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Robotics in the Gut

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Since the advent of ingestible temperature sensors and capsule endoscopes, rapid advances in electronics, robotics, nanotechnology, and material sciences have opened the door for the development of novel medical ingestible robots. The untethered robots provide direct, non-invasive access to the entire gastrointestinal (GI) tract. Furthermore, the tissues, gases, and fluids of the gastrointestinal lumen contain a multitude of biomarkers indicative of gut diseases and health. Ingestible medical robots equipped with advanced imaging and sensing techniques can enable the diagnosis and monitoring of diseases, while providing a better pathophysiological understanding of gastrointestinal disorders. In addition, various robotic actuation mechanisms in the macro- and microscale can realize enhanced drug delivery and surgical interventions for the treatment of diseases. In this paper, an overview of recent advances in ingestible robots toward imaging, sensing, drug delivery, and surgical applications in the GI tract is provided. Key challenges and strategies for the development of novel ingestible robots and future directions of ingestible robots toward precision medicine are also discussed.

1. Introduction

Significant advances in various fields of electronics have realized the miniaturization, accuracy, and power optimization of wireless-embedded sensors. Concurrently, remarkable discoveries in material sciences have enabled the development of biocompatible electronic and robotic devices in the macro- and microscale. Such breakthroughs in technologies have spurred the development of implantable and wearable medical devices. In many ways, electronic medical implants such as neurostimulators, pacemakers, and cochlear implants have already revolutionized the diagnosis and treatment of many diseases.[1] However, the implantable devices are invasive and long durations of use result in various complications and foreign body reactions.[2] On the other hand, wearable devices are often non-invasive. Non-invasive wearable electronics that sense vital physical and electrophysiological parameters have already seen commercial success, and wearable electrochemical sensors that detect various target analytes in sweat are being developed extensively.[3–5]

The digestive system extracts, metabolizes, and absorbs nutrients from food, while training the immune system to protect our body against the pathogens from food. Biochemical and microbiome balance is crucial to sustain the complex functionalities of a healthy gut. For example, in the esophagus, acid exposure from gastroesophageal reflux disease (GERD) can inflame and lacerate the esophageal mucosa;[6] gastric homeostasis can be broken by a *Helicobacter pylori* infection in the gastric walls, causing stomach diseases such as gastritis, gastric ulcers, and cancers;[7] *Clostridium difficile* infections after antibiotic treatment often lead to deadly colitis and diarrhea.[8] Imbalances in the gut bacteria can trigger autoimmune diseases such as coeliac disease and Crohn's disease, causing inflammations in the gastrointestinal wall and nutrient malabsorption.[9] In addition, a dysbiotic gut microbiome has also been linked to nervous system disorders such as Parkinson's disease and multiple sclerosis.[10–12] The molecular biomarkers for these diseases and their physical ramifications such as inflammations, lacerations, bleeding, and tissue neoplasms are crucial to scrutinize for effective diagnosis and treatment.

Traditionally, catheters have been placed for monitoring esophageal power of hydrogen (pH). Esophageal and rectum temperature probes have been used for core temperature monitoring.[6,13] Endoscopes have been inserted from the mouth or rectum to visualize physical indicators of disease, take biopsies for external analysis, and even conduct simple surgical interventions.[14] However, tethered probes, catheters and endoscopes are invasive and struggle to reach the small intestine. To overcome these limitations, various untethered robotic imaging and sensing capsules have been developed. Clinically available contemporary ingestible sensors primarily offer diagnostic value by taking images; and sensing temperature, pH, and pressure. However, many diseases are not visible to the bare eye, especially in the early stage. In addition, the GI tract has a constant supply of body fluids and gases rich in biomarkers that are indicative of gut health and disorders.[15] Therefore, various multimodal imaging capsules and molecular-sensing capsules are being developed to improve diagnostic yield and increase the range of detectable diseases.

In terms of disease treatment, ingestible capsules for the oral delivery of drugs are already prominent. Currently, however, the therapeutic capacity oral capsules are limited to the passive

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diffusion of drug molecules in the GI tract. Not all drugs are easily absorbed in the gastrointestinal tract, and not all diseases can be treated with drugs. Robotic strategies incorporating GI drug injection and drug-loaded microrobots have been explored to enhance the efficacy of drug delivery.[16,17] Also, various robotic structures have been prototyped to capacitate minimally invasive surgery in the gut.[18–22] In addition, several ingestible robot prototypes utilized the narrow passage through the pylorus for gastric retention, enabling prolonged drug delivery or gut health monitoring.[23–25]

This review summarizes the various robotic strategies implemented or proposed for minimally invasive diagnostics and therapy in the GI tract (**Figure 1**). The scope of the review includes untethered commercial products and prototypes in research. As the sections progress, the review analyzes various imaging and sensing robots for diagnostics, drug delivery, and surgical robots for therapy, and strategies for overcoming common challenges in ingestible robots. Lastly, microrobots and their potential for therapy in the GI tract are discussed.

2. Wireless Capsule Endoscopes

A capsule endoscope encapsulates a miniature imager and light source to capture images of the GI tract and transmit the acquired data to a wearable receiver. In a clinical capsule endoscopy procedure, the patient needs to fast for several hours prior to the ingestion of the capsule endoscope. A typical capsule endoscope acquires images with a complementary metal–oxide–semiconductor (CMOS) imager and transmits data over radio frequency (RF) communications to a wearable receiver that records the videos over an 8–12 h duration for the doctor to view. However, incorporation of different imaging, communication, powering, and computer-aided diagnosis technologies is being explored to improve the diagnostic yield and efficiency of capsule endoscopes.

2.1. Commercial Capsule Endoscopes

The first capsule endoscope was developed to directly visualize the inside of the small intestine, a region that is difficult to reach with conventional fiber optic endoscopes and colonoscopes.[26] The first capsule endoscope M2A was approved by the Food and Drug Administration (FDA) in 2001 to image and detect obscure GI bleeding in the small bowel. Since its birth, capsule endoscopes have improved greatly in resolution, battery life, field of view, and range of applications. A number of commercial capsule endoscopes have entered into the market in the past decade which are able to image different parts of the GI tract (**Figure 2**). Recently, a study showed that capsule endoscopes could detect GI bleeding in 64.3% of patients whereas traditional endoscopes could only detect bleeding in 31.1% of patients.[27] In addition, current capsule endoscopes are also used to evaluate Crohn's disease, polyps, tumors, and celiac disease.[28–31] Specialized capsules have also been developed to image different parts of the GI tract as well.

Medtronic has four PillCam products in its portfolio, each optimized for its purpose. PillCam SB3 is the successor of M2A, the first capsule endoscope (see Figure 2a1). PillCam SB3 adjusts its frame rate between 2 and 6 frames per second (fps) according to its travel speed, increasing mucosa coverage and personalizing tissue acquisition to each patient's motility. A variable frame rate can optimize battery life while increasing diagnostic yield in the small bowel.[32] PillCam Crohn's capsule enables the direct visualization of the progression or healing of Crohn's disease in the small bowel and colon. This capsule can also set its frame rate to 4 or 35 fps depending on movement speed, and its two camera heads on each side provide a 336° view (Figure 2a2). PillCam UGI was specially designed to aid in detecting gross blood in the upper GI tract (Figure 2a3). The capsule acquires images at 35 fps for the first 10 min, and then at 18 fps for the last 80 min. PillCam Colon 2 has a wide 344° field of vision and dynamic frame rate,

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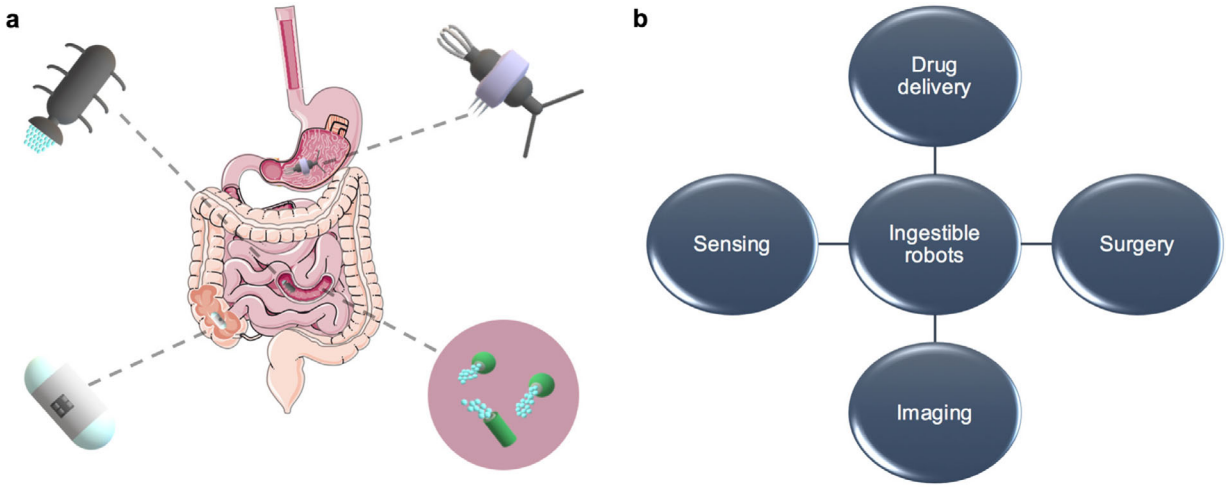

Figure 1. Overview of untethered ingestible medical robotics in the gut. a) Illustration of various ingestible medical robots in the GI tract. Reproduced with permission.[167] Copyright, Servier Medical Art. b) The medical applications of the ingestible robots.

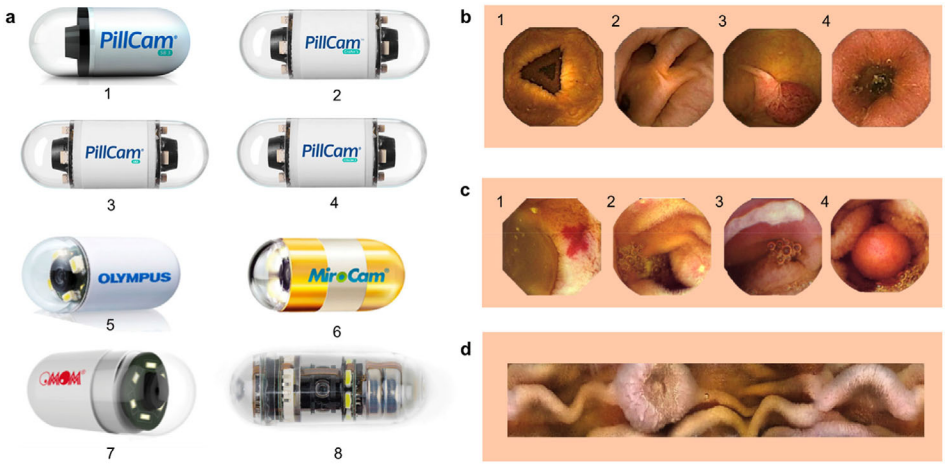

Figure 2. Commercial wireless capsule endoscopes. a) Images of commercial capsule endoscopes: 1) PillCam SB3 by Medtronic. 2) PillCam Crohn's by Medtronic. 3) PillCam UGI by Medtronic. 4) PillCam Colon 2 by Medtronic. 5) EndoCapsule by Olympus Corporation. 6) MiroCam by Intro-Medic Corporation. Reproduced with permission.[36] Copyright 2013, Elsevier. 7) OMOM by Jinshan Science & Technology. 8) CapsoCam Plus by CapsoVision. b) Colon images taken by PillCam Colon 2: 1) Normal colon. 2) Diverticula. 3) Polyps. 4) Ulcerative colitis. Reproduced with permission.[33] Copyright 2014, Baishideng Publishing Group. c) Small bowel images taken by MiroCam: 1) Angiodysplasia. 2) Ileal erosions. 3) Ileal ulcer (Crohn's disease at histology). 4) Jejunal adenoma. Reproduced with permission.[36] Copyright 2013, Elsevier. d) Panoramic image of ampulla of Vater taken by CapsoCam Plus.

enabling thorough detection of polyps and other abnormalities in the colon (Figure 2a4,b).[33]

Olympus Corporation's EndoCapsule offers high-resolution images with a proprietary algorithm that discards redundant images to accelerate the image review time by 64%, without decreasing the detection rate of major lesions (Figure 2a5).[34] Intro-Medic Corporation's MiroCam capsule transmits data through human body tissues via electric-field propagation, rather than through conventional radiofrequency technology (Figure 2a6,c).[35,36] This enables the elimination of power and space consuming RF components, making the MiroCam compact and power efficient. While Jinshan's OMOM capsule is low in price, its diagnostic yield was shown to be comparable with that of PillCam SB (Figure 2a7).[37] The CapsoCam Plus by CapsoVision has four laterally positioned cameras that provide a 360° panoramic lateral view of the small bowel (Figure 2a8,d). CapsoCam's panoramic vision provides better visualization of the duodenal papilla, a region that is difficult to image with end-mounted cameras.[38,39]

2.2. Research in Capsule Endoscopy

Various artificial intelligence software programs are being developed to aid the diagnostic yield of labor-intensive endoscope video review sessions in terms of efficiency and diagnostic

accuracy.[40,41] Traditionally, hemorrhages and lesions in images were detected by hand-crafted features based on color and texture information, and then classified through machine learning algorithms such as support vector machines (SVM), neural networks, or binary classifiers.[42–45] Recently, deep learning-based approaches such as convolutional neural networks (CNN) have shown improved performance for image-based recognition and classification via learned features.[46–49] However, deep learning-based computer-aided diagnosis requires a large database, and overfitting can be an issue.

Conventional white light imaging capsules lack the ability to visualize fine details under the surface of the GI mucosa. A lot of work is being put into the immersion of various imaging techniques into multimodal capsule endoscopes to enhance the quality of GI wall analysis. Ultrasound-sensing capsules, narrow band imaging capsules, fluorescence imaging capsules, X-ray-based imaging capsules, and endomicroscopy capsules are under various stages of development.[50–54]

Narrow band imaging capsules are well suited to visualize abnormalities in subsurface structures as different wavelengths have different penetration depths.[51] A wireless fluorescence capsule based on a single photon avalanche detector array was developed for both autofluorescence endoscopy and targeted fluorescence endoscopy.[52] Autofluorescence imaging can image abnormalities in endogenous fluorophore profiles, which have been linked to the existence of primary cancer.[55,56] In targeted fluorescent endoscopy, an exogenous fluorescent dye is used to label the diseased area of interest.

Various ultrasound capsule endoscopes are being developed under the Sonopill program. A Sonopill prototype was developed to take ex vivo microultrasound images of porcine bowel and esophageal samples.[57] The high frequencies used in microultrasound imagers result in an increase in resolution and decrease in tissue penetration, which is ideal for capturing quality images directly under the mucosa surface. Also, a closed loop magnetic control of a tethered ultrasound imaging capsule was achieved through digitized microultrasound feedback.[58] An external serial robot with a permanent magnet was used to maneuver the magnet-embedded ultrasound capsule endoscope's position, orientation, and attraction force to optimize the location of the onboard ultrasound transducers. The magnetic microultrasound servoing system was able to autonomously achieve ultrasound coupling and image the colon of a pig.

The small bowel access of capsule endoscopes has closed the diagnostic gap between conventional gastroduodenoscopy and colonoscopy.[59] Furthermore, technological advances in terms of power, data transmission, image acquisition, and data processing have improved the diagnostic yield and diagnostic territory of capsule endoscopes. Multimodal images and artificial intelligence are also promising for improving the diagnostic yield of capsule endoscopes. However, current commercial capsule endoscopes only operate for 8–11 h owing to the high power consumption of image acquisition and data transmission. Current capsule endoscopes cannot completely replace conventional endoscopes because the power and size restraints in capsule endoscopes limit the embedded imaging technology, and because current capsules cannot be easily steered. Challenges of ingestible medical robots such as power, localization, and locomotion will be discussed in detail in Section 6.

3. Capsules for Robotic Sensing

Visual cues of diseases alone do not always provide a wholesome understanding of the pathology of a disease. Analysis of temperature and molecular compositions inside the gut lumen can also be invaluable. Due to improvements and miniaturization of sensor technologies, ingestible medical robots can be equipped with various types of sensors to detect different kinds of biomarkers in the GI tract. Depending on the application, robotic capsules-sensing temperature and chemical compositions of the GI tract can be more cost effective, more power efficient, and produce less data than imaging sensors, enabling easier use and prolonged operation periods.

3.1. Temperature Sensing

Core temperature is important to monitor as thermal illness is common during sports injuries, and core temperature is linked to metabolic energy expenditure.[13,60] Rectal and esophageal temperatures are an accurate indicator of core temperatures; however, measurement at these sites are invasive and unsuitable during exercise. Ingestible core sensors are often a preferred alternative for measuring core body temperatures (**Figure 3**a). HQ Inc.'s CorTemp (10.9 × 22.4 mm, 2.8 g) and Philip Respironics' VitalSense (8.7 × 23 mm, 1.5 g) have been widely used over the years to monitor core temperatures in divers, athletes, and soldiers during activity.[61] Recently a few companies have developed new ingestible temperature sensors. BodyCAP's e-Celcius temperature sensor (8.9 × 17.7 mm, 1.7 g) can log data on its embedded memory and transmit later such that the user does not have to wear a receiver patch at all times.[62] This core temperatures sensor was used to measure the core temperature of athletes during the UCI Road Cycling World Championships, where core temperatures as high as 41.5 °C were recorded.[63] MyTemp is a startup company that created a battery-free ingestible temperature capsule (8 × 20 mm, 1.3 g).[64] A wearable waistband magnetically powers the temperature capsule, and receives the wireless temperature data. A study comparing the validity, reliability, and inertia of the four different temperature capsule systems concluded that all systems were able to reliably measure temperature, even though the VitalSense system was slightly less responsive to changes in temperature.[65]

3.2. pH Sensing

GERD, is a common digestive disorder where stomach acid overflows into the esophagus, causing heartburn or indigestion. While capsule endoscopes can be used to non-invasively view the inflammation and lacerations from the acid reflux episodes, invasive catheter-based pH monitoring is the standard diagnostic test for GERD. The Bravo pH wireless capsule system by Medtronic is less invasive and provides comparable diagnostic yields.[66] However, the Bravo pH capsule still needs to be temporarily implanted and removed using an endoscope. In addition, impedance measurements are also important for nonacid reflux monitoring.[67] A prototype of an ingestible capsule that can non-invasively

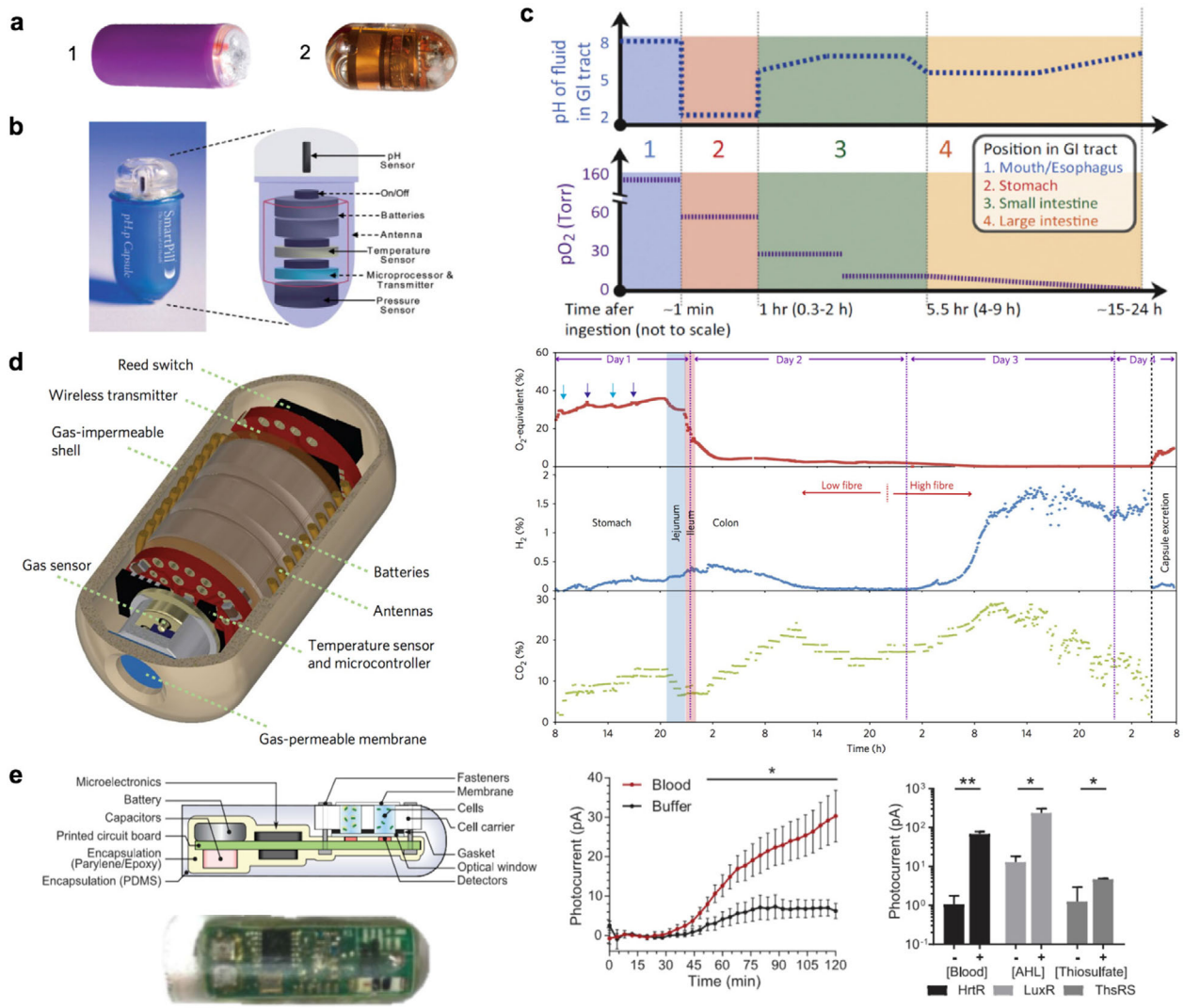

Figure 3. Robotic sensor capsules. a) Temperature-sensing capsules: 1) VitalSense by Philip Respironics. 2) e-Celcius by bodyCAP. b) SmartPill by Medtronic for wireless motility testing. Reproduced with permission.[71] Copyright 2009, Elsevier. c) pH and oxygen profiles of different regions of the GI tract. Reproduced with permission.[166] Copyright 2015, CellPress. d) Gas-sensing capsule capable of measuring oxygen, hydrogen, and carbon dioxide concentrations in the human GI tract. Reproduced with permission.[73] Copyright 2018, Nature Publishing Group. e) Ingestible micro-bio-electronic device (IMBED) for detection of biomarkers in the GI tract. Reproduced with permission.[78] Copyright 2018, AAAS.

monitor pH and impedance in the esophagus has been proposed.[68] Magnetic holding, rather than surgical affixation, is used to hold the capsule in place.

Gastroparesis is a motility disorder in the stomach that impedes the gastric emptying of food. Traditionally, gastroparesis is diagnosed by using scintigraphy tests to image the gastric emptying time of radiolabeled foods.[69] However, SmartPill (Medtronic), a multimodal ingestible sensor tracking pH, temperature, and pressure, can also be used for motility testing (Figure 3b).[70,71] The pH is different in different regions of the GI tract, enabling localization of the capsule. Correlations between capsule transit time and food transit time can be utilized to evaluate gastric emptying time, which is necessary for the diagnosis of motility disorders such as gastroparesis.

3.3. Gas Sensing

Various gases are produced in our gut due to chemical and enzymatic interactions, and bacterial fermentation. While hydrogen breath tests provide insight into the pathophysiology of small intestinal bacterial overgrowth and carbohydrate malabsorption disorders, gases measured from the mouth are low in concentration and location nonspecific.[72] In addition, gut oxygen levels, like gut pH levels, can be a rough indicator of the location of the capsule within the gut (Figure 3c). Recently an ingestible gas sensor that can measure oxygen, hydrogen, carbon dioxide, and methane in the human gut has been developed (Figure 3d).[73] A gas-permeable membrane protects the gas sensor from the gastric fluid, and heat modulation of the sensors is used to achieve

gas selectivity and sensitivity. The data is transmitted from the capsule to a pocket-sized receiver over 433 MHz communications, and then to a mobile phone over Bluetooth communications. The gas sensor was used for a human study on the effect of dietary fiber content on the gut gas profile. As shown in the graph from Figure 3d, the transition from a low fiber diet to a high fiber diet led to a drastic increase in colon hydrogen concentration, along with a significant shift in gut microbiota composition analyzed from fecal samples. In a repeatability study, high fiber diets, in comparison to low fiber diets, led to a longer small intestine transit time and a shorter large intestine transit time.

3.4. Gastrointestinal Bleeding Detection

Occult GI bleeding can often be easily detected by fecal occult-blood tests.[74] However, acute bleeding in the upper GI tract may require endoscopic imaging and therapy.[75] While commercial capsule endoscopes are non-invasive, they are expensive. Several cost-effective wireless capsules have been proposed to detect acute GI bleeding.

A ratiometric intensity-based sensor was developed to detect acute upper GI bleeding.[76] Blood has higher absorption of violet light (415 nm) than red light (720 nm). The capsule was able to determine low concentrations of blood by comparing light transmission at 415 and 720 nm inside a sensor cavity, located between LEDs and a phototransistor. Another study proposed a capsule that detects intestinal bleeding by color recognition of hue-saturation-light color space.[77] When there is intestinal bleeding, intestinal juice flows into the capsule and dyes a hemoglobin selective adsorptive film. When there is no intestinal bleeding, the adsorptive film remains white. A color sensor acquires color information every 5 min and transmits the data to an external receiver that triggers an alarm module, depending on the extent of bleeding.

Recently, probiotic sensor bacteria were integrated into a wireless electronic capsule to detect GI bleeding in pigs (Figure 3e).[78] A semipermeable membrane–traps-sensing bacteria in a chamber, while allowing diffusion of small molecules. Target analyte bonding emits light that can be detected, digitized, and transmitted to an external receiver by the embedded luminometer and wireless readout electronics. For the detection of blood, *Escherichia coli* Nissle 1917 was engineered with HrtR, an intracellular heme-binding protein, and bioluminescent bacteria. The resultant biosensor-based capsule was able to rapidly detect blood in a gastric cavity of a porcine model (see Figure 3e). The bacterial-electronic capsule can easily be modified to detect other relevant gut biomarkers. Thiosulfate, a potential biomarker of gut inflammation, and acyl-homoserine lactone, a potential indicator of gut microbiota dysbiosis were also sensed in vitro by the engineered probiotic *E. coli* (Figure 3e).[79–81]

3.5. Cancer Screening

Early signs of tissue neoplasms are the increase in microvessel density and resultant changes in capillary patterns beneath the epithelium. As aforementioned, robotic imaging capsules with various imaging strategies are being developed to analyze subsurface mucosa. However, current imaging capsules are not low in price and are demanding in power. In addition, they require labor-intensive video analysis sessions for diagnosis. A cost-effective high-sensitivity fluorometer capsule was developed for efficient early-stage cancer detection.[82] Six laser diodes and six photodiodes were used to excite exogenous fluorophores and detect the emitted fluorescence. In addition, a Hall effect sensor and an accelerometer was used to adjust sampling rate according to the movement speed of the capsule. In an ex vivo experiment, the device traveled through a swine intestine impregnated with indocyanine green, a fluorescent-labeling agent used for the early detection of cancer in the gut.[83] The capsule was able to detect nanomolar to micromolar concentrations of indocyanine green in the small intestine.

3.6. Electrochemical Sensing of Other Physiologically Relevant Analytes

The GI tract has a constant supply of biomarker rich body fluids that can be reached minimally invasively by ingestible sensors. While there are significant challenges to overcome, ingestible electrochemical sensors show promise in detecting various physiologically relevant analytes in the GI tract. An ingestible electrochemical sensor has been developed and used to perform voltammetric measurements in human stool.[84] Stable measurements were shown across different samples, but the measurements are not specific due to lack of a biorecognition layer. The selectivity of the electrochemical sensors could be improved by incorporation of advanced materials such as ion-selective membranes, selective enzymes, or biomarker specific bioreceptors. However, these sensors may be subject to fouling and may degrade under the harsh and complex conditions of the GI tract. Gas-sensing capsules were successful because the gas-permeable membranes shielded the sensitive electrodes from the GI fluids. Similarly, selective electrochemical sensors can be protected by the use of novel materials. Stable glucose monitoring in acidic environments of varying pH have been achieved using carbon-paste biosensors prepared from edible materials, such as olive oil and activated charcoal.[85] The materials shield the degradation of embedded glucose oxidase enzyme from acidic fluids.

While capsule endoscopes have the capacity to reliably detect GI occult bleeding and tissue abnormalities, incorporation of power-efficient and cost-effective photosensors and biosensors can offer an alternative means of diagnosis. While rich in information, the local real-time chemical composition of the GI fluid has yet to be well explored in the molecular level. pH sensors have been successfully integrated in several commercial robotic capsules; gas sensors and bacterial biosensors have shown potential for in vivo analysis of gut lumen biochemical composition. However, sensor selectivity and robustness remains a major challenge as the GI fluid composition can be extremely complex and abrasive. In addition, the sensitivity of the sensor can be limited by the small size of the robotic sensor capsule, and the sensor data acquisition should require low power consumption. Further advances in biorecognition layers, sensor protection, sensor

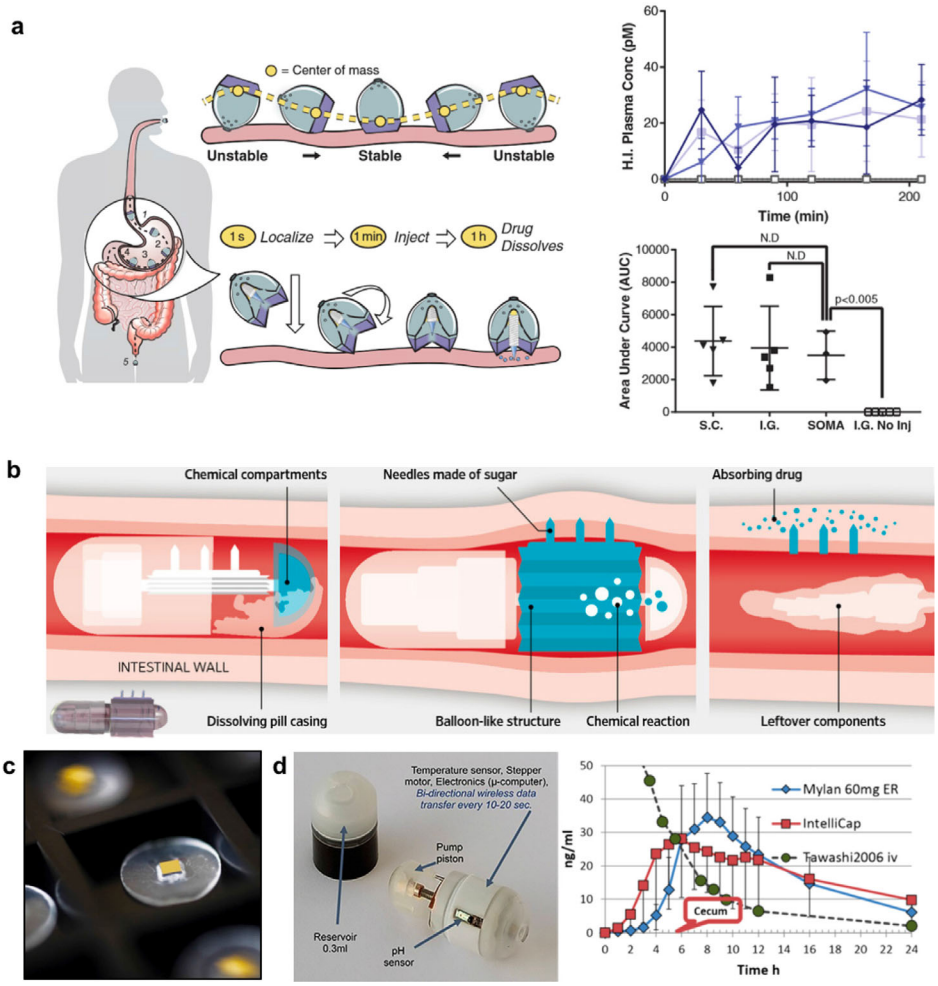

Figure 4. Therapeutic robots for drug delivery. a) An ingestible self-orienting millimeter-scale applicator for the oral delivery of macromolecules. Reproduced with permission.[16] Copyright 2019, AAAS. b) RaniPill by Rani Therapeutics for the pain-free injection of drugs in the small intestine. c) Medication adherence monitoring sensor by Proteus Digital Health. Reproduced with permission.[94] Copyright 2015, IEEE. d) IntelliCap by Medimetrics for the quantification of regional drug absorption in the human GI tract. Reproduced with permission.[95] Copyright 2014, AAPS PharmSciTech.

miniaturization, and low power electronics will facilitate biochemical sensing technologies in the gut. Biochemical sensing in the gut will aid diagnosis and understanding of various gut disorders and the gut–brain axis.

4. Ingestible Robots for Drug Delivery

Oral administration is often the preferred route for therapy because it is non-invasive. The major challenge in oral delivery of a drug is to maintain therapeutically efficacious concentrations over a desired period of time. While advances in polymer technologies have realized the sustained release of a drug through polymer degradation or steady state diffusion through the polymer, there are still many limitations in contemporary oral capsules.[86] Many drugs cannot be absorbed in some or all parts of the GI tract; the total delivery window is limited by the GI transit time; and drug delivery capsules cannot perform complex surgical therapies. Robotic capsules can actively tackle these challenges.

4.1. Injection of Macromolecules

Biomacromolecules such as insulin are essential for treating diseases. However, their large size adds an additional challenge toward targeted delivery. While most traditional pharmaceutical drugs consist of smaller molecules that are easily absorbed in the GI tract, macromolecular drugs have difficulty penetrating the thick mucus layers, and cellular tight junctions of the GI tract to reach systemic bioavailability.[87] Permeation enhancers, nanoparticles, and mucus adhering devices have been developed to increase uptake of macromolecules in the GI tract. However, such techniques cannot safely increase the bioavailability of the drugs over 1%.[88–90] Therefore the use of biomacromolecules is mostly limited to subcutaneous administration, which is painful.

Recently, several robots were developed to inject macromolecules within the GI tract where there are fewer pain receptors. Firstly, leopard tortoise inspired ingestible self-orienting millimeter-scale applicator (SOMA) has been developed to autonomously inject drug-loaded milliposts into the stomach walls (see **Figure 4**a).[16] Inspired by the self-orienting mechanisms of a

leopard tortoise, the SOMA has a mono-monostatic body. Its low center of mass and a high-curvature upper shell enables rapid self-orientation while resisting external forces such as fluid flow, peristaltic motion, and exercise. A stainless steel spring was used as a power source for the time-delayed actuation of a 7 mm drug-loaded milllipost that was inserted into the stomach tissue without perforating the tissue. A hydration-dependent actuator was made with sucrose and isomalt to enable millisecond scale actuation. The SOMA targets the stomach mucosa, rather than the gut lumen for drug injection because the stomach mucosa is thicker and because variability in gastric emptying time makes dose delivery time unpredictable in the small intestine. Animal trials of SOMA millipost placement in swine showed comparable systemic intake with that of subcutaneous manual injections and intragastric surgical millipost placement as shown in Figure 4a.

Rani Therapeutics is taking an alternate approach toward the oral delivery and GI injection of macromolecules.[91] The enteric coating of RaniPill protects itself from the acidic environment of the stomach, and dissolves in the intestines, instigating a chemical reaction that inflates a balloon and injects drug-loaded dissolvable microneedles into the small intestine walls (Figure 4b). However, for both approaches, the drug delivery dosage is mainly limited by the size of the drug-loaded needle/millipost. Larger milliposts may damage the GI walls; and contaminants must not be able to permeate through the mucosa along with the milliposts. Nonetheless, oral injection of macromolecules offers a simpler and pain-free alternative to subcutaneous injections, potentially leading to higher medication adherence.

4.2. Medication Adherence and Extended Release

In the United States, medication nonadherence is responsible for ≈125 000 deaths, 10% of hospitalizations, and $100 billion in health care services annually.[92] To address this issue, Proteus Digital Health, Inc. developed a medication adherence monitoring system where an ingestible sensor transmits its identification code to a wearable receiver patch upon contact with gastric fluid (see Figure 4c).[93,94] Another approach to reduce medication nonadherence is to simplify the administration regimen. Decreasing the oral administration frequency can ameliorate medication nonadherence.

There is a high demand for extended release dosage forms in the market as many drugs have a short half-life, requiring multiple daily ingestions. For therapeutic efficacy of the extended release drug, the drug plasma concentration should be maintained above a minimum threshold for over 12–24 h. A sustained release dosage form continuously releasing the drug in the GI tract over 10–20 h can be simple and effective. However, the typical transit time in the small intestine is below 5 h, necessitating colonic absorption of the sustained release drug. Many drugs are not absorbed in the colon. Therefore the colonic absorption of a drug should be thoroughly analyzed prior to the formulation of the sustained released drug.

The 27 × 11 mm IntelliCap (Medimetrics) device can effectively determine and quantify the colonic absorption of a drug.[95] As shown in Figure 4d, the IntelliCap houses an electronic system that can acquire and transmit data from the temperature and pH sensors, while controlling a stepper motor for extended release of the drug. The real-time pH sensor data enables localization of the device. The release profile and location of the drug can be programmed prior to ingestion or controlled manually in real time through sub-Ghz communications. A commercially available sustained release drug formulation, Mylan 60 mg ER, was compared with the IntelliCap. In a human study, both systems continuously released diltiazem in the intestines, and their plasma concentrations were compared over time as shown in Figure 4d. Comparable systemic availability achieved by the two sustained delivery mechanisms informs that the controlled drug release robot can be used for preliminary assessment of colonic absorption prior to the development of a sustained release drug. Furthermore, various pump and microchip systems are being developed to improve controllable drug delivery in electronic capsules.[96–98]

4.3. Strategies for Prolonged GI Retention

Typically, the total GI transit time circumscribes the duration of extended drug release in the gut. However, an oral dosage form that can achieve extended drug release over multiple days or weeks can further mitigate complications with medication adherence. There are multiple attempts to prolong the gastrointestinal retention of drug delivery systems, including mucoadhesion and structural expansions. The expansion in size of an ingestible device can inhibit its passage through the pylorus, while allowing passage of food. Gastric retention enables not only prolonged therapeutics in the gut, but also prolonged monitoring in the gut.

Figure 5a illustrates a robotic drug delivery capsule that can steadily release therapeutically relevant levels of ivermectin for over 2 weeks, to eliminate the transmission of malaria.[23] A thermoset elastomer recoils the cylindrical capsule into a star shape in the stomach. Enteric linkers between the drug-loaded rigid polymers are weak points that dissolve sequentially at intestinal pH, allowing the periodic passage of drug-loaded polymers through the pylorus. As shown in the table in Figure 5a, Stromectol, a commercially available ivermectin pill, was therapeutically effective for up to 2 days in swine; on the other hand, the long-acting robotic formulations of ivermectin were therapeutically effective for 10–16 days in swine.

Furthermore, gastric retention of electronic devices can serve as a minimally invasive alternative to medical implants, capable of therapeutics, diagnosis, and physiological monitoring. A multifunctional 3D printed long-term gastric resident electronic device was developed.[24] The robotic pill was designed to unfold its arms in the stomach to inhibit its passage through the pylorus for up to 36 days (Figure 5b). Despite the tissue attenuation of 2.4 GHz transmission frequency, the electronic robot was able to establish bilateral Bluetooth connection in swine stomach for up to 14 days, enabling the controlled release of drugs. After the extinction of bilateral connection, the device could continue to unilaterally transmit temperature data for 20.1 days.

Rapidly swelling hydrogels serve as another attractive method for gastric retention due to their excellent mechanical compliance and biocompatibility.[25,99,100] The ingestible hydrogel device shown in Figure 5c can inflate up to 100 times in volume within 10 min after ingestion by absorbing water, and deflate through the ingestion of a biocompatible salt.[25] A temperature sensor

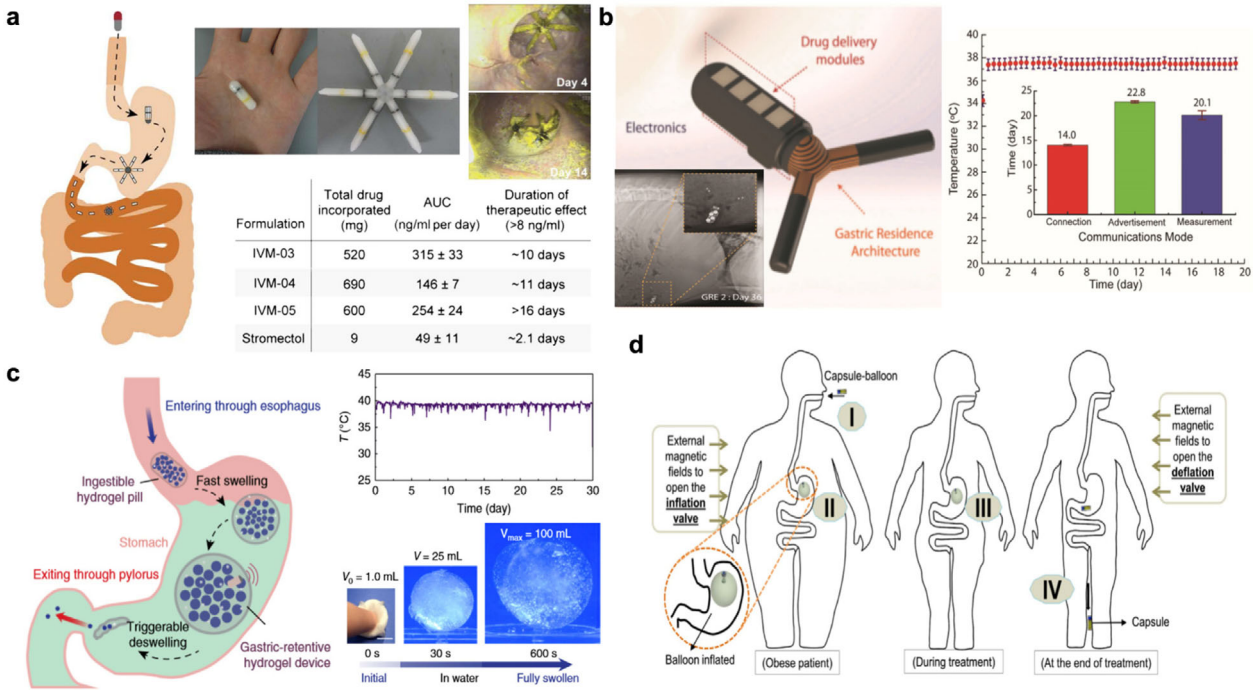

Figure 5. Strategies for enhanced retention in the GI tract. a) A prolonged drug delivery capsule that expand into a star shape and deliver a sustained therapeutic dose of ivermectin for up to 14 days in a swine model. Reproduced with permission.[23] Copyright 2016, AAAS. b) A 3D printed electronic device that can expand its arms to reside in a swine stomach for over a month for drug delivery and temperature sensing. Reproduced with permission.[24] Copyright 2018, John Wiley & Sons, Inc. c) An ingestible hydrogel device that can swell rapidly while maintaining mechanical robustness for gastric retention for up to 1 month. Reproduced with permission.[25] Copyright 2019, Nature Publishing Group. d) A magnetically actuated tetherless inflatable capsule as an intragastric balloon for weight management. Reproduced with permission.[101] Copyright 2016, Nature Publishing Group.

embedded in the hydrogel device measured temperature data for a month. In addition, in vitro data suggested that the hydrogel device could also be used for ultra-long sustained drug delivery. Inflatable capsule devices could be used for bariatric intervention.[101] While conventional intragastric balloons are an efficient way to treat obesity, they typically require an invasive procedure using a catheter or endoscope to insert and remove the intragastric balloons from the stomach. Using external magnetic fields to control its valves, a tether-free ingestible capsule can be inflated with biocompatible effervescent chemicals, then deflated after treatment (Figure 5d).

Medication adherence and targeted drug delivery are major challenges to be overcome by ingestible robots. As aforementioned, medication adherence can be improved by simplifying the medication administration regimen. Traditionally, incorporation of advanced materials in oral capsules have enabled the development of extended release dosage forms to reduce the administration frequency of oral pills. Material innovations have also fueled the targeted delivery of orally administered drugs through enteric coating, and release through external stimulation. While in the early stage, robotics offers innovative solutions to tackle the challenges of oral medication. Expanding robotic structures can enable several-week-long gastric retention of drug delivery capsules, realizing single dosage treatment of diseases. Robotic structures capable of autonomous intragastrointestinal injection of macromolecular drugs have the potential for substituting painful and laborious manual injections. Also, novel robotic and electronic technologies have the potential to improve the accuracy and autonomy of targeted drug delivery. Biocompatibility and safety of robotic structures must be evaluated further, and precise digital control of release dosages may be required for dosage critical drugs. Furthermore, cost effectiveness must be considered when mounting robotic and electronic capabilities onto single-use oral capsules.

5. Ingestible Robot for Surgical Intervention

Endoscopic techniques have enabled image-guided surgical manipulation of local GI tissue for minimally invasive surgery. However, insertion of endoscopes into the GI tract may cause discomfort to the patient, and endoscopes cannot reach all parts of the small bowel. Untethered ingestible robots present a great opportunity to perform surgical interventions in all parts of the GI tract with minimal discomfort.

Firstly, an inflatable device was developed for the closed loop detection and treatment of GI hemorrhage by the balloon tamponade effect (**Figure 6**a).[18] A lightweight automatic bleeding detection algorithm quantifies the number of blood-colored pixels from an endoscope image to determine the extent of the bleeding. For treatment, a micromotor linear actuator initiates an endothermic reaction that inflates a silicone balloon to apply controlled pressure against the GI walls at the bleeding site. A wireless capsule with a surgical clip was also prototyped to treat GI

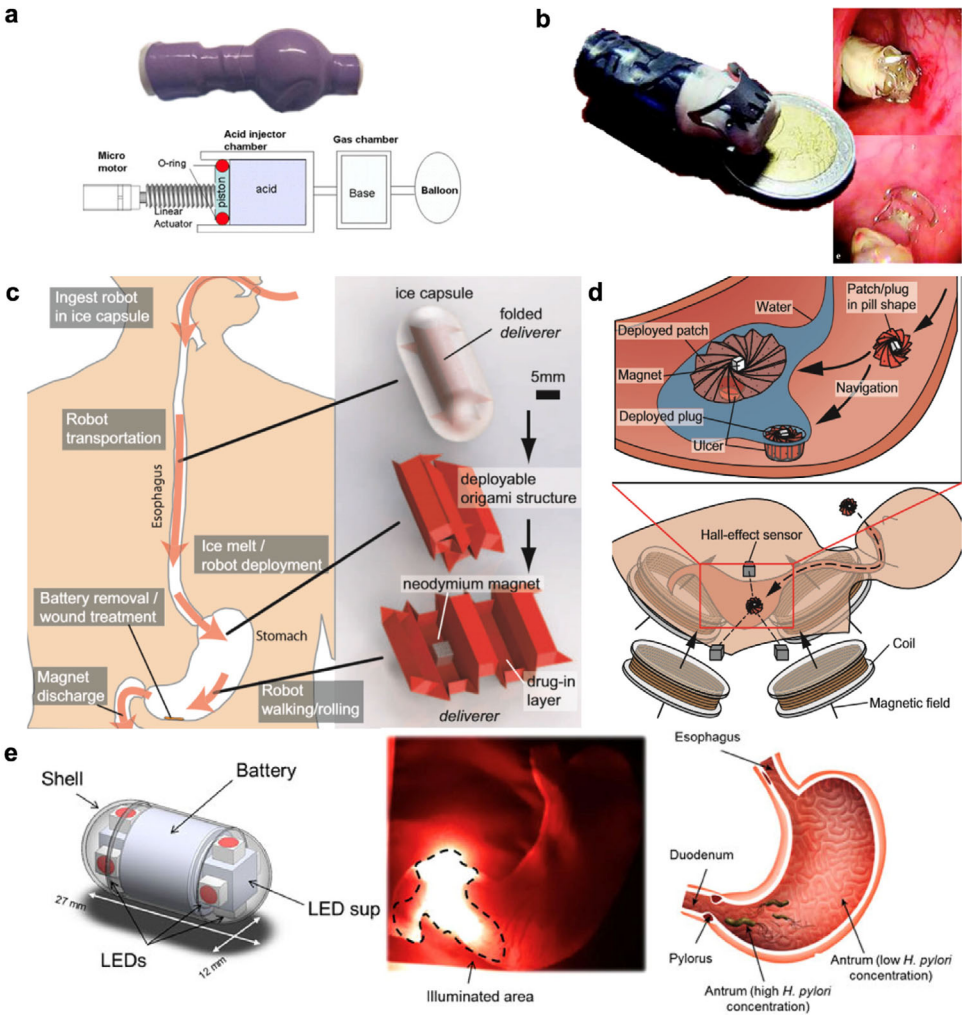

Figure 6. Therapeutic robots for surgical intervention. a) An inflatable wireless capsule for the therapy of GI hemorrhage by balloon tamponade effect. Reproduced with permission.[18] Copyright 2017, IEEE. b) A clip-releasing wireless capsule for the in vivo surgical clipping of iatrogenic bleeding in the GI tract. Reproduced with permission.[19] Copyright 2008, Thieme Medical Publishers. c) An ingestible origami robot for removing batteries and patching stomach wounds in the stomach. Reproduced with permission.[103] Copyright 2016, IEEE. d) An autonomous ingestible origami hydrogel patch and plug for the treatment of stomach ulcers. Reproduced with permission.[104] Copyright 2018, IEEE. e) A wireless ingestible capsule for the photodynamic treatment of *Helicobacter pylori* infections. Reprinted with permission.[106] Copyright 2016, IEEE.

hemorrhage.[19] Inside a fresh porcine colon, the capsule was magnetically steered toward a bleeding site, where an electromagnetic motor released a biocompatible nitinol clip to heal the wound (Figure 6b). In addition, a wireless robotic capsule was developed to release bioadhesive patches in the GI tract.[102] The patch release was triggered by a spring.

Several robotic capsule designs were proposed for biopsy in the GI tract. One proposed wireless capsule is able to anchor itself in place by using SMA springs to push outriggers against the GI wall.[20] Once aligned in place, a spiral spring is used to rotate an inner cylindrical razor against an outer cylindrical razor and cut the tissue. A magnetically controlled capsule without electronics was developed for biopsy.[21] This device cuts tissue with two coaxial cylindrical magnetic razors, actuated by magnetic fields. Another capsule design, positioned in place and controlled with magnetic fields, can release and retrieve untethered microgrippers that can self-fold to grab biopsies.[22]

Origami-based robots have the potential to be versatile in performing in vivo surgical tasks. These robots have minimal onboard electronics, and hold a cubic magnet such that they can be actuated by magnetic fields created by four external coils. Composite material origami robots can be folded up and deployed in the stomach to remove ingested button batteries and treat the remaining wounds (see Figure 6c).[103] An initial robot can grab the battery through magnetic attraction, then remove it. A second robot laminated with biodegradable drug-including sheets can patch the area of inflammation. A deployable origami hydrogel patch and plug was created for gastric ulcer therapy (see Figure 6d).[104] Once ingested, the origami structure can absorb water and expand up to ten times in surface area. Three Hall effect sensors can magnetically localize the robot, and external

coils can automatically create rotating magnetic fields to guide the robot toward the ulcer location. A constant magnetic field can then be applied to place the robot on the ulcer lesion as a patch, or in the perforated ulcer as a plug.

H. pylori infections are a major culprit of gastric ulcers and many other deleterious diseases. The efficacy of pharmacologic treatments of *H. pylori* infections is low due to side effects and antibiotic resistance.[105] Meanwhile, *H. pylori* contains natural photosensitizers and can be killed by excitation at specific wavelengths. Taking advantage of this opportunity, light emitting diode (LED) sources were integrated in an electronic capsule for the photodynamic therapy of *H. pylori* infections (see Figure 6e).[106] Preliminary results show that the device can kill the bacterium at a high efficiency of 96%.

Tetherless ingestible robots have the great potential for performing minimally invasive surgery in the GI tract. Unlike endoscopic surgery, the surgical robot can access all regions of the GI tract without causing discomfort to the patient. At the region of interest, ingestible robots can remove objects, treat wounds, perform biopsies, kill pathogens, and more. However, localization and locomotion are critical limitations that stunt the feasibility of ingestible surgical robots. Precise localization and locomotion strategies are necessary in order to steer the surgical robot to the targeted area of interest. Various strategies for achieving fine localization and locomotion are discussed in Sections 6.2 and 6.3.

6. Technical Challenges of the Robotic Systems in the Gut

Many ingestible robotic systems share common technical challenges such as power, localization, locomotion, and safety. The use of batteries often limits the duration of operation, wireless communication capacity, and the size of the electronic capsule. The ability to localize an ingestible robot is crucial for locating diseases in the gut for follow-up monitoring and treatment. Additionally, locomotion enables the robot to navigate to the target of interest. Last but not least, safety is always a primary concern in the development of medical devices.

6.1. Power

Currently, most commercial ingestible electronic robots are powered by silver oxide batteries as the more energy dense lithium oxide batteries pose more health hazards.[107] However, the myTemp core temperature monitoring capsule utilizes wireless power transfer via inductive coupling, and the Proteus Discover medication adherence sensor is able to harvest energy from a galvanic reaction in the stomach.[94]

The button cell silver oxide batteries used in wireless capsule endoscopes can provide around 25 mW of power; yet incorporation of more advanced imaging and robotic capabilities would demand several hundred milliwatts of power.[108] Wireless power transfer via inductive coupling in the near field has the potential to provide high levels of power to robotic capsules. Various solenoid and Helmholtz coil configurations have been explored to wirelessly provide up to several hundred milliwatts of power to a robotic capsule.[109–112] However, most systems were not tested in vivo. Tissue attenuation will decrease the transfer efficiency, and high levels of electromagnetic radiation pose health risks. A simulation suggests that a robotic capsule can safely receive up to 100 mW of wireless power in the human gut.[113] Near-field power transfer by inductive coupling can provide a lot of power, but orientation is crucial and it necessitates the patient or user to wear a power transmitter.

Energy harvesting systems are ideal for robotic capsules with low power demands as they can generate power in the microwatt level without an external power source. The commercial Proteus medication compliance sensor is powered by a magnesium copper cell to transmit its radio-frequency identification (RFID) in the near field for a few minutes. Prolonged energy harvesting in a pig gut was achieved with a zinc copper galvanic cell powering the measurement and transmission of temperature data.[114] While a copper magnesium cell provided a higher average peak power density, it corroded rapidly and was not feasible for long-term energy harvesting. Throughout multiple in vivo trials, the capsule's zinc copper cell was able to harvest energy (average power, 0.23 $\mu W\ mm^{-2}$) for an average of 6.1 days in a pig gut, while transmitting temperature data every 12 s over 920 MHz communications (**Figure 7**a).

Biodegradable batteries can be used to power biodegradable ingestible electronic robots. An edible sodium-ion battery with a bio-derived melanin-based electrode could output ≈1.03 V with a maximum specific capacity of 16.1 mAh g^{-1}.[115] A paper-based, fully biodegradable primary magnesium-molybdenum trioxide ($Mg–MoO_3$) battery could generate a stable output voltage of 1.6 V at a desirable capacity of 6.5 mAh cm^{-2} and a prolonged lifetime of 13 days.[116]

6.2. Localization

Crude approximations of robot location in the gastrointestinal tract can be provided by pH values in pH-sensing capsules, oxygen concentration in gas-sensing capsules, and visual landmarks in imaging capsules.[71,73] While such methods may be adequate for monitoring transit times in different digestive organs, more precise localization strategies are needed for localizing lesions for future monitoring and targeted therapy. Various imaging techniques, as well as triangulation methods based on RF signal strength and external magnetic fields have been explored for the precise localization of robots in the gut. Vector position calculations based on RF signal strengths received by an array of external receivers are simple, but lack precision with centimeter scale error margins.[117–119] On the other hand, the magnetic flux of a permanent magnet embedded in a robot can be sensed by an array of external magnetic sensors.[120–122] While this method requires extra magnetic sensors and is not as simple, it yields millimeter scale accuracy.

Submillimeter scale localization accuracy is achievable. Inspired by concepts from nuclear magnetic resonance, addressable transmitters operated as magnetic spins (ATOMS) offer a novel approach for microscale device localization with magnetic resonance imaging (MRI)-like precision, without the need of superconductive magnets (Figure 7b).[123] When a magnetic-field gradient is applied, these microscale chips (1.8 × 1.2 mm)

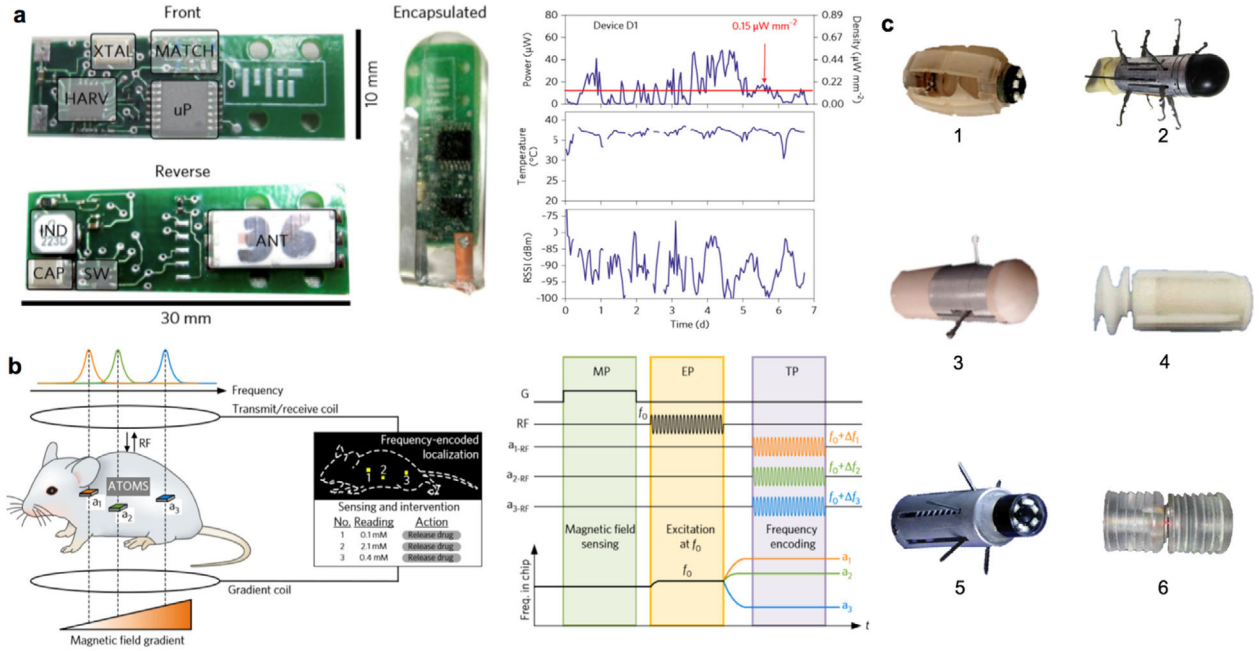

Figure 7. Strategies for overcoming the current technical challenges in power, localization, and locomotion. a) A prolonged energy harvesting capsule powered by a galvanic cell to transmit measured in vivo temperature data of a swine gut for nearly a week. Reproduced with permission.[114] Copyright 2017, Nature Publishing Group. b) Addressable transmitters operated as magnetic spins (ATOMS) device for the submillimeter scale localization of in vivo microscale devices. Reproduced with permission.[123] Copyright 2017, Nature Publishing Group. c) Mechanisms for locomotion of macroscale robotic capsules: 1) Magnetically actuated soft robotic capsule. Reproduced with permission.[128] Copyright 2012, IEEE. 2) Robotic capsule with legged locomotion. Reproduced with permission.[129] Copyright 2009, IEEE. 3) Hybrid locomotion robotic capsule with both legged and magnetic actuation. Reproduced with permission.[131] Copyright 2010, IEEE. 4) Screw propelling robotic capsule. Reproduced with permission.[132] Copyright 2017, IEEE. 5) Robotic capsule with paddling locomotion. Reproduced with permission.[133] Copyright 2009, Elsevier. 6) Robotic capsule with inchworm-like locomotion. Reproduced with permission.[137] Copyright 2005, IEEE.

register the local magnetic field, an indicator of location. After an RF signal is applied to oscillate the devices at a specific frequency, the devices emit a shifted frequency proportional to the measured local magnetic field. An in vivo study in anesthetized mice showed that ATOMS-enabled devices can be localized with an error of less than 500 μm.

Next, odometry can be used to measure the distance a robotic capsule has traveled inside the small intestine.[124] In the OdoCapsule, three retractable miniature legs with a soft rubber wheel function as micro-odometers to measure the distance traveled from a particular landmark. Furthermore, the extended legs stabilize the capsule from tumbling. This method is desirable because it does not necessitate external components for localization.

6.3. Locomotion

Most contemporary ingestible robots rely on passive locomotion via peristaltic motion. However, the inability to steer a capsule within the GI tract is a major setback of capsule endoscopes in comparison to traditional endoscopes. Future ingestible robots with therapeutic functionalities would rely even more on locomotion capabilities to navigate toward the site of interest.

Locomotion of magnet-embedded capsules can be externally activated by controlling a magnetic field created by coils and/or permanent magnets.[125,126] Limitations in external magnetic locomotion are that it can lead to large forces applied on body tissue, and that robots can get stuck in collapsed regions of the intestine.[127] Figure 7c1 shows a prototype of a magnetically actuated compressible soft robot that attempts to address these issues.[128] The elastomer-based compliant robot embeds two internal permanents magnets such that an external magnetic force can anchor the robot to a GI tract wall and a subsequent external magnetic torque can roll the robot to the desired location. Furthermore, magnetic actuation can compress the soft robot in the axial direction to provide an extra degree of freedom and perform therapeutic functions. Legged locomotion of a robotic capsule is shown in Figure 7c2.[129] Two direct current (DC) brushless motors are able to simultaneously generate 0.63 N of average propulsive force at each of the 12 leg tips. The legs can act as anchors for stable locomotion in the tubular small intestine, which is covered by a thick slippery mucus layer with a low coefficient of friction (10^{-3} to 10^{-4}).[130] The locomotion module consumed 430 mW of average power while generating a speed of 5 cm min^{-1} in a lower GI phantom model. The hybrid locomotion robot depicted in Figure 7c3 combines internal legged actuation with external magnetic dragging.[131] External magnetic actuation enables power-free locomotion most of the time. However, when the device gets stuck or entrapped in the intestines, a DC brushless motor can actuate the legs to generate 3.85 N and take over. The device could propel at a speed of 8 cm min^{-1} during in vivo pig experiments. Figure 7c4 shows a screw propelling capsule with a high velocity of up to 6 cm s^{-1} in a rubber tube.[132]

A DC motor can actuate a spiral screw impeller to propel the device forward and backward through fluid dynamic pressure and mucosal friction. The paddling-based capsule endoscope shown in Figure 7c5 has six long paddles actuated by a microbrush DC motor.[133] The robot could traverse 60 cm min^{-1} in a silicon tube, and 17 cm min^{-1} in the colon of a live pig while consuming 1.2 W of total power for locomotion, imaging, and data transmission. Inchworm-like locomotion can be achieved through shape memory alloy or piezoelectric actuators.[134–137] The piezoactuator-based inchworm-like locomotive robot shown in Figure 7c6 repetitively elongates and retracts to achieve controlled motion. Inside an extracted porcine intestine, the device would travel at around 13.4 cm min^{-1}.

Various locomotion strategies have been proposed and many of them have been effective in in vivo experiments. However, they may cause strain and damage to the GI tissue during locomotion. In addition, a lot of locomotion mechanisms require electromechanical actuators that require too much power to be run on a typical coin cell battery.

6.4. Safety

In the case of passive robotic-sensing capsules, the main safety concern is capsule retention, which can lead to GI obstruction. In the case of capsule retention, surgical removal may be necessary. While capsule retention in patients have been reported to be 1.4%, the retention rate depends significantly on the device dimension and patient gut health.[138] The size of the ingestible capsule can be decreased through the miniaturization of electronic, battery, and sensor components. Also, softer and deformable capsules may decrease retention rate. Compartmentalized robotic capsules that break down into smaller parts, or dissolvable capsules are possibilities as well. To evaluate a patient's individual retention risk factor, PillCam patency capsule has been developed. The patency capsule is a self-dissolving dummy capsule the same size as a capsule endoscope that can be ingested prior to a capsule endoscopy procedure.[139]

Robotic capsules with active robotic structures for gastric retention, surgery, and locomotion may cause physical strain on the GI tract walls. Components such as legs and magnets for locomotion can cause perforations or unsafe amounts of strain on the GI tract walls. Capsules with active robotic structures must be evaluated with extensive precaution. Soft and dissolvable materials are more favorable for the safety of ingestible robots.

7. Microscale Robotics in the GI Tract

Compared to the existing medical macroscale robots, synthetic microrobots can perform tasks that are impossible for conventional macroscale robots, thanks to the scaling down in size.[17,140–147] While endoscopes and capsules provide good visualization and sensing of GI environment, their macroscale size limits the possibility of cargo delivering at hard-to-reach locations with high specificity. Microrobots, however, serve as a great tool in targeted delivery in hard-to-reach areas. Tremendous progress has been achieved in microrobots in autonomous and controlled motion, and the design of microrobots for GI tract applications has been broadly investigated.[148]

Just as biological motors such as myosin that perform autonomous motion by hydrolysis of biological units, a large number of ingestible microrobots have been designed with the capability of converting chemical or other forms of energy into autonomous motion.[149–152] For example, the first use of ingestible microrobots in vivo was demonstrated with a tubular polyaniline/Zn rocket-like structure constructed with template-assisted electrodeposition (see **Figure 8**a).[153] Once administered into the mice stomach, these microrobots exhibit excellent propulsion, which is generated by the thrust of hydrogen bubble from the reaction between zinc with gastric acid. The strong mechanic propulsion resulted in the enhanced retention of microrobots in the stomach. To eliminate the gastric barrier for controlled release, a microrobot-based strategy to neutralize the gastric acid through the chemical reaction of magnesium with water was reported.[154] The autonomous locomotion and pH-responsive surface coating of the microrobots resulted in the spontaneous drug release into stomach. Mg-based microrobots were designed for in vivo treatment of *H. pylori* infection in the mouse stomach (see Figure 8b).[155] With the Mg–acid reaction as the source of propulsion, the drug-loaded Mg microrobots penetrate the bacterial biofilm and enhanced the drug delivery. Further investigation revealed that the enhanced retention may be attributed to the penetration of gastric mucus layer, and the microrobots were also developed to encapsulate the microrobot into pills for better administration.[156,157]

Although gastric acid can serve as a fuel for microrobot propulsion, it also poses a natural barrier for bare microrobots to reach intestines. To overcome this barrier, enteric coating was applied (Figure 8c).[158] The enteric coating remains stable and protects the Mg microrobot in acidic gastric environment (pH 1–3) but breaks down in intestinal fluid (pH 6–7). Once the enteric coating gets fully dissolved, the Mg microrobots get exposed to the intestinal fluid, and a spontaneous propulsion is achieved with the Mg–water reaction. Furthermore, the distance traveled in GI tract before propulsion can be controlled by tuning the thickness of the enteric coating. Following this work, a therapeutic investigation of the enteric micromotors was carried out by coating of red blood cell membrane to enhanced generation of mucosal immunity.[159] Compared with the conventional passive delivery, the microrobots with active motion and enteric coating elevated the retention and uptake of antigenic material, opening a new door for active oral delivery for the development of vaccine.

The autonomous propulsion of microrobots has revealed tremendous opportunity for in vivo applications, but to realize the controlled locomotion in GI tract, powerful imaging techniques are necessary to visualize and locate the microrobots.[160] Magnetically powered locomotion of helical microrobots was achieved in stomach and visualized.[161] Actuated by the external magnetic field, the helical microrobots were imaged with fluorescence imaging, and a controlled movement of fluorescence in stomach was seen (Figure 8d). However, fluorescence imaging has limited penetration depths for practical applications. To improve the penetration depth, MRI was employed to image the microrobots in stomach, thanks to its excellent tissue-penetration capability, high spatial resolution, and superior tissue contrast. MRI-guided helical biohybrid magnetic microrobots were

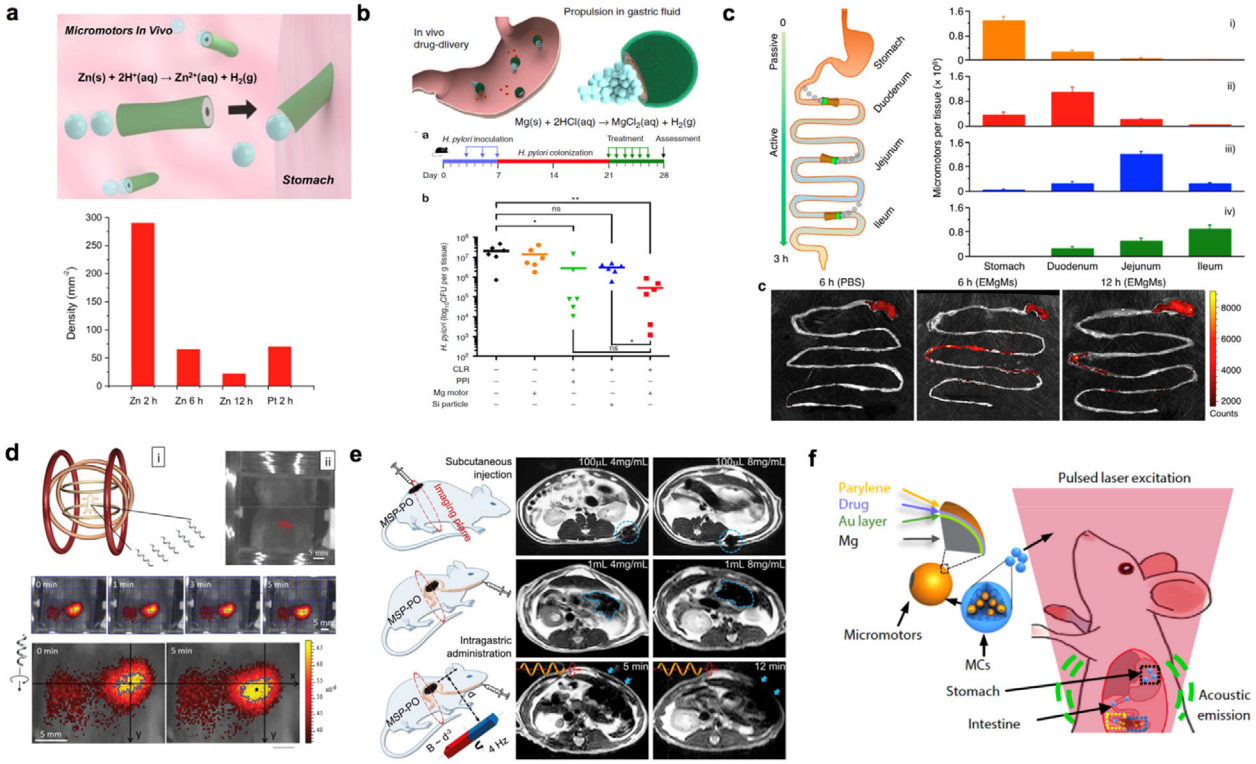

Figure 8. Synthetic microrobots for active drug delivery in the GI tract. a) Acid-driven PANI/Zn rocket-like microrobots for enhanced retention in stomach. Reproduced with permission.[153] Copyright 2015, American Chemical Society. b) The magnesium-based microrobots for the treatment of *Helicobacter pylori* infection. Reproduced with permission.[155] Copyright 2017, Nature Publishing Group. c) Enteric microrobots for precise position and retention in GI tract. Reproduced with permission.[158] Copyright 2016, American Chemical Society. d) Controllable propulsion and fluorescence imaging of magnetic helical microrobots in stomach. Reproduced with permission.[161] Copyright 2015, John Wiley & Sons, Inc. e) MRI imaging of the magnetically powered motion of the biohybrid microrobots in vivo. Reproduced with permission.[162] Copyright 2017, AAAS. f) A microrobotic system guided by photoacoustic computed tomography for targeted navigation in intestines in vivo. Reproduced with permission.[163] Copyright 2019, AAAS.

developed for image-guided therapy (Figure 8e).[162] With the high contrast of magnetic materials, the microrobots accomplished a monitored locomotion inside stomachs upon MRI. Despite the great tissue penetration and tissue contrast, MRI requires long acquisition time (seconds to minutes), which is too slow for imaging dynamics, and strong magnetic field, which may impose constraints on microrobot design. Most recently, a photoacoustic computed tomography (PACT)-guided microrobotic system was developed and implemented in mouse model (Figure 8f).[163] Drug-loaded Mg-microrobots were encapsulated in enteric coating and migrated through the GI tract. With a high spatiotemporal resolution, deep penetration, and anatomical and molecular contrasts, PACT monitored and visualized the migration in real time in vivo. As the microcapsules reached the target delivery area, the microrobots were released upon instantaneous disintegration of the microcapsule upon continuous-wave near-infrared irradiation. Once released, the Mg-microrobots delivered the drug at target area with autonomous and efficient propulsion, with prolonged retention time. This integration of PACT and microrobotic system realizes deep imaging and precise control of microrobots in vivo and shows great potential for practical biomedical applications such as drug delivery.

8. Conclusion

In this review, we have summarized and highlighted recent advances in utilizing untethered robots for diagnosing and treating diseases non-invasively in the GI tract. Although development of ingestible sensors has mostly been focused on imaging devices, there is an increasing interest toward the development of ingestible drug delivery, surgical, and molecular-sensing systems in the gut. One attractive future direction is ingestible robots for gut microbiome monitoring: the human gut hosts over 1.5 kg of microbiota that formulate neurotransmitters and respond to various neuroactive compounds, modulating cognition, behavior, and immune responses; minor fluctuations in gut composition can affect mood and cognition, while major imbalances of the gut microbiota can lead to harmful disorders/pathologies.[164]

Incorporation of advanced imaging technologies in capsule endoscopy are limited mostly by size and power consumption. Ingestible robotic sensors for gut lumen biochemical analysis suffer from difficulties in achieving selectivity, robustness, sensitivity in the complex and acidic GI fluid. Moreover, power, localization, locomotion, and safety are common critical challenges for ingestible robots that need to be solved. Materials, devices,

and systems innovations are strongly desired for designing future generations of ingestible diagnostic robots with miniaturized size, low power consumption, and powerful imaging and sensing capabilities.

Successful development of therapeutic robots is often hindered by the need for incorporation of bulky electromechanical motors and actuators that are not biocompatible and consume lots of power. Novel actuation mechanisms used in soft robots, magnetically controlled origami robots, artificial muscles, and micromotors can aid in resolving these constraints.[17,103,104,165] Furthermore, macroscale ingestible sensor robots can encapsulate drug-loaded micromotors for the controlled and localized deployment of microrobots, realizing closed loop active treatment of diseases.

The ingestible capsule market is expanding rapidly, and there is plenty of room for breakthroughs in robotic capsule technology. Currently, many diseases cannot be diagnosed or cured by the simple ingestion of an oral capsule. However, the incorporation of various robotic functionalities into the oral capsule can broaden the range of diseases that can be diagnosed and treated through ingestible medical robot administration. Ingestible medical robots will continue to enlighten the recondite aspects of gastrointestinal pathology, and simplify the therapeutic regimen followed by patients, likely improving compliance to therapy.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

capsule endoscopy, drug delivery, gastrointestinal tract, robotics, sensors

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