical personnel was detected with an accuracy of 100%, and unobserved taking adherence was 99.4% throughout the study. Therefore, RFID tagging can provide reliable measurements of the intake and timing of intake of drugs.

Improvement in clinical outcomes was first demonstrated in patients with uncontrolled hypertension and type 2 diabetes[86]. Compared with conventional medication, systolic blood pressure was significantly reduced in patients receiving RFID-tagged medication (mean reduction in blood pressure 9.1 mmHg, 95% CI 14.0–.3 mmHg, after 4 weeks). Moreover, diastolic blood pressure, diabetes status (glycated haemoglobin A_{1c} (HbA_{1c})) and lipid metabolism (low-density lipoprotein-C (LDL-C)) were nonsignificantly reduced. In these patients, the RFID chip was co-encapsulated with the patient's conventional medication in the study arm.

pH, temperature and pressure sensors

Single-use orally ingested multimodal systems can be used to monitor easily accessible biomarkers, such as GI pH, temperature and pressure. SmartPill is an FDA-approved, wirelessly communicating capsule[87], distributed by Medtronic, which contains sensors for pH, temperature and pressure. SmartPill is marketed as a motility testing system and can be applied, for example, to measure gastric emptying time — an important parameter for the diagnosis of gastroparesis[88] (TABLE 2). Current clinical guidelines recommend further validation before this procedure can replace the current standard of care for diagnosing gastroparesis, which involves complex and time-intensive procedures, such as scintigraphy[35,89].

FDA-approved ingestible temperature sensors (TABLE 2) are also available to measure core temperature over time and have been used by athletes, soldiers and firefighters for decades[7]. In general, readouts of peripheral sensors are influenced by fluctuations of the external temperature and thus are associated with low accuracy, even when the external temperature remains constant[90].

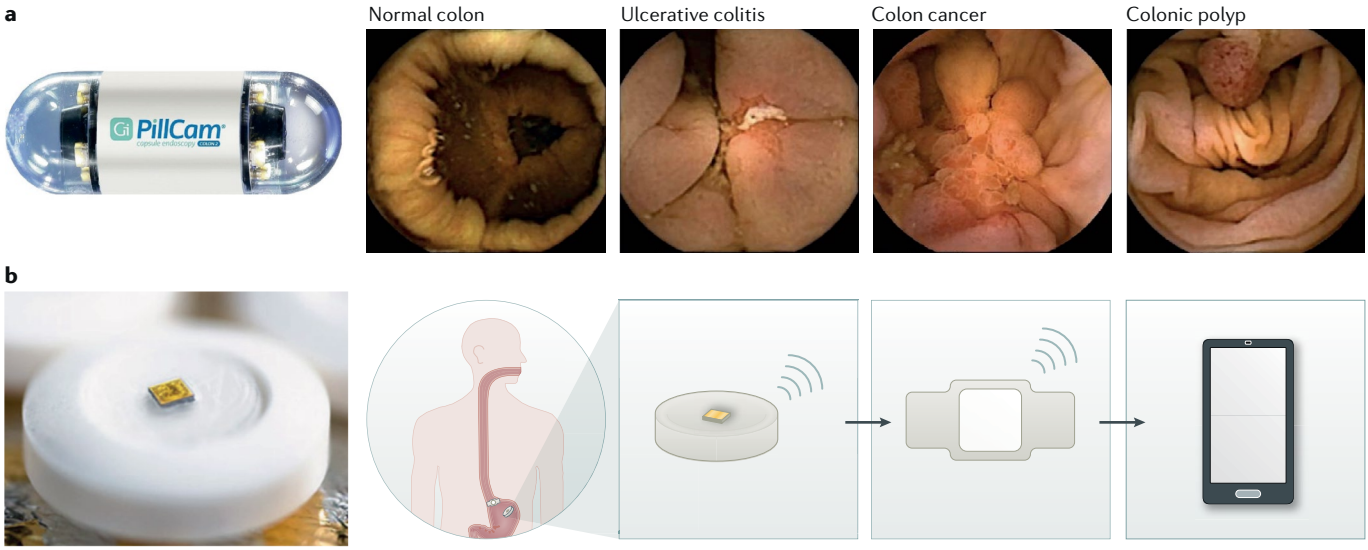


Fig. 3 | **Clinically applied ingestible electronics. a** | An ingestible video capsule endoscope can be applied to record images of the gastrointestinal tract. The four images taken by the video capsule show potential readouts. **b** | Digital compliance measurement using an ingestible radio-frequency identification chip. Ingestion is registered by a wearable patch, which gives healthcare providers the possibility to adapt the therapy based on an unbiased data set. Panel **a** is reproduced with permission of Medtronic, Inc. Panel **b** is adapted with permission from REF.[12], Elsevier and REF.[84], PLOS.

The combination of accuracy, easy application and long duration of measurement constitutes an important advantage of ingestible electronic devices over other marketed systems (for example, oral thermometers).

Sensing technologies and targets

Monitoring biomarkers

Numerous biomarkers present in the GI tract, including small molecules[91], electrolytes[92], physiological gases[93–95], proteins[96] and DNA[97], can potentially be leveraged to assess health and disease states in real time (TABLE 1). The diagnostic potential of some of these biomarkers has been demonstrated, for example, in faecal analysis, which can help to inform the design of ingestible electronic devices. For example, blood in the stool is a faecal marker for the screening of colorectal neoplasia, which is commonly tested by the guaiac test or immunochemical assays; however, ingestible electronic systems can also be applied to test blood in the stool, which has been demonstrated in preclinical settings[98,99].

Other faecal markers[60,100], such as lactoferrin and calprotectin, have been associated with ulcerative colitis, which is an inflammatory disease affecting the colon[101]. Although calprotectin has low diagnostic value compared with the standard of care, which comprises blood tests, radiographic methods and endoscopic procedures[60], its monitoring shows promise when used as a method for early relapse detection[102–104].

Ingestible electronics with sensitive and specific sensing elements can be applied to identify compounds in complex biofluids[99,105–107]. For example, a swallowable capsule with an electrochemical sensor can be used to investigate biomarkers in GI fluids ex vivo by applying a multitude of measurements, including cyclic, square-wave and differential-pulse measurements[108]. This device operates autonomously and transmits signals in real time. Voltammetry techniques can be used to monitor various compounds in biological fluids, including active pharmaceutical ingredients[105–107].

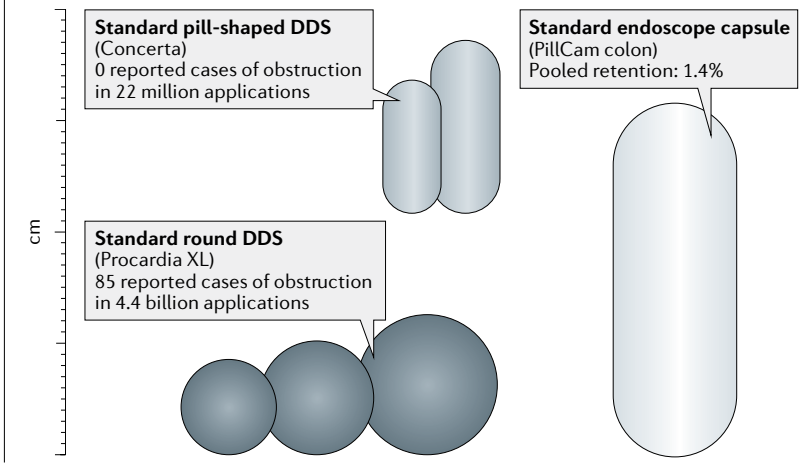
The analytical performance of biosensors in vivo can be substantially improved by coupling electrochemical transduction with advanced materials[109]. For example, conjugates of biomarker-specific antibodies or aptamers can be combined with electrochemical transducers. The transducers can then be modulated by standard electrochemical concepts (that is, voltammetry)[110,111]. Similarly, ion-selective membranes can be used to increase electrode selectivity for relevant electrolytes[112–114]. Such combinations expand the analytical design space of ingestible electronics; however, enabling device operation in the caustic and highly variable environment of the GI tract is challenging owing to sensor fouling. Therefore, research is required to explore different sensing concepts and adapt current technologies for use with GI fluids.

In contrast to liquid-phase sensing, monitoring GI gases with ingestible electronic devices has already been demonstrated in humans[95]. Gas-sensing capsules are made of gas-permeable membranes, which shield the sensitive electrodes from the GI environment, thereby attenuating sensor fouling (FIG. 4a). Semiconducting and thermal conductivity sensing elements can be used, which undergo consecutive heating cycles to achieve sensitivity and specificity towards hydrogen, methane and carbon dioxide. Pilot trials of intestinal gas measurement systems have demonstrated the potential of these ingestible capsules to sense different gastric gases[95,115–117]. For example, the devices were used to detect the distribution pattern of gases along the GI tract of pigs, which were fed different diets[115–117]. In humans, interindividual fermentative patterns were observed in a crossover study with alternating consumption of low-fibre and high-fibre diets[95].

Nanoporous materials, such as metal organic frameworks[118] and carbon nanotubes[119], can also be applied for

Box 1 | **Size restrictions of ingestible electronics**

The risk of device retention and obstruction of the gastrointestinal (GI) tract caused by non-deformable drug delivery systems (DDSs) and ingestible electronics can be linked to size and form factors[178,180–183]. Ingestible electronics require numerous space-occupying components to sense, process and transmit signals. Device retention of a conventional capsule endoscope occurs with a rate of 1.4%[178], and this can be linked to obstruction of the GI tract[180–183], which constitutes a medical emergency. Dimensions and form factors of conventional pill-shaped and round non-deformable DDSs with a known safety profile can be used as a reference point for safe dimensions of ingestible electronics. The size range shown in the figure is taken from REF.[184].



gas-sensing applications. For example, these materials can be placed in arrays to monitor gas profiles within the GI tract, including gases originating from volatile organic compounds[120].

Spectrometric studies of the luminal content of the GI tract can be performed for the detection of intestinal bleeding, based on the absorption characteristics of protoporphyrins[121,122]. For example, two ingestible electronics systems have been developed for blood testing using either a phototransistor[123] or a colour detector[124] to measure the absorption of LED-emitted light shined through the GI fluid. These devices identify blood based on spectrometric methods and thus the approach works for analytes that have unique light-absorption characteristics and are present in high quantities.

Recently, a bacterial–electronic ingestible device, which combines biomarker-sensing bacteria with spectrometric methods[99], has been developed to monitor GI health. In this device, probiotic bacteria are engineered to function as sensors by integrating the luxCDABE operon of the bacterium *Photorhabdus luminescens* into the genome of *Escherichia coli*. The LuxCDABE operon is a light-generating bioreporter that can be used as a bioluminescent reporter for gene circuits. In the device, a haem-sensing circuit is used to detect GI bleeding. Alternatively, different circuits can be used to detect biomarkers such as thiosulfate and acyl-homoserine lactone. Photodetectors inside the ingestible electronic device read the luminescent signal, and antennas wirelessly transfer the information to an external device. The system was evaluated in vivo in a porcine model for the detection of gastric bleeding[99], and the possibility to include different circuits may enable the sensing of other biomarkers as well.

The spectrometric performance of ingestible electronics may be further improved by incorporating advanced spectrometric methods, such as surface plasmon resonance and surface-enhanced Raman scattering; these methods can achieve high sensitivity and specificity through the coupling of optical features with biochemical affinity tests, such as antibody–antigen interactions[125]. However, they currently require complex equipment and are challenged by high and variable background response owing to unspecific absorption, especially in complex biofluids[126,127].

Tissue evaluation

X-ray-based ingestible electronic devices can be used for evaluation of the GI tract[128]. For example, a capsule can be used to map the GI tract by emitting and detecting 2D X-ray beams (FIG. 4b). To achieve wall-centred beam scattering, the patient must first ingest a contrast agent before administration of the capsule. Such a device also contains an integrated electromagnetic tracking system to measure the position and orientation of the capsule. This data set can then be used to generate a 3D image of the GI tract based on a 2D data set. Clinical safety and proof-of-concept studies have already been performed, and larger clinical assessments are ongoing[129–131].

Optical biopsy for evaluation of the GI tract may be realized by applying microscopic and endomicroscopic approaches to capsule endoscopy or pill-shaped tethered systems[132]. For example, in confocal laser endomicroscopy (CLE), a laser is used to focus coherent light at a predefined tissue depth[133,134]. The light is then reflected and refocused through a pinhole to a detector. CLE can generate images at depths of up to ~250 µm with ~1 µm resolution[135]. Medical consensus[135,136], supported by clinical data, provides clinical evidence that CLE can support gastric cancer diagnosis[137], colonic polyp characterization[138] and diagnosis of Barrett's oesophagus[139] with a level of accuracy comparable to that of the current standard of care, although further confirmatory studies are required.

In a tethered confocal microscopy capsule, a CLE-based imaging technique, called spectrally encoded confocal microscopy, can be applied to create 3D reconstructions of the GI tract and to visualize cellular patterns of Barrett's oesophagus[140]. In this imaging method, a rapid wavelength-swept source is used to scan the tissue. Similarly, tethered capsules for imaging have been developed using optical coherence tomography (OCT)[141] or optical frequency-domain imaging (OFDI) for the diagnosis of oesophageal diseases[142,143] (FIG. 4c). OCT is based on low-coherence interferometry, using long-wavelength light to obtain images at penetration depths of up to 3 mm with resolutions of 10–15 µm (REF.[144]). In OFDI, frequency-domain ranging techniques are used to increase sensitivity and imaging speed in comparison with the delay-scanning procedure used in OCT[145]. These imaging methods have the capacity to display histological structures but have limits in visualizing cellular-level details.

Ingestible ultrasound probes can also be used to analyse GI histology[146] and to characterize structural alterations, for example, precancerous tissue[147]. Prototypes

Table 2 | **FDA-approved ingestible electronics**

Type	Name	Company	System
Video capsule endoscopy	• PillCam series • MiroCam series • EndoCapsule series • CapsoCam Plus	• Medtronic • Intro Medic • Olympus • Capsovision	Oesophagus, small intestine and colon systems
pH, pressure, temperature	SmartPill	Medtronic	Multimodal system
Temperature	VitalSense	Phillips	Singular system
	CorTemp	HQ	
Digital compliance management	Proteus Discover	Proteus Digital Health	RFID

FDA, US Food and Drug Administration; RFID, radio-frequency identification.

of a tethered ultrasound drug delivery capsule[148] and an ultrasound imaging capsule[149] have been developed. For example, an ultrasound imaging capsule, which contains an ultrasound transducer array, can be used to visualize different layers of a porcine bowel ex vivo. Although tissue penetration is higher, conventional ultrasound has 1–2 orders of magnitude lower resolution than OCT[150].

Multispectral optoacoustic tomography can be used to assess disease activity, for example, the severity of symptoms in patients with Crohn's disease[151,152]. In this technique, a pulsed laser is used, which is externally directed towards the intestine, where it is absorbed and partly converted to heat. During this process, ultrasound is emitted, and the multispectral emission can provide information on the localization of disease-relevant biomarkers and other molecules (for example, haemoglobin or lipids). The method can be used to distinguish between healthy and diseased states, for example, inflammation and remission of GI diseases. Although this is an externally applied technique, it demonstrates the potential of imaging approaches along the GI tract to monitor disease states.

Monitoring signals from other organs

The GI tract resides in close proximity to major organs (FIG. 2). Therefore, healthy and diseased states of adjacent organs can be assessed from within the GI tract. For example, in a prostate exam, the physician palpates the potentially enlarged prostate through the wall of the rectum. In cardiology, a transoesophageal ultrasound probe is clinically used to determine haemodynamic parameters owing to the close proximity of the oesophagus to the heart[153]. Expanding this approach to ingestible electronics, a microphone inserted into the GI tract of a porcine model can be used to determine the animal's heart rate and respiratory rate using sound[22].

Drug delivery

Oral delivery. Patients usually prefer the oral route for pharmaceutical administration over other routes; however, several challenges associated with the GI tract prevent or complicate the dosing of certain drugs via the oral route, for example, oral delivery of drugs with low solubility, low stability or poor permeability. Despite efforts in academia and industry to overcome these issues and to create new methods for drug delivery, for example, by improving pharmacokinetic drug profiles by co-crystal formulation or co-formulation with permeation enhancers[154–156], these fundamental challenges continue to limit the field of oral drug delivery.

Miniaturization and cost reduction of electronic devices have opened the way for electronic systems in oral drug delivery; for example, preclinical concepts for improved ultrasound-mediated drug permeation[154,157] and clinical concepts for electronically controlled delivery of active pharmaceutical ingredients[158,159] are being explored. Such devices with wireless telemetry functionalities can be used to shuttle drugs to preferred absorption sites along the GI tract. They also provide a tool for personalized and integrated delivery concepts; for example, drug delivery systems that reside in the body can automatically release drugs based on a personalized treatment plan[160]. Similarly, the systems can be used to adjust systemic drug levels, which can be monitored by integrated sensors and regulated by autonomous feedback loops[161,162]. In addition to delivering chemical pharmaceutical ingredients, the field of electroceuticals explores the hypothesis that electrical stimulation can be used to excite neurological networks in the body, providing therapeutic benefits for indications such as neurological diseases or motility-related GI disorders[35,163,164]. Owing to the complex nerve wiring of the GI tract, ingestible electronics may eventually play a role in delivering therapeutic electrical pulses as well as drugs[164].

The market of ingestible electronics for drug delivery is more cost sensitive than other areas in the field of ingestible electronics, because patients must regularly take oral drug delivery devices and the devices are usually not reusable. However, the potential to combine electronics with drug delivery and thus provide solutions to problems such as dose control and bioavailability offers an exciting avenue of future research.

Targeted drug delivery. In 2013, results from a clinical trial provided the proof of concept for the first electronically controlled GI drug delivery system — IntelliCap[165] (FIGS 1,4d). This device has similar dimensions to capsule endoscopes (BOX 1) and contains a drug compartment, a microprocessor, pH and temperature sensors, batteries, a motor to release the drug, a transceiver and an antenna. The IntelliCap system controls drug delivery by precisely tuning a screw-rod-driven plunger inside the drug compartment. Safe passage of the device through the GI tract was confirmed in first-in-human studies, and the release mechanism was validated using scintigraphic imaging, confirming the expulsion of ^{99m}Tc from the system[165]. Scintigraphy was further used to confirm the localization concept. The integrated pH sensor enables the device to assess the pH profile of the GI tract to autonomously determine the localization of the device.

In follow-up studies, it has been demonstrated that the IntelliCap system can be used to tailor the release pattern of model compounds, such as metoprolol[159] and diltiazem[158]. With this ability to simulate in vivo drug release patterns, the company marketed the system as a research tool for early clinical development.

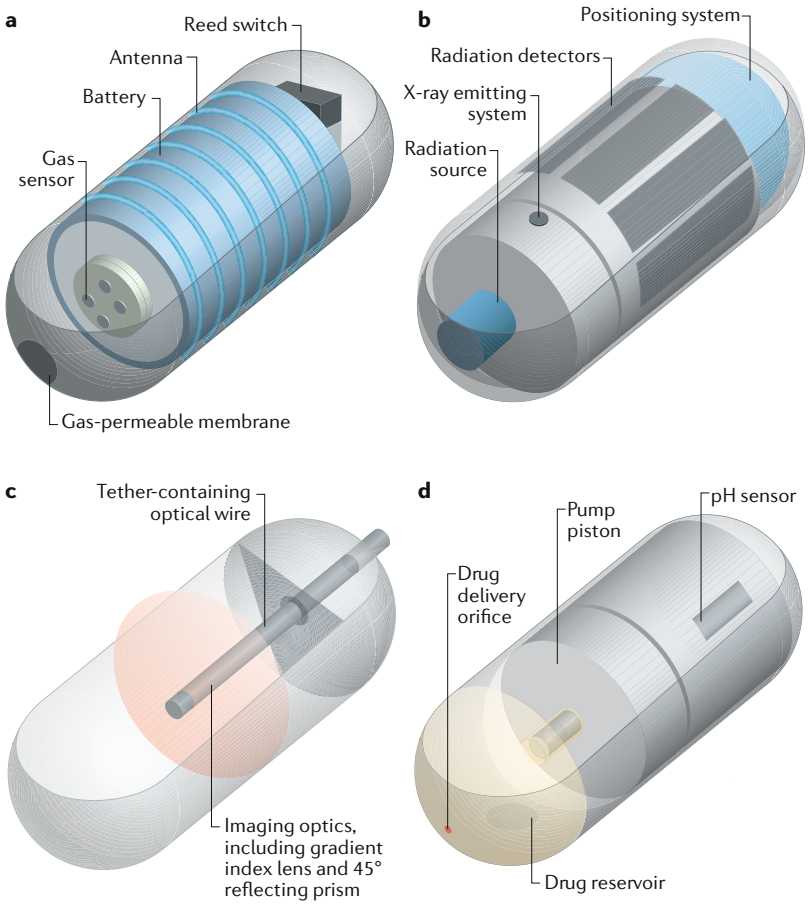


Fig. 4 | **Technologies for ingestible electronics. a** | Gas-sensing capsule. **b** | X-ray scanning capsule. **c** | Optical coherence tomography. **d** | IntelliCap for drug delivery. Panel **a** is adapted from REF.[95], Springer Nature Limited. Panel **b** is adapted with permission from Check-Cap. Panel **c** is adapted from REF.[142], Springer Nature Limited. Panel **d** is adapted from REF.[158], CC BY license.

Less technologically complex concepts employing gas-based[166], spring-based[167] or corrosion-based[37] attenuation can also be applied to control drug release. 3D printing may further be used to design customized drug delivery systems, enabling personalized treatment modes[168].

Permeation enhancement. Multiple electromechanical techniques, including iontophoresis[169], electroporation[170], microjets[171] and ultrasound[172], have been profiled as tools for permeation enhancement in transdermal drug delivery. Microjets and ultrasound have also been suggested for GI applications[157,171]. Ultrasound transiently permeabilizes biological membranes to aid in the diffusion of therapeutic molecules, including macromolecules, through tissue barriers[173], which can be explored for applications in the GI tract[148,154,157,174].

In a proof-of-concept study in various animal models, we demonstrated that rectal ultrasound-mediated delivery of the anti-inflammatory drug 5-aminosalicylic acid leads to a tenfold permeation enhancement as compared with a control group receiving only 5-aminosalicylic acid. Similarly, ultrasound-mediated rectal insulin delivery translates into a hypoglycaemic response, in contrast to rectal insulin delivery without ultrasound[157]. Profiling the pharmacodynamic effects of ultrasound-mediated 5-aminosalicylic acid treatment with chemically induced colitis showed that ultrasound treatment achieved a decrease in disease progression compared with the progression observed in mice receiving non-ultrasound-mediated 5-aminosalicylic acid treatment.

Ultrasound can also be applied to deliver small interfering RNA and mRNA[175], and ingestible ultrasound systems are being explored for rectal and oral drug delivery and as imaging devices[176,177]. Ingestible electronics can be applied to adapt permeation enhancement concepts originally designed for other routes of administration (for example, dermal) for the oral route and to report successful placement of drugs for disease management.

Challenges and solutions

Safety

Ingestible electronics require numerous working components, and thus, the size of the device plays an important role in the design. Large capsules allow complex functionality owing to the possibility to incorporate more components, but the risk of device retention is in direct association with device size[178] (BOX 1). Capsule endoscopy retention occurs at a rate of 1.4% in patients with suspected bowel disease[178], and patient populations with known or suspected Crohn's disease show retention rates of up to 13%[179]. Based on case reports, capsule retention can lead to GI obstruction[180–183]; however, quantitative incidence of obstruction following retention remains elusive. Retention rates obtained by post-marketing surveillance for a series of commercially available non-deformable pills can be used as a reference point for safe dimensions of ingestible electronics[184] (BOX 1). A non-degradable, round osmotic pump drug delivery system measuring 12 mm in its longest dimension caused only 85 reported obstruction cases in a timeframe during which 4.4 billion delivery systems were distributed in the United States[184] (Procardia XL, BOX 1). Similarly, no obstruction was reported in a timeframe during which 22 million comparable pill-shaped delivery systems were administered (Concerta, BOX 1).

Flexible or degradable materials and electronics may also decrease the risk of device retention, for example, through modifications of the different components of ingestible electronics, such as flexible batteries[185,186], antennas[187,188], sensors[189] or other structural parts of ingestible devices[16,190,191] (FIG. 5). Moreover, 3D printing can be applied to integrate electrical circuits into materials such as food or pharmaceutical products. For example, organic semiconductors can be transferred onto oral capsules using a tattoo-paper-like transfer approach[20]. Alternatively, a pulsed laser can be used to generate graphene on carbon-based materials, including coconuts and bread[192], to incorporate power-storing supercapacitors in edible materials. The development of edible and printable electronics[18,19,193,194] has the potential to contribute to the design of disintegrating, non-obstructive ingestible electronics[12]. However, the versatility and complexity of electronic systems and their integral parts (for example, microelectromechanical systems (MEMS)) make the integration of individual manufacturing techniques such as 3D printing challenging[195].

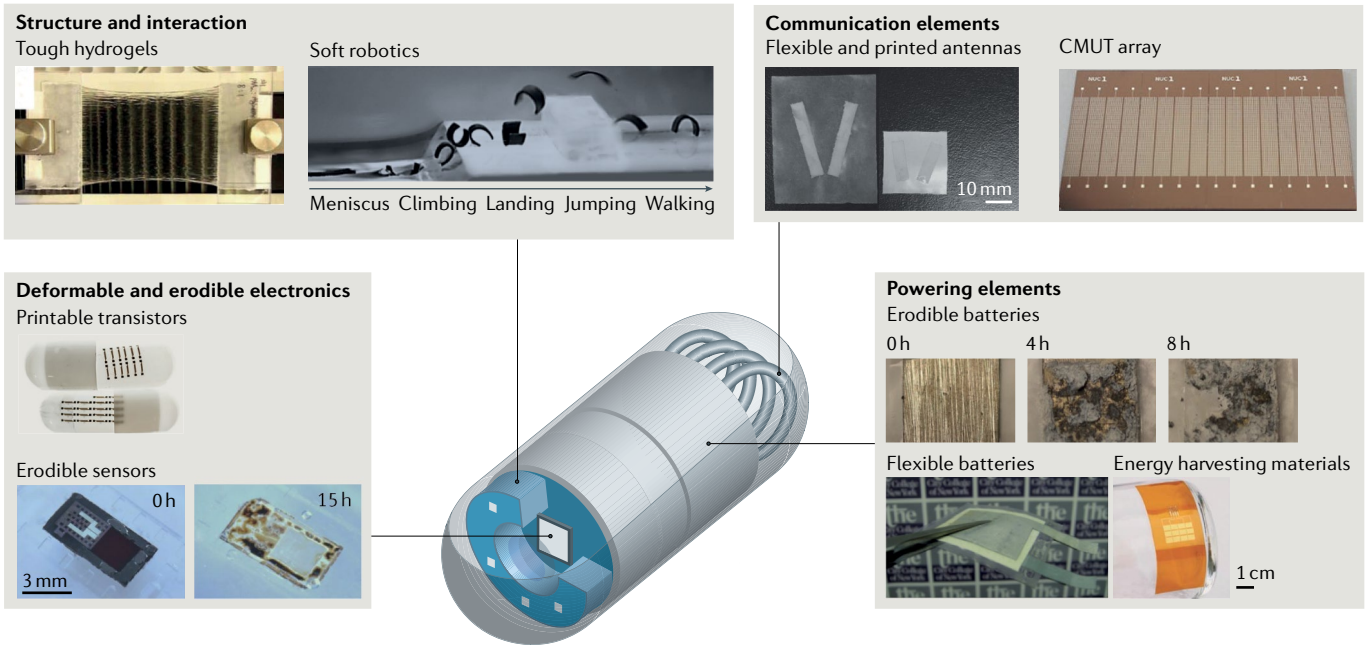


Fig. 5 | **Material design for ingestible electronics.** Material design concepts are shown for structural components, sensors, power supply and communication elements. Soft, degradable or erodible materials and electronics can be used to address the obstruction risk associated with non-deformable ingestible electronics; such materials can be applied to refine functional components, such as antennas, and structural components, such as the housing. Soft robotics may be used to manipulate tissue or manoeuvre devices through the gastrointestinal tract. Flexible batteries, such as Zn–MnO_2 batteries; erodible batteries, such as Mg–X batteries (X = Fe, W, Mo); and energy harvesting materials, such as lead zirconate titanate, can be used as power supplies. New communication technologies, for example, small capacitive micromachined ultrasonic transducer (CMUT) arrays or printable antennas based on cellulose nanopaper composites may be used to address challenges of radio-frequency communication in deep tissue. Tattoo-paper transfer of electrodes on capsules can be applied to design printable transistors, and bioresorbable silicon-based sensors may be used as erodible sensors in ingestible devices. Antenna adapted with permission from REF.[187], Wiley-VCH. CMUT array adapted from REF.[254], Springer Nature Limited. Erodible battery adapted with permission from REF.[14], Wiley-VCH. Flexible battery adapted with permission from REF.[255], Wiley-VCH. Lead zirconate titanate device adapted from REF.[193], Springer Nature Limited. Hydrogel adapted from REF.[256], Springer Nature Limited. Soft robot adapted from REF.[15], Springer Nature Limited. Sensor adapted from REF.[257], Springer Nature Limited. Tattoo-paper platform adapted with permission from REF.[20], Wiley-VCH.

Communication

Ingestible electronics can generate a lot of data, which has to be wirelessly communicated in near-real time to avoid the need to retrieve the capsule at the end of the test. Far-field radio-frequency (RF) communication is the dominant technology used for wireless communication, but it requires a specific antenna size within the device. The dimension of the antenna must be at least one-fourth or greater the wavelength for efficient communication. Body tissues propagate RF signals more efficiently at longer wavelengths (IFAC, dielectric properties of body tissues), and therefore, large antennas are needed to provide adequate communication. However, the size of the device is limited by retention concerns (BOX 1), and therefore, a compromise must be made between antenna size, operating frequency and tissue attenuation. RF transmission works reasonably well for video endoscopy capsules, which usually have a length of a few centimetres and a diameter of 1 cm, with an optimal transmission within the frequency range of 450–900 MHz (REFS[196,197]). Despite requiring centimetre-scale antennas, the key advantage of far-field RF signals is that they are nearly omnidirectionally radiated from the device, allowing any capsule orientation. Furthermore, outside of the high-attenuation environment of the body, far-field RF signal power decays as a function of distance squared, which is advantageous compared with near-field communication because it enables communication to base stations that are up to a few metres away from the body.

For ultrasmall millimetre-scale devices, far-field radiation is difficult or impossible to achieve; however, near-field communication can be realized by applying a specific design, if the communication distance is short. For example, in the 1 mm × 1 mm × 0.3 mm Proteus Discover medication adherence monitoring system, a near-field communication mechanism is applied by electric field modulation at a distance of approximately 10–20 cm from the RFID within the stomach to the body-worn receiver patch[82]. The inclusion of an insulating 'skirt' disk of 5 mm diameter around the device is required to spread the electric field and promote reception at the surface of the body by the body-worn patch.

Magnetic field modulation, which is the complement of electric field modulation, was used in early ingestible electronic devices, for example, pressure sensors, and is still used in systems such as the CorTemp

sensor[2,198]. The disadvantage of both electric and magnetic near-field systems is that the signal is available along only a limited number of axes, making capsule orientation difficult. This issue can be addressed by including additional transmitters or receivers to cover multiple orientation axes. Another disadvantage is that the signal decays with the fourth power of distance or less, which substantially limits the communication range. However, the frequency choice is not as much limited by the dimensions of the antenna as for far-field systems, which simplifies electronics design, enables lower frequency operation and saves power. For example, the Proteus Discover system operates at 10–30 kHz and is powered by a small and brief pulse of electric charge, generated from a galvanic reaction with stomach acid[82].

Alternatively, cutaneous electrodes can be applied for electric in-body communication to improve the communication efficiency of ingestible devices[199] (FIG. 6). For small implants, ultrasound waves can be used for communication owing to the good propagation of sound waves in tissues. Using sound waves, up to a 8.5 cm communication depth can be achieved with a 30.5 mm^3 implant[200]. To improve the efficiency of RF communication, the antenna design, for example, size (small size translates into low radiation efficiency) or bandwidth, can be modified by exploring biocompatible and transient antenna concepts (FIG. 5), for example, antennas printed on cellulose fibres or composed of degradable poly(vinyl alcohol)-based composite films[187,201,202]. Similar to how satellites unfold antennas to remain compact during launch, unfolding or expanding transient antennas may be used for ingestible electronics to overcome size limitations, which define the safety profile (BOX 1).

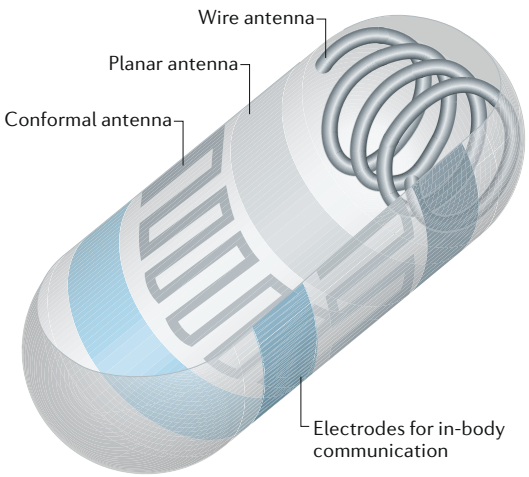


Fig. 6 | **Communication concepts for ingestible electronics.** Many capsule endoscopes possess wire antennas to address specific stipulations of radio-frequency (RF) communication within the gastrointestinal tract, for example, omnidirectional radiation pattern or path loss. Alternatively, antennas can be integrated into the device design, for example, by printing antennas onto components. Conformal design serves to further refine antenna characteristics. Electric field propagation can be applied to address challenges of RF communication.

Powering

Electrical power is a fundamental bottleneck in the development of ingestible electronics (FIG. 7), because available power determines operation life and the capacity to communicate. On-board batteries require a large part of the capsule volume (FIG. 7), and therefore, they play a major role in determining the size of the device, which is associated with the risk of obstruction (BOX 1). To overcome problems related to size, novel battery materials, energy harvesting strategies and remote powering possibilities are being explored.

Standard Li-ion technologies are associated with safety issues, such as the risk of toxicity or self-ignition[203], and thus, silver oxide batteries are preferred as on-board power supplies in ingestible electronics[204]. Ingestible electronics may further benefit from new battery technologies[205], for example, approaches in which conventional graphite anodes are substituted with materials with higher charge capacity, such as silicones[206]. Similarly, all-solid-state batteries are being explored to address leakage of the electrolyte and associated safety challenges[207,208]. Biocompatible and transient batteries made from melanin[13] or biodegradable metals[14] may also provide alternatives to avoid retention of the device through partial or total decomposition (FIG. 5).

Galvanic couples are clinically used for energy harvesting in ingestible electronics — a concept already introduced in the very first reported ingestible electronic device, which contained iron and gold electrodes[2]. Clinically used oral digital compliance measurement devices contain magnesium copper cells, which power near-field communication for several minutes[82]. Zinc copper couples can also be applied for powering ingestible electronics[37], providing lower voltage but longer battery life than magnesium copper cells. However, coupled with a temporary storage capacitor to boost low voltages, a device with zinc copper cells can deliver an average power of 0.23 μW mm^{-2} and transmit data on the core body temperature in a large animal model for an average of 6.1 days[37]. Biocatalysts, such as enzymes or nutrients (that is, glucose), provide an alternative for powering preclinical medical devices, and microorganisms can also be exploited for power generation. For example, microbial fuel cells can supply power in the low-mW range in a colon model in vitro[209]. Finally, thermal-based[210] and vibration-based[211] energy harvesting techniques could also be translated for GI applications.

Remote powering of medical devices has been widely explored for subcutaneous systems and was among the first powering approaches used for ingestible electronics[212,213]. Antennas with defined orientation can be incorporated into a device to enable remote powering, with the advantage that electromagnetic waves do not experience substantial path loss when passing through superficial tissue layers. However, ingestible electronics operate in deep tissue, and therefore, path loss, antenna size and misalignment impair the use of RF-based communication and powering.

Regulatory frameworks, such as guidelines from the US Federal Communications Commission (FCC) or the International Commission on Non-Ionizing Radiation Protection (ICNIRP), further limit the

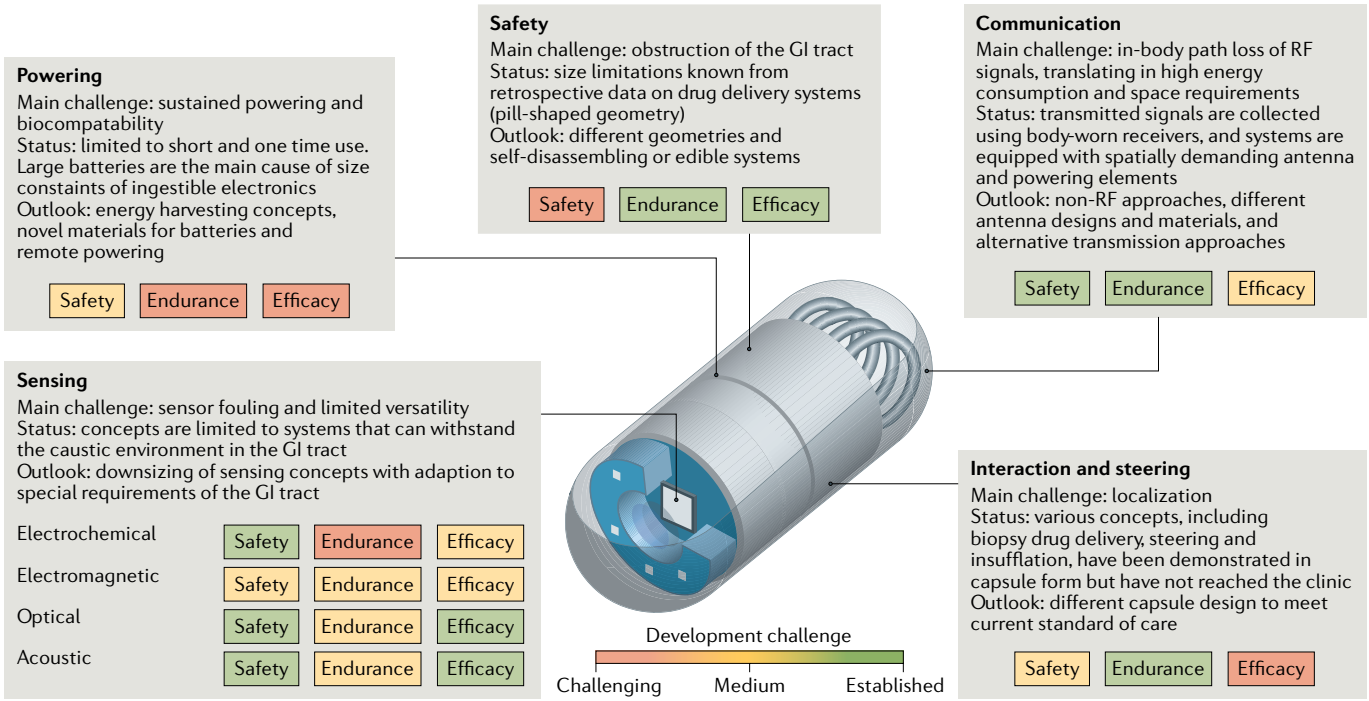


Fig. 7 | **Major challenges for ingestible electronics.** Main challenges for powering, sensing, communication, safety and tissue interactions are illustrated using a standard ingestible capsule design. GI, gastrointestinal; RF, radio frequency.

maximal power transmission. Up to 150 mW can be generated in a wireless camera capsule model containing 3D-oriented secondary coils[214]; however, practical constrains, such as the complexity and size of the primary and secondary coils, limit its clinical use. Similarly, the antenna size has a substantial impact on the optimal frequency for power transmission. The optimal transmission power is in the GHz range for millimetre-scale antennas and in the sub-GHz range for centimetre-scale antennas[215]. For the powering of in-body devices, hardware-based approaches to focus energy to a specific region[197] and software-based concepts to improve signal strength[216] are being explored.

Sensing

The use of ingestible electronics for sensing in the GI tract (TABLE 1) is challenging owing to the harsh environment and thus requires separation of the sensing element from the environment (for example, in gas sensors)[95] or, alternatively, extremely durable sensing elements. Ideally, sensors are specifically designed for the GI environment, which is characterized by high pH variability and the presence of digestive enzymes, bile acids, mucus and other compounds involved in the degradation and digestion of food. Collaboration between medical, material, device and electrical engineering is needed to provide a solution for how to maintain functionality in the GI tract while measuring relevant markers of health and disease states[217]. For example, durable, antifouling and selective membranes may help to enable the sensing of specific and relevant biomarkers while protecting the sensing element. GI-optimized sensors (for example, GI resilient bacteria sensors[99]) could be used for the sensing of biomarkers without sensor fouling.

Steering

Ingestible electronics generally lack the ability to steer themselves, limiting the possibility to target specific sites in the GI tract, which is a major problem in capsule endoscopy[78–81,218]. Shape memory alloys and robotic endoscopes[78,79] are being explored to overcome this limitation. These systems rely on leg-based locomotion, stimulation and magnetic manipulation. Different concepts of leg-based systems have been developed, such as rigid leg structures[80], gecko-like adhesive legs[81] and paddle-like legs[218]. Electrical stimulation of the intestinal wall triggering local muscular contraction has been tested in porcine models in vivo and in other models ex vivo. The contractions propel the endoscope through the GI tract and can be stopped when the device reaches a specific location[219,220]. To our knowledge, none of these approaches has been clinically tested thus far owing to safety and powering issues[221].

By contrast, the development of magnetic shells for endoscopic capsules and the fabrication of magnetic actuators have led to first clinical trials of magnetically steered capsule endoscopes[222–230]. For example, manually handled external magnets can be used to guide capsule endoscopes through gastric environments[231–233]. More complex external magnetic robotic systems have been used to profile gastric environments in ex vivo models[234–237]. Comparison with hospital-centred procedures, such as endoscopy, will allow assessment of the clinical impact of these technologies.

The potential to implement untethered microrobots[238,239] in capsule endoscopy may help to circumvent the need for a hospital infrastructure for the use of magnetic steering. For example, soft robots with multimodal locomotion can be applied for in-body

locomotion[15] (FIG. 5), which might set the stage for a novel generation of steerable devices. Ingestible electronics with the possibility of locomotion might also contribute to telemedicine efforts, particularly given the value of remote clinical input and interventions in patient care.

Tissue interaction

During endoscopic procedures, physicians interact with GI tissue to remove polyps, take biopsies, insufflate the area of interest, deliver drugs or stop bleeding. Ingestible devices may be used to perform similar actions[240]. For example, a magnetically actuated soft capsule endoscope can deliver either drugs or surgical biopsy tools to a confined area of the GI tract in porcine ex vivo models[241,242]. The device uses a camera for localization and is operated by an external magnetic system. As suggested by ex vivo proof-of-concept studies, systems using magnets or electrical signals for actuation can also be applied to take one large biopsy section, using a spring to generate power[243,244].

Magnets can further be used to actuate capsule systems for wireless insufflation of the intestinal environment[245], using chemical reactions to convert liquid or powder in the capsule into gas. In such capsules, bicarbonate and citric acid are mixed to produce 110 ml of CO_2. This approach has already been demonstrated in an ex vivo swine colon. Ingestible capsules can also be equipped with bioadhesive patches and electronics to trigger their release[246]. Capsules for the wireless inflation of balloons can be applied for the treatment of GI haemorrhage[247]. The balloons can control haemostasis within 5 minutes in an in vivo swine model, but their large size (14 mm × 60 mm) may present an issue in a clinical setting. A capsule prototype that can release a drug dispensing needle has also been developed, but to our knowledge, this capsule has not yet been tested in animal models[248]. Numerous applications have been explored to equip capsule endoscopes with techniques for tissue interaction; however, none of these has translated to the clinic thus far owing to the fact that capsule localization and manipulation cannot be as accurately controlled as an endoscope, and thus, the efficacy of these devices cannot be compared with that of the current standard of care.

Outlook and conclusions

Ingestible electronics enable the transient and non-invasive implantation of sensors inside the body. Many ingestible devices are currently employed to visualize and sense abnormalities of the GI tract during routine screening sessions, but widespread use requires optimization in multiple areas, including sensor design, safety and cost (FIG. 7).

Ingesting a conventional capsule endoscope or a similarly sized gastric gas sensor provides a measurable risk for GI obstruction (BOX 1). High retention rates are considered an acceptable risk by the FDA, if the capsule is swallowed under the supervision of a physician at infrequent intervals for specific diagnostic indications (for example, occult bleeding). The development of ingestible electronics as sensors for diagnostics or as drug delivery tools has the potential to augment or decentralize physician care by maximizing their capability to autonomously collect data. The data set can be processed and interpreted by auxiliary data management systems and sent to a healthcare team. Such devices can be designed for daily, weekly or even monthly use but must have a substantially improved safety profile compared with current single-use capsule endoscopes that are applied under tight supervision of a physician. These safety needs can be met by implementing soft or biodegradable materials and electronics and by miniaturization (FIG. 5). Biodegradable materials may also provide an answer to the pollution of waste waters and other ecological issues related to the use of ingestible electronics.

To become the new standard of care, ingestible electronics must either execute a function that a physician cannot perform or operate cheaper and more safely than the standard of care. Traditional endoscopy continues to outperform capsule endoscopy in terms of evidence-based medicine and cost-efficacy for the vast majority of indications[64–67,72,249,250]. Progress in MEMS technology has enabled the development of new features, such as ultrasound, reducing the cost of technologies used in ingestible capsules and the power required to produce equivalent results as endoscopes[251]. Similarly, wireless MEMS microphone technology for consumer electronics, such as cell phones, was also redesigned for biomedical applications in the early 2000s[252]. The new ultrasound technology might eventually be used in ingestible electronics to deliver drugs or perform imaging, and similar innovations will follow for other technologies (FIG. 5).

Capsule size is a key parameter for the safe clinical translation of ingestible electronics (BOX 1). Ingestible capsules for sensing are currently on the centimetre scale owing to battery and antenna sizes, as well as the integration of multiple heterogeneous electronic technologies. Improving the battery energy density and thus decreasing battery size are difficult. However, innovations in ultralow-power electronics and alternative energy-delivery approaches will help to drive the miniaturization of ingestible electronics. In addition, the antenna size can be reduced beyond the limits imposed by far-field radiation by implementing ultrasound-mediated communication, in-body coupling or mid-field wireless communication. Integration of heterogeneous process technologies into a single die and smart packaging approaches, such as 3D integration through die-stacking, will help to reduce the footprint of electronic components.

Ingestible electronic devices are moving from professional hospital-centred applications towards decentralized use by patients. To support this transition, scientists and engineers must now focus on safety and economic concerns (FIG. 7). Progress in materials science, energy storage and sensor technologies for ingestible electronics, as well as recent device approvals in this area, demonstrates the potential of ingestible electronics to have an impact on human health.

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Competing interests
All authors are co-inventors on multiple patents or patent applications describing ingestible electronics and auxiliary systems. G.T. and R.L. have financial interest in Suono Bio, Celero Systems and Lyndra, Inc. These companies are developing a set of distinct approaches to drug delivery and, in some instances, incorporate electronics into their systems. P.N. is an employee of Analog Devices, Inc.

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