Magnetically guided capsule endoscopy

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Wireless capsule endoscopy (WCE) is a powerful tool for medical screening and diagnosis, where a small capsule is swallowed and moved by means of natural peristalsis and gravity through the human gastrointestinal (GI) tract. The camera-integrated capsule allows for visualization of the small intestine, a region which was previously inaccessible to classical flexible endoscopy. As a diagnostic tool, it allows to localize the sources of bleedings in the middle part of the gastrointestinal tract and to identify diseases, such as inflammatory bowel disease (Crohn's disease), polyposis syndrome, and tumors. The screening and diagnostic efficacy of the WCE, especially in the stomach region, is hampered by a variety of technical challenges like the lack of active capsular position and orientation control. Therapeutic functionality is absent in most commercial capsules, due to constraints in capsular volume and energy storage. The possibility of using body-exogenous magnetic fields to guide, orient, power, and operate the capsule and its mechanisms has led to increasing research in Magnetically Guided Capsule Endoscopy (MGCE). This work shortly reviews the history and state-of-art in WCE technology. It highlights the magnetic technologies for advancing diagnostic and therapeutic functionalities of WCE. Not restricting itself to the GI tract, the review further investigates the technological developments in magnetically guided microrobots that can navigate through the various air- and fluid-filled lumina and cavities in the body for minimally invasive medicine. © *2017 American Association of Physicists in Medicine* [https://doi.org/10.1002/mp.12299]

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1. INTRODUCTION

1.A. Historical development

The earliest descriptions of endoscopes, in the form of specula and tubular devices, which utilized ambient light to visualize body orifices for diagnostic and therapeutic purposes, are found in ancient Greek and Indian texts on medicine.[1,2] Modern rigid and semi-flexible rod-shaped endoscopes, incorporating nonambient sources of light, mirrors, and lenses, appeared in the 17th century and allowed examination of previously inaccessible regions.[3] The invention of mechanically flexible, optical fiber endoscopes in 1954 was a key advancing technology for optical screening of the upper and lower human gastrointestinal (GI) tract.[4] However, it was not a complete screening solution, as it could not visualize the small intestine (bowel), a locale for many health disorders. The very first swallowable untethered devices, which could measure internal pressure[5,6,7] or pH-values,[8,9] appeared in 1957–58. This leap into wireless telemetric devices, which could transmit signals from within the body, was made possible by the invention of the first transistors in the early 1950s enabling miniaturized radio transmission circuitry to be embedded in the pill.

It was not until the 1990s that cameras were integrated into the capsule, and by doing so, constructing the first capsule endoscope (CE), small enough for swallowing, passing through, and imaging the entire GI tract. Power efficiency and miniaturization of the following technologies were crucial to the development of the first capsule endoscope: (a) CCD and CMOS cameras for imaging, (b) application specific integrated circuits (ASICs) for radio transmission, and (c) the light-emitting diode (LED) as a light source.

Independent research work from groups at the Royal London Hospital (led by C.P. Swain) and at Raphael (led by G.J. Iddan), a government defense R&D group in Israel, delivered the initial concept of the wireless capsule endoscope (WCE)[10] and the first patent filings (1995)[11,12] followed by the first animal imaging demonstrations (1997).[13] The two groups combined their efforts and conducted a successful first study with ten healthy volunteers in 1999.[14] This work culminated in the commercialization of *the first wireless capsule endoscope* by Given Imaging in 2001.[15] Since its release, the capsule known as the M2A™ (or PillCam SB) capsule has been the gold standard for the full screening of the small intestine. Since then, other manufacturers of endoscopic capsules have entered the market. Olympus Medical Corp released a competing product, the EndoCapsule in 2005, incorporating higher resolution and real-time viewing. It was launched immediately in Europe (2006) and USA (2007) in succession.[16] Chinese manufacturer, Jianshan Science and Technology Ltd., is the market leader in China with their OMOM capsule.[17] For an interesting historical account of the commercial interest in WCE development, the reader is referred to Ref. 18. In addition to diagnosis of the GI tract in adults and children, CE has been found to be an important diagnostic tool in animal and veterinary investigations.[19,20]

1.B. Capsule endoscope design

The main concept of a capsule endoscope has not changed significantly over the years. The outer shell of the capsule is made of a biocompatible polycarbonate. The half-spherical ends are transparent and hold the imaging sensor surrounded by multiple LEDs. Directly behind the sensor is the ASIC for signal processing and control of the radio transmitter unit. The radio signal is usually transmitted on the ISM-band (Industrial, Scientific and Medical Band, 433.05–434.79 MHz). Power is provided by one or more button cells, which fit compactly inside the capsule. The electronic components utilize flexible printed circuit boards and flat cables. The size of commercially available capsules is typically less than a maximum dimension of 32 mm in length and 13 mm in diameter for ease of swallowability.

A single camera approach does not guarantee a 100% screening, as capsule orientation control is not possible.[21] This problem was addressed by the introduction of a camera with wider viewing angles in newer versions of the commercial capsules. Capsules with multiple cameras have been also introduced. For example, the PillCam COLON for colonoscopy and the PillCam ESO for esophagus examinations include two end-facing cameras. CapsoVision introduced the Capsocam, a fully transparent capsule with four orthogonally arranged cameras, each with a viewing angle larger than 90° allowing for a stitching algorithm to deliver 360° panoramic images. For a review of technical data and images of commercially available CEs, see table 1 in Ref. 22.

2. STATE OF THE ART IN RESEARCH AND DEVELOPMENT

Up until 2010, commercially available WCEs lacked active propulsion and orientation control and were primarily targeted toward video-based screening and diagnosis of mucosal pathology of the esophagus, the small intestine, and the large intestine. The complete screening of the stomach region as in conventional gastroscopy was impossible. The clinical introduction of magnetically guided capsule endoscopy (MGCE), which uses magnetic fields to orient and propel the capsule in a fluid-distended stomach, from several manufacturers including Siemens Healthcare & Olympus Medical Corporation, set the stage for a patient friendly capsule-based alternative to gastroscopy. Unfortunately, the magnetic locomotion capabilities of these capsules cannot be presently utilized to navigate the lower GI tract. An ideal WCE of the future would not only be able to visualize the entire GI tract starting from the oral cavity to the anus in a single procedure,[23] but can additionally perform advanced tasks such as precise delivery of medication, long-term physiological monitoring, and obtaining biopsy samples.

The design of externally guided, untethered multifunctional capsules for gastro-intestinal applications is challenging. Conventional WCE relies on a combination of gravity and peristalsis for capsule movement along the entire gastrointestinal tract. Developing a one-size-fits-all active capsule, with miniaturized power source and locomotion-drive system and therapeutic modalities, is difficult considering the intricate and varying morphological and physiological landscape of the GI tract (Fig. 1) through which the capsule has to pass.

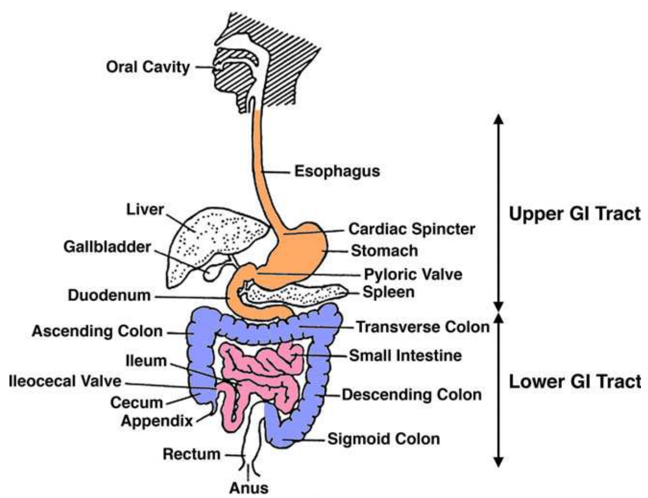

Fig. 1. The human gastrointestinal (GI) tract (adapted from Ref. 205). The upper GI tract consists of the esophagus, stomach, and the duodenum, while the lower GI tract consists of the small intestine, the large intestine, and the rectal region. [Color figure can be viewed at wileyonlinelibrary.com]

The esophagus of an adult is a distended muscular tube of length 18–26 cm and which can be stretched in diameter to 2–3 cm to aid swallowing. For the investigation of the esophagus along its length until the cardia sphincter, the valve-like muscle that is a common site of various pathologies, the capsule must have a stopping, temporary gluing, or clamping mechanism so that it does not fall into the stomach. Capsular navigation in the stomach requires 3D steering and locomotion to explore its relative large cavity (approximately 15 cm wide and 30 cm long).[24] To allow for its complete screening, the stomach needs be distended using suitable liquids before the capsule endoscopy procedure. In comparison to the stomach, the small intestine (or the small bowel, luminal diameter of 2.5–3.0 cm) and the large intestine (or the colon, diameter range of 2.5–7.5 cm) have a smaller wall-to-wall distance and a system might utilize a crawling or a corkscrew technique to move.

In the scientific literature, one can identify several research communities focusing their efforts in developing miniaturized systems for wireless diagnosis, therapy, or targeted interventions in the human body. This large body of contemporary research is driven by proven practical and commercial successes in actual minimally invasive medical methods, which have minimal impact on the patient's body, a lowered infectious risk, and higher patient comfort. Engineering research groups specialized in *small-scale robotics* and *in vivo robotics* have developed very promising approaches for future intracorporeal applications. As an established diagnostic method, the WCE could already be defined as an intracorporeal robot. Moglia et al.[25] foresee the future development of WCE into a multipurpose robotic system.

Among the various available technologies, the usage of body-exogenous magnetic fields provides for an excellent body-permeable wireless technique for powering advanced diagnostic and therapeutic functionalities in the capsule. Static and dynamic magnetic fields and field gradients at well-defined amplitude-frequency bands are currently used in clinical practice for a variety of interrogations, including magnetic resonance imaging (MRI), magnetic hyperthermia,[26,27] magnetic catheter maneuvering,[28] and magnetic particle imaging (MPI).[29] The physical phenomena of magnetism can be harnessed for technological solutions to three main challenges in advanced capsular endoscopy, namely guided locomotion, power generation, and capsule localization in the body.

In the following sections of this review, important works in this search for optimal, miniaturized, and actively guided systems for *in vivo* intra-corporeal applications are reviewed. Both academic and industrial research developments are presented, as there is great commercial and scientific interest to fast-forward WCE technology.[18] After a brief review of the state-of-the-art in nonmagnetic technologies for advanced WCE, the use of magnetic technologies in WCE will be thoroughly reviewed, and lastly we will explore the field of magnetic microrobotics, as technologies developed there may have potential interest for MGCE development.

2.A. Nonmagnetic minimally invasive methods in gastroenterology

2.A.1. Active locomotion

Since the clinical success of WCE as a powerful diagnostic tool for the gastrointestinal tract, the development of an active propulsion system has been the foremost goal of research groups working on advancing WCE technology. Passive capsular motion, driven by peristalsis and gravity, is limiting in terms of diagnostic efficacy. The lack of position, orientation, and velocity control leads to incomplete pathological screening. This section focuses on developments in active propulsion mechanisms and other technological advances in WCE that do not involve the use of magnetic fields.

The design and development of active locomotion systems calls for a thorough understanding of the geometry and biomechanics of the GI tract.[30] An innovative concept for active capsular locomotion in the esophagus and intestines was proposed by Swain's group in late 2000.[31] Their capsule incorporates a pair of peripheral electrodes for circular stimulation of the intestinal muscles; 12–15 electrostimulations per second was reported to cause localized muscular contraction that propels the device up to 6 mm s^{-1} and 4.5 mm s^{-1} in either direction of a porcine esophagus and small intestine, respectively. This *radio-controlled electrostimulation capsule* (RESC) was further tested in the GI tract of a healthy volunteer (2005).[32] Although showing great promise, no commercial product has been released based on this technology. A similar electrically stimulated capsular propulsion system was reported by Woo et al.[33] from South Korea in 2011 [Fig. 2(a)]. The authors mathematically modeled the electromechanical behavior of the capsular movement in the small bowel. Their electrocapsule prototype achieved a mean speed of approximately 2.5 mm s^{-1} in *ex vivo* porcine small intestines. Electrostimulation for capsular locomotion has to be carefully investigated for its safety, as it caused reduction in heart rate in a human volunteer,[34] possibly due to inadvertent stimulation of the vagus nerve adjacent to the small intestine.

For capsular locomotion in the intestines, the CRIM Lab at Scuola Superiore Sant'Anna in Italy, led by Professor Paolo Dario, developed an *inchworm* device in 2002.[35] The prototype consists of a pneumatic actuator/extender and a clamper to mechanically secure onto the walls of the intestine. The blind device (24 mm in diameter and 115–195 mm in length) was externally tethered with flexible air tubings to a pneumatic pump. *In vivo* experiments on an anesthetized pig demonstrated that the device could propel around 400 mm into the colon at an average speed of 19 mm s^{-1}, demonstrating potential for rectum sigmoidoscopy, the tract which harbors approximately 60% of all diagnosed colon cancers. Kim et al.[36,37] have described several crawling capsular locomotion schemes using shape memory alloys (SMAs), piezoelectric actuators, and motor-driven paddles as actuators. Modeled after the motion of an earthworm, the concept uses

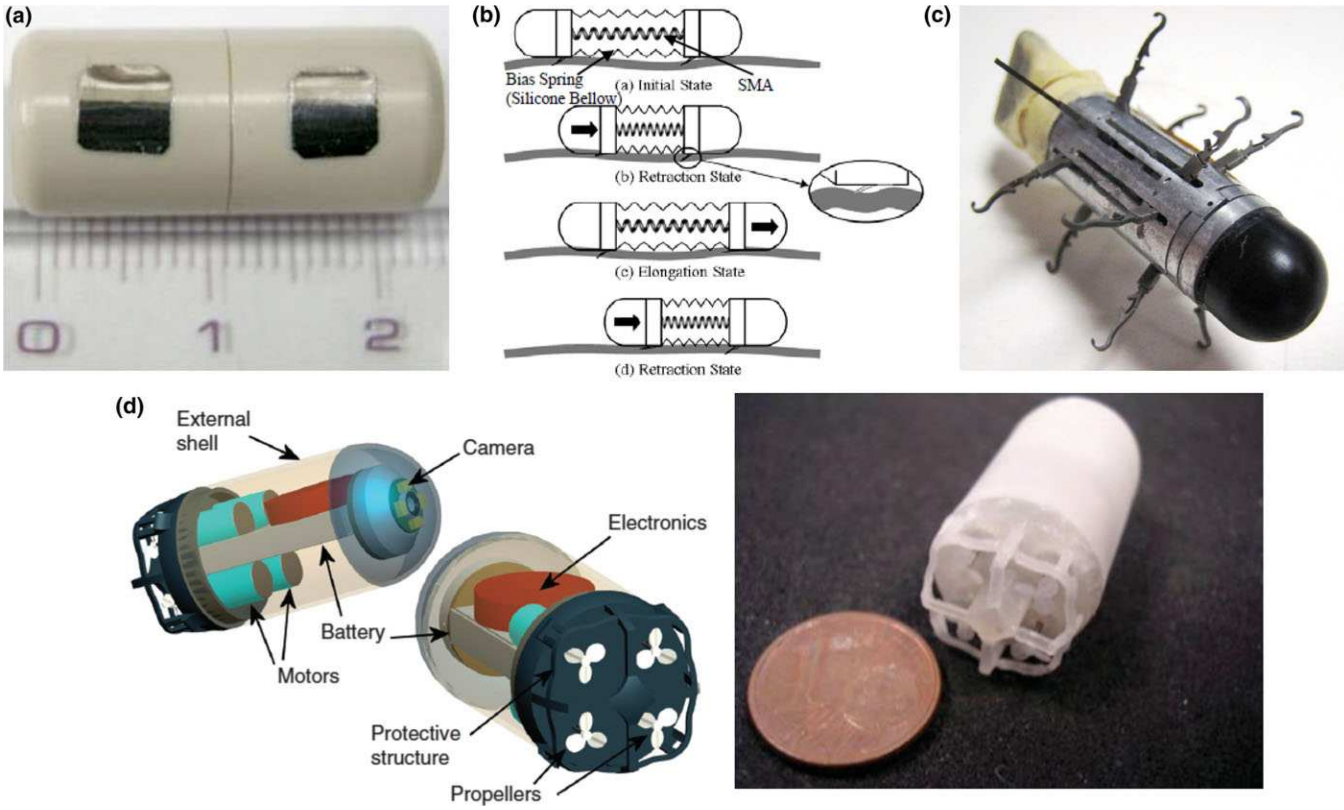

FIG. 2. Advanced WCE prototypes: (a) Capsule with patch electrodes for intestinal locomotion via electrically induced muscular contraction.[33] (b) SMA-based "Earthworm" capsule for intestinal locomotion.[37] (c) Twelve-legged capsule for crawling motion in the intestine,[38] (d) capsule with four propellers for swimming in a liquid-distended stomach.[40] [Color figure can be viewed at wileyonlinelibrary.com]

SMAs that shrinks when it is electrically heated and widens again when cooled. The capsule has a flexible middle part with a SMA spring inside and has solid capsule endings with needles [Fig. 2(b)]. The typical disadvantage of SMA actuators is the relatively long heat-up cool-down times resulting in slow locomotion, with a reported 3.4-mm movement per cycle (2 s of heating and 6 s cool-down-phase). They also detailed crawling capsular concepts using piezoelectric actuators and electromagnetic stepper-motors, which achieved faster locomotion speeds of approximately 5 mm s^{-1} each. The proposed concepts are currently not compact enough and do not incorporate cameras or radio-transmitters necessary for WCE. The CRIM Lab also developed a 12-legged capsule endoscopy robot capable of traversal in compliant, slippery tubular environments (2009).[38,39] Powered by two brushless motors, the circular in-out motion of the 2 × 6 legs in the capsule shell produces a crawling motion [Fig. 2(c)]. The force of the legs was reported to be strong enough to extend the intestine walls for better image capturing. A mean speed of 0.8 mm s^{-1} was recorded. The current prototype with camera system is 33 mm long and needs further miniaturization for swallowability. For all the above-described systems, the need for external tethering for pneumatic and electrical powering of the locomotion module in the capsule is a serious drawback.

For active locomotion in the stomach, the CRIM Lab demonstrated a swallowable capsule endoscope (size 15 × 30 mm^2), actively driven by four motor-driven propellers, for swimming in the liquid-filled human stomach (2009).[24,40] It encapsulates a wireless microcontroller, a battery, and a magnetic turn on/off switch. This blind neutral-buoyancy prototype is wirelessly controlled by a joystick input device and can reach speeds of up to 7 cm s^{-1} [Fig. 2(d)]. The power design was planned to allow steering and image capturing for 30 min when using speeds of 1.5 cm s^{-1}. The capsule was successfully tested *in vivo* in PEG-distended porcine stomach models. In 2014, an updated and larger prototype (22 × 32 mm^2) of the system with an integrated camera is described in Ref. 41. Built from off-the shelf components, a single prototype reportedly costs less than 100 euros. The new system was tested in an *ex vivo* porcine stomach, but has not yet been tested *in vivo* in animals or in humans.

Given Imaging owns a large patent portfolio on capsule endoscopy.[42] One of their early patent filings in 2002[43] describes a WCE with at least one "tail" that can be moved in one or several directions. This movement could lead in some situations to a stimulation of the peristalsis, but it could also allow changing the pose of the capsule, if it is stuck, or to help movement through a certain area more quickly. How the tail movement is achieved is left open in the invention claim. This could be done by an integrated motor or with help of an external magnetic field. This broad patent claim could also apply to swimming fish-like capsules in the stomach. For an exhaustive review of active locomotion strategies for WCE, the reader is referred to Ref. 44.

2.A.2. Physiological sensing and therapeutics

In addition to video imaging, WCE technology to measure intraluminal physiological conditions can be extremely useful for gastric functionality monitoring. Disorders such as gastroparesis and chronic constipation can disturb normal gastric motility. In addition to physiological parameters, such as intraluminal pH, temperature, and pressure, the whole and regional gastrointestinal transit times (GITT) are a useful measure for diagnosing these gastric disorders. The first demonstration of a truly multisensing capsule (16 mm × 55 mm) was presented in 2004 by Johannessen et al.[45] who showed *in vitro* measurements of pH, temperature, dissolved oxygen, and conductivity. Since clearing FDA approval in 2006, Given Imaging markets the SmartPill® capsule technology, which determines gastric motility and GITT by measuring and recording pH, pressure, and temperature. The SmartPill does not have an inbuilt camera system. Previously, GITT was measured using ingestible radiopaque markers or radioactive tracers with intermittent fluoroscopy or scintigraphy, respectively. The Bravo® pH monitor (Given Imaging) and the OMOM pH monitor (Jianshan Science and Technology) are two commercially available capsules for luminal anchoring and long-term (48 hr) monitoring of pH in the esophagus.

Measuring of vital signs (pulse rate and respiratory rate) is important for detecting and monitoring medical problems. While wearable vital signs sensors currently exist, monitoring via the GI tract has important advantages for assessment of patients with acute long-term trauma and also for condition monitoring and training improvement of athletes. A proof-of-concept for real-time monitoring of heart and respiratory rates, internally through the GI tract, was demonstrated using acoustic signals recorded in the GI tract with a capsule-sized microphone sensor in a porcine model.[46] Recently, transluminal impedance measurements[47] or electrical permittivity[48] has also been proposed to be important indicators of GI health monitoring. Other recent developments include an LED-based WCE that can detect bleeding in the upper GI tract[49] and an FDA-approved temperature monitoring pill (CorTemp® sensor from HQ Inc) that is accurate to ±0.1°C.[50]

Therapeutic capabilities are currently lacking in most commercial capsules. Integrating surgical and biopsy sampling capability into WCEs could make it a valuable therapeutic tool for *natural orifice transluminal endoscopic surgery* (NOTES).[51] A capsule-based photodynamic treatment was recently demonstrated in Ref. 52 with preliminary results revealing that a multi-LED capsule can be used for *in vitro* killing of *Helicobacter pylori* (*H. pylori*), a Gram-negative bacteria, which affects the stomach mucosa causing severe gastric diseases. The authors think that this could pave the way for capsular nonpharmacological treatment of gastric disorders. The IntelliCap® capsule developed by Medimetrics B.V. (the Netherlands) allows for custom liquid-based drug loading and tunable release profile.[53] Other recent developments in WCE technology include tele-operated, global access, and cloud-based architectures for screening and therapeutics.[54,55,56]

2.B. Magnetic minimally invasive methods in gastroenterology

The earliest modern use of the *action-at-a-distance* effect of magnetic fields for medical applications has been in the removal of metallic splinters and shrapnel from human body parts.[57] In 1951, the magnetic guidance of steel-tipped catheters was demonstrated in a rabbit aorta.[58] The use of external magnetic fields for noncontact maneuvering of foreign inserts in body cavities has been patented since the 1960s.[59,60,61] More recently, they have been used for catheter maneuvering for neurosurgery (2000).[62] Currently in clinical practice, magnetic guidance is used to navigate magnet-tipped catheters for ablation procedures for arrhythmia[28] and for magnetically guided capsule endoscopy (MGCE).

Magnetic fields, produced outside a patient's body, can be used to exert translational and rotational forces on capsules with embedded permanent magnets or magnetizable materials. Active locomotion strategies using SMA, piezo-drives, and electrical motor drives, also termed as internal locomotion mechanisms,[44,63] need additional on-board power supplies for operation or must be externally tethered via flexible power cords. The use of magnetic fields for capsule locomotion makes the WCE truly wireless or untethered and is generally termed as an external locomotion mechanism. In addition to position, orientation, and velocity control of the capsule, magnetic fields can also be harnessed for capsular power generation and battery charging and for capsule localization and imaging within the body.

In 2001, the year of commercial release of the first WCE (M2A™), Siemens AG filed patent applications in Germany and in USA for a magnetically controlled endoscopic robot which could be moved and oriented using magnetic fields and gradients.[64,65] In the following year (2002), Olympus Corporation filed Japanese and US patent applications for a endoscopic capsule that magnetically "rotates to develop thrust."[66] A few patent applications were filed in later years by other research groups for magnetically propelled capsule endoscopes.[67,68] Both time-varying magnetic fields and field gradients can be used to generate propulsion in magnet-embedded WCEs in a fluid-filled or near-surface region. Surprisingly, a patent filed in 1963 and granted in 1967 to E.H. Frei and S. Leibinzhon describes all such methods.[59] Aptly titled "Magnetic propulsion of diagnostic or therapeutic elements through the body ducts of animal or human patients," the patent application describes several different propulsion strategies utilizing fields and field gradients (Fig. 3) and also details a drug delivery module [Fig. 3(d)]. Incorporating magnets within them, the longitudinally asymmetric designs can overcome fluid or surface friction utilizing alternating fields for swimming motion [Fig. 3(a)], rotating fields for

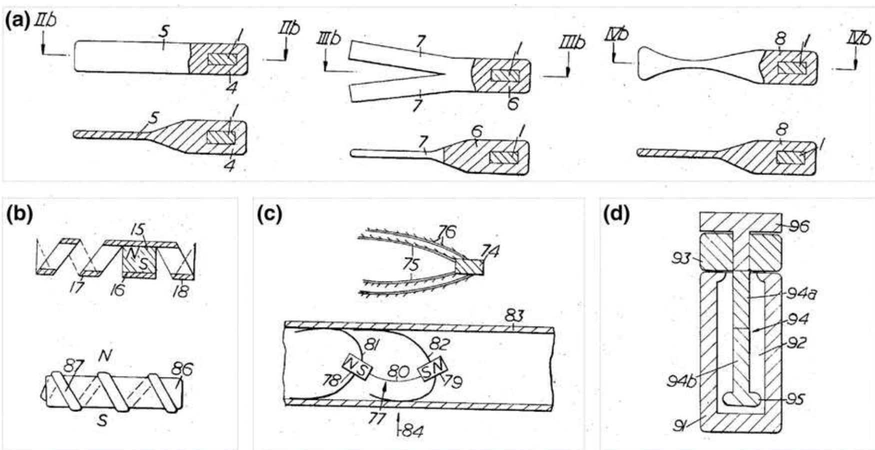

FIG. 3. A selection of devices for magnetic propulsion adapted from the patent application of Frei and Leibinzhon:[59] (a) Endorobots with single or multiple tails.[33] (b) Screw-like robots which are transversely magnetized and can propel longitudinally forward. (c) Robots for swimming inside tubes by utilizing surface friction. (d) Robot for propulsion and drug release.

corkscrew motion [Fig. 3(b)] and pulsed fields for impact-driven motion through tubular channels.

In the following sections, we will review the different modalities for magnetic field generation and the various strategies for magnetically guided capsule propulsion in the various sections of the GI tract.

2.B.1. Magnetically guided capsule gastroscopy

While the WCE has been widely adopted for small bowel investigations, the screening of the stomach or gastroscopy was and is still done manually with a flexible endoscope. Lacking active propulsion, the WCE was unable to screen the large stomach volume relying purely on gravity or peristalsis. For a complete capsular screening of the stomach, its preoperative expansion or distention is required to flatten out its folds. Conventional gastroscopy employs the use of CO_2 gas, but this would not be a possibility for capsular endoscopy, as the air would leave the stomach through the cardia, unlike in the tethered endoscope where the endoscope closes the stomach's entrance. Liquids such as water, polyethylene glycol (PEG), or sodium phosphate (NaP) can be used to inflate the stomach,[69] and this would make swimming-based locomotion favorable for a miniaturized robotic system. After partial water-based distention, a further gas-based distention may be performed by ingesting CO_2 producing powder.[70,71] This implies that swimming-based mechanisms may be employed for magnetically guided capsule gastroscopy.

Aware of the various patent filings on magnetic endoscopic robots, Carpi et al.[72] from the University of Pisa (Italy) proposed an elegant modification of an existing WCE (M2A from Given Imaging, size 11×25 mm^2, weight 3.23 g) for MGCE (2006). The capsule was tightly encased with an elastic shell, made from 1:1 weight percentage mixture of silicone and Neodymium Iron Boron (NdFeB) powder. The capsule–shell complex, with the shell radially magnetized, was then used to demonstrate "translations, rotations, and roto-translations" on the surface of *ex vivo* tissue in an air-based environment. The magnetic field was generated using a pair of hand-held permanent magnet stacks. Alternative shell magnetization profiles and the possibility of using a commercial robotic magnetic steering system were also presented.[73]

Getmann and Swain[74] demonstrated *magnetically guided capsular cystoscopy* in a porcine bladder in early 2009. They introduced a commercial WCE (11×27 mm^2, Given Imaging) with an incorporated magnet into a fully filled bladder using an obturator-based deployment technique, and maneuvered the capsule using a hand-held magnet and were able to optically evaluate the entire bladder mucosa and all anatomic landmarks. The authors admit that current capsular technology is unsuited for human cystoscopy as the capsules designed for GI diagnosis have to be further miniaturized for deployment through physiological pathways, for example, through the urethral lumen.[75]

Given Imaging, in collaboration with Swain, reported their first *in vivo* human demonstration of remote magnetic manipulation of a WCE in the upper GI tract in 2010.[76] The device consists of a modified PillCam Colon (11×31 mm^2), with one camera end removed and replaced by a permanent assembly. The position and orientation of a large hand-held permanent magnet ($100 \times 100 \times 30$ mm^3) relative to the patient is varied to maneuver (rotate and translate) the capsule in the water-filled stomach. All stomach regions were screened, but the control of the capsule pose was reportedly difficult and not intuitive, especially as the operator only had the real-time images of the capsule's camera and no other tracking mechanism. A larger clinical study involving ten healthy participants was conducted successfully, and the capsular system was named as the *Magnetic Maneuverable Capsule* (MMC).[70,77]

Ohta et al.[78,79] report another hand-held permanent magnet field generator for guided capsule endoscopy (2011). The generator consists of two pairs of cylindrical magnetic bars, with each pair having two perpendicularly arranged magnets. The group compared their system with conventional gastroscopy in a trial of ten people. They report a sensitivity of 98 percent and specificity of 92 percent and concluded that the system is not inferior to conventional endoscopy. This manually controlled method is very cost efficient, but most likely not very intuitively to manipulate, and similar to the results of Swain et al.[76] Other researchers have also shown demonstrations of hand-held magnet field generators for magnet capsule maneuvering, such as in Ref. 80, where they used a hand-held rotary magnet to fixate, drag, and rotate a magnet-bound capsule along the mucosal wall of the GI tract in *ex vivo* trials.

The OMOM Controllable Capsule System (Jianshan Science and Technology, Chongqing, China) and the MiroCam® Navi MC1000-WM (Intromedic Ltd, Seoul, Korea) are two commercially available capsular technologies, which use hand-held magnetic field generators and have demonstrated upper gastrointestinal tract maneuverability in human models.[81,82,83] Hand-held magnetic field generators are quite inexpensive and exhibit a short-learning curve for the endoscopist. At the same time, to project large enough fields and field gradients into the GI tract, especially in obese patients, larger and bulkier magnets have to be used. The usage of such hand-held systems over the course of an entire gastroscopy session is physically taxing for the operator.

In 2009, the CRIM Lab reported the first ever use of a robotic platform to steer a capsular endoscope.[84,85] They used a six-degrees-of-freedom (DOF) industrial robotic arm with a permanent magnet as an end-effector that could be moved along the patient's body to drag a magnet-incorporated capsule along the mucosal lining of the GI tract [Fig. 4(a)]. In addition to a magnet, the capsule prototype (14×38 mm^2, weight 7.5 g) incorporated a camera, microcontroller, wireless transmitter, and a magnetic field sensor. The operator used a 6-DOF joystick system (3D SpacePilot, 3Dconnexion Inc., USA) to control the robotic end-effector and magnet. The system was successfully tested and compared to manual hand-held magnetic capsular maneuvering in *in vivo* experiments on porcine large intestines. Robot control was more effective than manual magnetic control in terms of accuracy, precision, and stability of steering. The manual approach was better suited and faster for large-scale point-to-point movements.

A similar robotic platform and its uses for magnetic capsule maneuvering were demonstrated by the Telerobotics Lab from the University of Utah (2013).[86,87,88] Their 6-DOF robot arm had a motor-rotatable permanent magnet as an end-effector [Fig. 4(b)]. In the various studies, this system controlled untethered magnetic devices (UMDs), like rolling spherical devices, helical microrobots, threaded capsule endoscopes, and a swimming capsule endoscope with a magnet inside. The stomach endoscopy capsule prototype (9.5×24 mm^2) holds a cubical NdFeB (N52) magnet arranged parallel to the capsule's longitudinal axis. The blind capsule was controllable in 5-DOF with visual servoing with two tank-mounted cameras, as rotation around the magnetic dipole-axis of the capsules magnet cannot be controlled. The capsular density is higher than water as the robot's working space is above and beside the water-filled tank. This can be used for downward propulsion by moving the external magnet a short distance away from the capsule.

Ankon Technologies (Wuhan, China) has a robotic magnetic capsule guidance system, patented, clinically approved, and recently reported to be installed in over hundred medical centers in China.[81,89,90] Their robotic system consists of a 5-DOF (two rotational and three translation) arm [Fig. 4(c)]. The field generation is achieved using a single spherical magnet and can reach field strengths up to 0.2 T in a working area is $50 \times 50 \times 50$ cm^3.[91] Field strengths of 5–30 mT are typically used for maneuvering a magnet-embedded video capsule (12×28 mm^2). Live video feed at 2 fps is possible. A pilot study on 34 healthy volunteers was conducted in 2011 and was followed by a self-controlled study gastroscopy on 68 patients to compare MGCE with normal gastroscopy.[71,92] The cardia (the opening of esophagus into the stomach) and the fundus (the upper region of the stomach) were found to be the toughest to examine, as also reported by the group which tested the MMC from Given Imaging.[70] The endoscopist found it difficult to localize the capsule at times, relying purely on visual feedback from the endoscopic camera. The conclusion was that the MGCE was comparable to conventional gastroscopy of the stomach in terms of it is diagnostic efficacy.

A group from Huazhong University of Science & Technology (China) proposed a multipermanent magnet robotic system for WCE manipulation (2010).[93,94] They used a capsule endoscope embedded in a magnetic shell. The external magnetic field is produced by several external permanent magnets that can be moved along linear axes [Fig. 4(d)]. This allows for a 5-DOF control of the capsule and was successfully tested in an intestine phantom and an *ex vivo* porcine small intestine. The speed of the blind capsule (11×26 mm^2, 8.82 g in weight) was measured with 10.75 mm s^{-1}.

In 2009, Carpi at the University of Pisa presented a concept to use the commercially available Magnet Navigation System Niobe® (Stereotaxis) for guidance of a magnet-embedded PillCam capsule endoscope (13×26 mm).[95,96] The Niobe system consists of two large permanent magnets, which are mechanically moved in 2-DOF around a pivot point [Fig. 4(e)]. It can generate fields of up to 0.08 T in any arbitrary direction within an approximately spherical working volume of 20 cm^3 inside the patient's body. The magnets can be mechanically moved in 2-DOF around a pivot point. It is used clinically for guidance of magnetic-tipped catheters for treating arrhythmia. A fluoroscopy system allows for catheter visualization and tracking to control the direction of the magnetic tip. They demonstrated the use of the Niobe for steering and noninvasive 3D localization of a capsule in each of the main regions of the porcine GI tract (esophagus, stomach, small bowel, and colon).[97] The magnets allowed for precise orientation control (within 1°) of the capsule, but since no field gradients could be produced, translational motion was not achieved. A limited control on translation was, however, possible by moving the patient or the patient table.

Magnetic field generators, employing commercial multi-DOF robotic arms, pose a danger to the patients, as it may

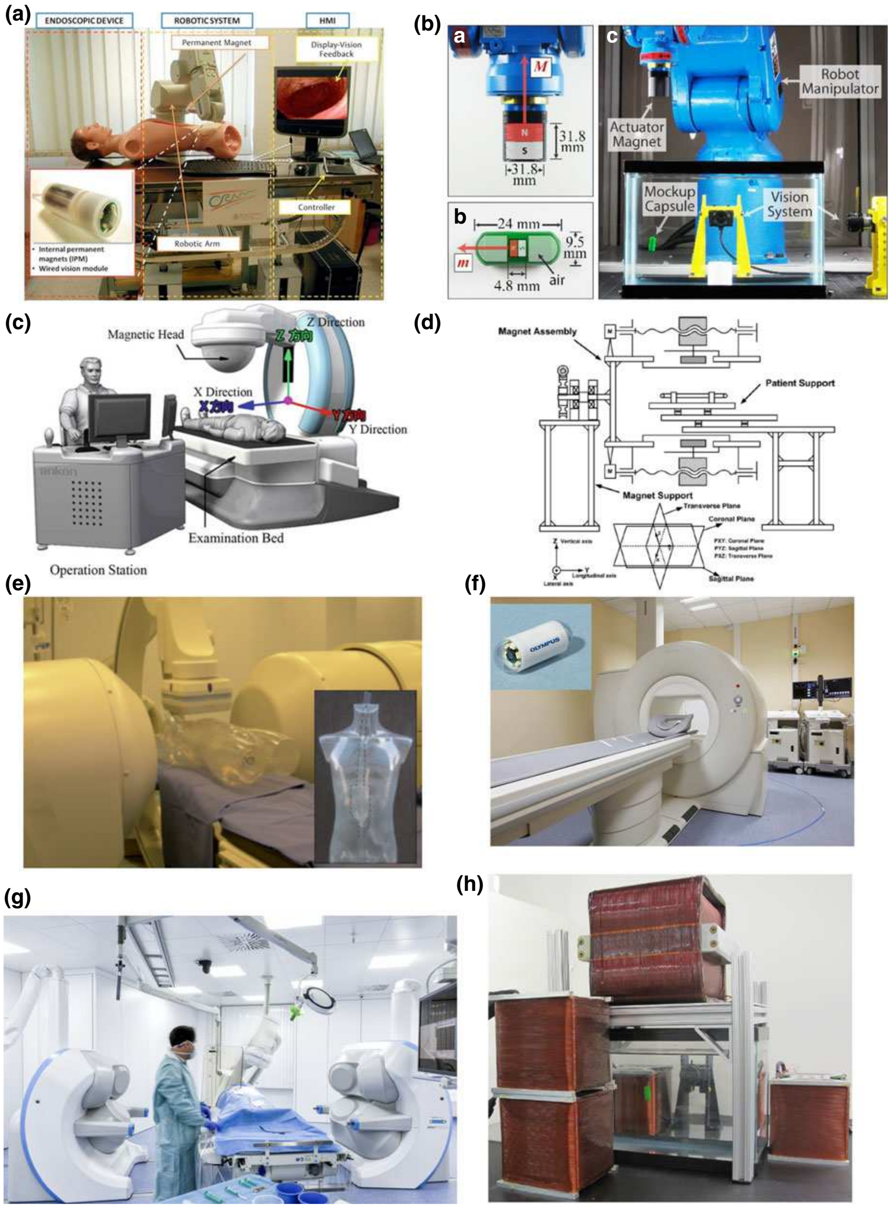

FIG. 4. Magnetically Guided Capsule Endoscopy (MGCE) systems. (a) Robotic system by Ciuti et al.[84] (b) Capsule endoscope guided with robot arm for 5-DOF. Manipulation in human stomach by Mahoney et al.[86]: The actuator magnet (a) controls the capsule endoscope prototype (b) in a water-filled tank with a visual tracking system (c). (c) Ankon System.[81] (d) Multipermanent magnet navigation system.[93] (e) NIOBE System (inset: GI tract phantom).[96](f) Siemens-Olympus clinical MGCE system (inset: capsule).[100] (g) Aeon–Phocus electromagnetic system. (h) A reconfigurable assembly of Omnimagnet.[108] [Color figure can be viewed at wileyonlinelibrary.com]

physically contact the patient's body unless proper safety and feedback measures are implemented. To alleviate the dangers of industrial robots in contact with the patient, Salerno et al.[98] propose a pressure sensitive textile-based cloth to be worn by the patient under examination for magnetic WCE. This active pressure sensing scheme can be used to control the pressure applied on the abdomen or other body parts by the magnet-wielding robotic arm ensuring that maximum forces are not exceeded.

Electromagnetic coil systems provide another way to generate varying magnetic field vectors in a well-defined workspace. They can create complex spatiotemporal field distributions for advanced motion schemes. Electromagnets offer increased versatility and speed in independent generation and control of fields and field gradients as the field-generating components do not have to physically moved as is required in permanent magnetic assemblies.[99] In addition, with respect to safety considerations, there is no danger of moving parts as in a robotic arm when using coil-based systems, as they are physically immobile and either safely engulf the patient's body (air coils) or project the field from a distance (core-wound coils).

Siemens Healthcare and Olympus Medical Corp have jointly developed a magnetic capsule manipulation technique, named the Magnetically Guided Capsule Endoscopy (MGCE), using a multicoil configuration.[100,101,102] The system uses 12 body-external electromagnetic coils that allow for 5-DOF control of a swimming capsule endoscope. The system generates up to 0.1 T magnetic flux density in a working volume large enough for a patient to lie in [Fig. 4(f)]. By turning the patient during the examination, an additional DOF is achieved. The swallowable, single-use capsules are 31 mm long and 11 mm in diameter. They are designed to swim upright at the surface, if no external forces are applied. They incorporate two cameras, batteries, a wireless transmitter, a microcontroller, and a small permanent magnet. The capsules are controlled in the water-filled stomach via a joystick user-interface, while the captured frames are displayed on external monitors at 2 fps for each camera. The system is the first fully functional electromagnetic capsule endoscope system that had been successfully evaluated in *in vivo* clinical trials with over 200 published patient and volunteer cases to date.[101,103,104] Siemens AG holds the patents on the working concept[64,65] and the electromagnetic system.[105] Two other commercially available whole-body multicoil electromagnetic systems are the Catheter Guidance Control and Imaging (CGCI) system from Magnetecs Corp (California, USA) and the Aeon Phocus system from Aeon Scientific AG (Zurich, Switzerland) [Fig. 4(g)].[28,106,107] Both these systems are CE certified and are primarily targeted for magnetic catheter maneuvering for heart ablation procedures. They use an assembly of eight ferromagnetic core solenoids with specially shaped pole pieces to project user-defined fields and gradients into a central workspace. These systems could be employed for magnetic WCE applications, but there have been no reported studies so far.

Since the CGCI and the Aeon Phocus systems use custom-geometry pole pieces, the workspace field distribution is highly nonlinear and typically requires finite-element modeling and *in situ* field calibration for quantitative force determination. To alleviate this need for extensive calibration, the Telerobotics Lab at University of Utah has developed a reconfigurable electromagnet system, using *Omnimagnets*, each comprising a spherical ferromagnetic core nestled within three orthogonal solenoids [Fig. 4(h)].[108,109] The field distribution in the workspace and the forces and torques experienced by a magnetic body within the workspace due to an arbitrary arrangement of *Omnimagnets* can be analytically determined. The system has not yet been used for *ex vivo* or *in vivo* trials.

Hosseini and Kamassei[110] of the University of Waterloo (Canada) describe a much smaller multicoil electromagnetic system capsular guidance in. The field generator consists of six coils arranged in a circular manner and positioned above the laying patient's torso. It generates a magnetic field primarily oriented in the vertical direction and variable gradient fields to produce translational forces on the capsule in 3-DOF. Although the authors state that the system is applicable to the whole gastrointestinal tract, their system appears less suited for the stomach as the orientation of the capsule cannot be controlled. Consequently, his follow-up work describes a capsule (5×12 mm^2) aimed at treatments of the esophagus.[111] Their field generator is based on earlier work on magnetic levitation systems.[112,113] Numerical optimization of electromagnetic end-effectors and permanent magnetic assemblies for capsule maneuvering is a field of active research.[114,115]

Magnetic resonance imaging (MRI) is the most ubiquitous magnetic system in use for medical applications. It generates body-uniform uni-directional fields of up to seven tesla, and in addition can generate gradient-like pulses and RF signals. It has a dual-advantage for WCE. It can be used to simultaneously power capsular locomotion and to image and localize the capsule in real time. The base magnetic field B_0 direction is fixed, and this renders orientation control of a magnetic object impossible. An innovative solution, to utilize MRI technology for capsule endoscopy has been proposed and conceptually demonstrated in[116,117,118] and patented[119] by a team from ETH Zurich and the Brigham and Women's Hospital in Boston. The proposed capsule has flexible tails that hold one or more miniature coils. Generation of alternating currents in these coils in turn generate magnetic fields that will try to align to B_0, resulting in movement of the flexible tails to achieve a propulsion force. The energy source for the capsule is either a nonmagnetic battery or is harvested via induction through additional coils. The imaging capabilities of the MRI scanner can then be used to track the capsule and build a closed-loop motion control. The published prototypes are 23–29 mm long and 10 mm in diameter and produced a propulsion force of 430 μN.

The group of Sylvain Martel at Polytechnique Montréal (Canada) has also worked on the concept of MRI powering and guidance of magnetic robots. In 2007, they reported the control and tracking of a 1.5 mm ferromagnetic bead in the carotid artery (lumen diameter of 5 mm) of a living pig inside a clinical MRI system.[120] They used the orthogonal gradient coil system to apply translational forces on the bead. Recently, they proposed a new strategy, *Fringe Field Navigation* (FFN), whereby they take advantage of the extremely large field gradients (2–4 T/m) caused by the fringe fields around a MRI scanner, for navigation of magnetic guidewires and catheters in a whole-body area.[121] These field gradients produced by the superconducting scanner coils are much higher and cover a larger workspace than which can be produced by resistive coils or permanent magnet assemblies. Although practically cumbersome, they propose to robotically maneuver the patient's body to take advantage of the immobile fringe field for magnetic endorobotics. A modified strategy to generate large gradient fields, without moving the patient, is to use soft ferromagnetic inserts to distort the large uniaxial field of the scanner to simultaneously produce large fields and gradients. Named the *Dipole Field Navigation* (DFN), the concept can produce 0.3 T/m gradients in a whole-body workspace.[122] While the distortion of internal field prevents conventional MRI imaging, this limitation can be circumvented in specific regions in the scanner.[123] For a comparison of the magnetic field generation systems for MGCE, please see Table I.

Table I. Magnetic field generators and their modifications that have been used in preclinical and clinical trials for intracorporeal robotic applications. The systems may not be able to simultaneously achieve the maximum field and field gradients. In addition, the systems have different workspace volume coverage. Operating fields for capsule navigation are typically below 30 mT.[71]

Type	Name	Field and field gradients (max)	Description
Electromagnet	MGCE (Siemens-Olympus)	100 mT. Entire stomach workspace	12-coil system; CE approved Undergoing active clinical evaluation for MGCE[101,103,104]
	Aeon Phocus (Aeon)	50 mT and 250 mT/m simultaneously (early prototype)	8-coil system; CE approved; has not been demonstrated for MGCE
	CGCI (Magnetecs)	140 mT, 700 mT/m[106]	8-coil system; CE approved; has not been demonstrated for MGCE
Magnetic resonance imaging	Martel et al.[192]	1.5 T, 40 mT/m simultaneously	Ferromagnetic bead guidance demonstrated in carotid artery; has not been demonstrated for MGCE
	Fringe Field Navigation[121]	2–4 T/m	Requires external 6DOF robotic manipulation of patient table; Has not been demonstrated for MGCE
	Dipole Field Navigation[122]	0.3 T/m	Requires complex spatial arrangement of ferromagnetic inserts into MRI; reduced working distance and imaging distortion
Permanent magnet	MiroCam® Navi MC1000-WM (Intromedic)	n/a	Hand-held magnets; CE approved; undergoing active clinical evaluation for MGCE[82,83,206]
	OMOM Controllable Capsule (Jianshen)	n/a	Hand-held magnets; System reported in Refs. 81,207
	Magnetic Maneuverable Capsule (Given Imaging)	n/a	Hand-held magnets (NdFeB) in size $100 \times 100 \times 30$ mm^3; underwent clinical MGCE evaluation[70,77]; currently not in development
	Ankon MCE (Ankon)	200 mT, $50 \times 50 \times 50$ cm^3 (workspace)	Magnet on 5-DOF robotic arm; SFDA approved in China; Extensive clinical evaluation for MGCE[71,92]
	NIOBE (Stereotaxis)	80 mT; spherical 20 cm^3 (workspace) No gradient control	Dual magnets on a horizontal pivot assembly; CE and FDA approved for magnetic catheter guidance; demonstrated for WCE guidance[95,96]; lack of gradient generation makes it unsuitable for MGCE

2.B.2. Fish-like magnetic capsules

The magnetic capsules reviewed so far were navigated using dragging and orientation control. Overcoming the resistive fluid forces requires large magnetic field gradients. Since field gradients spatially decay fast and generation of well-controlled and whole-body gradients are difficult to be produced, especially with hand-held and permanent magnet systems, the torque generated on a magnetic dipole under the action of magnetic field is an attractive alternative for capsular locomotion.

One of the first reports of fish or tadpole-like swimming robots is the para-operational device or the POD (1966) reported by Frei et al.[124,125] It is a device with a flexible tail with a small permanent magnet attached to it [Fig. 5(a)]. An angular oscillation of an oscillating magnetic field causes the tails to flap and propel the device forward. A cylindrical magnet (1 mm diameter) with an attached tailed (3–4 mm) is reported to propel 300 mm s^{-1} in water under an alternatively magnetic field of 10 mT amplitude and 60 Hz frequency.[126] Various groups have reported *in vitro* swimming of tail-flapping magnetic microrobots.[127,128,129] Design concepts for larger fish-like robots for underwater and marine exploration, employing streamlined and flexible bodies with single oscillating tails[130] could be miniaturized and explored for potential use in stomach endoscopy.

In 2008, Morita et al. from Osaka Medical College (Japan) reported a capsule endoscope with a permanent magnet-embedded fin at its rear that propels via fish-like motion in a gastric model.[131] Named the *self-propelling capsule endoscope* (SPCE), the device was successfully tested *in vivo* in the water-filled stomach of a dog.[132] The SPCE consisted of a commercially available capsule endoscope PillCam SB, with attached fins and a foam covering for surface buoyancy [Fig. 5(b)]. It was 14 mm in diameter and 52 mm long with the fin and 35 mm without it. A simple electromagnetic coil system produces an alternating magnetic field (5–12 mT) to flap the fin. A joystick controlled the direction and speed of the swimming motion, and a maximum speed of 50 mm s^{-1} was achieved. A year later, an updated swallowable version, the SPCE-MM1, was demonstrated, with a capsule size of 12×45 mm^2 and which moved under the fluid, along the lining of the human stomach.[133] While all regions of the stomach were apparently screened, it is not clear if stable close-up views of any part of the anatomy were possible. A recent publication from the same group[134] tested the efficacy of various commercial capsules (PillCamSB2, ESO2, and COLON2 from Given Imaging) with magnet-attached fins to diagnose lesions in a porcine stomach model. The PillCamESO2 was found to be the best capsule for such a diagnosis as its dual cameras provided a wider field-of-view and its faster real-time video update rate of 18 frames-per-second

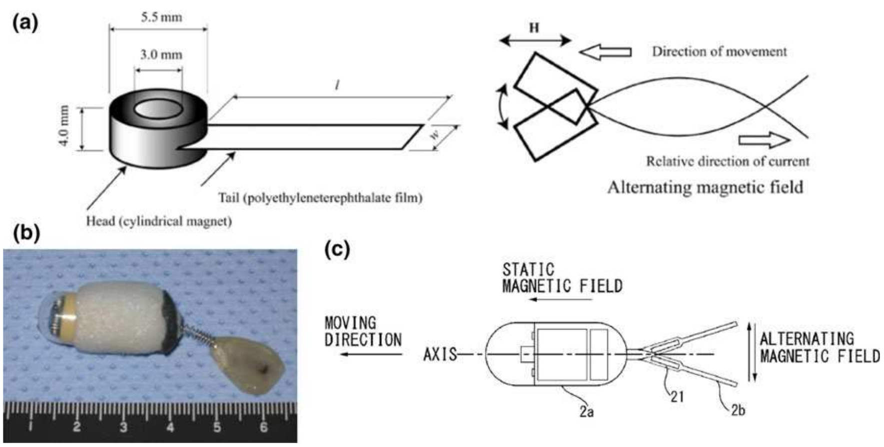

FIG. 5. (a) Magnetic swimming mechanism by use of alternating magnetic fields and a flexible tail by Sudo et al.[128] (b) Capsule with permanent magnet in a fin by Morita et al.[132] (c) Schematic from patent filing showing fish-like robot.[135] [Color figure can be viewed at wileyonlinelibrary.com]

made maneuvering easier. A US patent for a capsule which additionally incorporates a capsular-axis magnetized permanent magnet for orientation control has been filed in the name of Mu Ltd. Japan [Fig. 5(c)].[135]

2.B.3. Spiral-type magnetic capsules

The concept of *spiral capsule endoscopy* employs rotation-induced linear propulsion of capsules to screen the GI tract. There are some promising and independent research approaches on the mechanism of magnetically driven spiral capsules. The rotation of spiral-structures can generate a translational motion in both a viscous environment and in a wall-constrained environment due to asymmetric contact friction. These robotic capsules typically consist of a radially magnetized magnet or magnetic shell with a spiral or screw-like exterior.

Possibly not aware of the POD design by E.H Frei, the revival of the spiral capsule came from Tohoku University (Japan) in 1996.[136] An untethered robot, inspired by the bacterial flagellum, consisting of a permanent magnet ($1 \times 1 \times 1$ mm^3) attached to a rigid spiral wire (five turns of copper wire of diameter d=150 µm, and helix pitch of 3 mm), is described [Fig. 6(a)]. Under low-Reynold's number condition and under a rotating magnetic field, the robot can propel forward in a cork-screw manner. The group demonstrated several variants, which could even drill through bovine tissue.[137,138] The propulsion speed was dependent on the rotational magnetic velocity and went up to 14 mm s^{-1} in the liquid and 1 mm/s going through tissue. A next-generation spiral swimmer was specifically designed for movement inside the GI tract (2003).[139] The blind capsular prototype (11×30 mm^2) was driven forward and backward through an intestinal phantom with a rotating magnetic field, and maximum speeds of 20 mm s^{-1} were reported [Fig. 6(b)]. Newer propulsion results in *ex vivo* porcine large intestine were published in cooperation with Olympus Medical Corp. (2007).[140] Zhang et al.[141,142] have also demonstrated a swimming spiral capsule with orientation and translational control driven by a 3D Helmholtz coil pair system. The blind prototype (12.5×25 mm^2) was tested in a fluid-filled spiraling pipe and in an *ex vivo* porcine large intestine. The capsule achieved maximum swimming speeds of 8.27 mm s^{-1}. Higher rotational velocities can increase translational speeds but can also cause increased damage to the intraluminal wall. The Telerobotics Lab at University of Utah demonstrated propulsion of *untethered magnetic devices* (UMDs) in a lumen using rotating magnetics.[87] They mathematically prove and experimentally demonstrate that if the position of the UMD is tracked, the rotating magnetic field for propulsion can be generated with a single rotating actuator magnet from any position in space. This is an important factor to be able to use a robotic system in the operating room where space constraints exist such as to avoid collisions with the patient's body.

The first demonstration of a magnetically driven spiral WCE with an integrated camera was reported by Bo et al. (2015).[143] They used a hand-held rotary magnetic actuator to navigate the WCE through an excised porcine small intestine. They used a commercially available capsule (Hitron Co. Ltd, Hangzhou, China) wrapped with a radially magnetized NdFeB magnetic shell [Fig. 6(c)]. In addition, the capsule is wrapped with brass wire to form a two-turn spiral, which transfers the rotational movement into a forward/backward motion. The operator using the hand-held device can easily modulate the speed and direction of the capsule. Experimental results in laboratory conditions showed a movement speed of about 15 mm/s when the actuator rotates at about 4 Hz. In a clinical setting, visualizing the mucosal features with a rotating video feed is clearly cumbersome for diagnosis. Using postprocessing techniques to create a motion steady video or using a combination of rotational fields for fast translation and gradient fields for slow movements could provide techniques for efficient diagnosis when using spiral capsule endoscopy.

2.B.4. Hybrid locomotion capsules

A collaborative project between Tianjin University of Technology (China) and Kagawa University (Japan) resulted

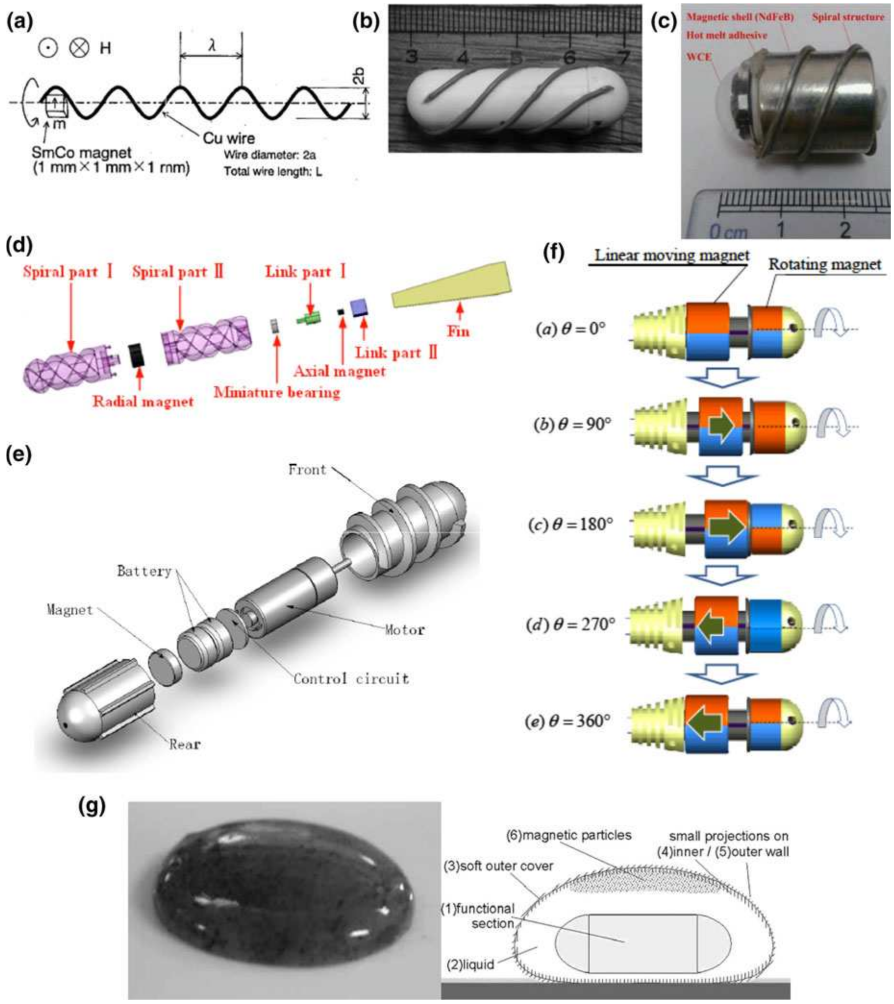

FIG. 6. Spiral and Hybrid Capsule Designs: (a) First reported spiral robot, Honda et al.[136] (b) Chiba et al.,[140] (c) Bo et al.,[143] (d) Guo et al.,[144] (e) Wang et al.,[146] (f) Yim et al.,[147] (g) Magnetically controlled crawling movement by Nokata et al.[149]: (left) soft model prototype for crawling in an uneven surface, (right) structure of a rolling object using magnetic derive principle with sample magnetic field. [Color figure can be viewed at wileyonlinelibrary.com]

in a novel magnetically propelled millimeter-sized robot that uses a hybrid motion merging fish-like locomotion together with spiral motion.[144,145] In addition, it includes a gravity compensation method. By merging these two different motion techniques, the researchers have tried to define a more universal approach to allow movement in the heterogeneous environment of the GI tract. The structure and 3D-printed prototype can be seen in Fig. 6(d). The robot incorporates a body-radially oriented magnet to control rotation with the spiral body and a body-axially oriented magnet to produce fin movement. The smaller version of this robot is about 90 mm long (40 mm without the fin) with a diameter of 10 mm. *In vitro* lateral and vertical speeds of about 30 mm s^{-1} and 8.5 mm s^{-1}, respectively, were reported.

Another hybrid capsular locomotion mechanism, based on coupling an internal motor with externally generated magnetic forces, was reported by Wang et al. from the Chinese University of Hong Kong.[146] Their blind spiral capsule prototype (18 × 64 mm^2) consists of two parts: a DC micro–motor attached spiral and a second part containing a radially magnetized permanent magnet, batteries, and a microcontroller [Fig. 6(e)]. The motor can rotate the spiral capsular section, propelling it forward and backward, using the friction generated on the mucosal wall. External magnetic forces, generated by a large permanent magnet on a 6-DOF robotic arm, can generate additional translational force and can control capsule orientation. Experiments were conducted with different spiral sizes in excised porcine large intestines, and a maximum speed of 4.2 mm s^{-1} was reported.

Yim and Jeona reported a spiral capsule that combines a micro-motor with an internal multimagnetic assembly for aided propulsion, but one that does not utilize an external magnetic field (2009).[147] The blind device (10 × 30 mm^2) has three parts: (a) a rotatable magnet with spiral outer shell, driven by the motor, (b) a magnet that moves on a linear shaft, and (c) a capsule-affixed spiral end. The rotatory motion of the front part, driven by the motor, attracts the linear moveable magnet periodically generating a instantaneous kick, which assists forward propulsion [Fig. 6(f)]. Yim reports speeds of 1.6 mm s^{-1} in a porcine small intestine coated with silicon oil. The current prototype has an externally tethered power supply; however, miniaturization is still possible. Another example of a hybrid locomotion for intestinal traversal is a legged-crawling endoscope combined with a force driving mechanism based on permanent magnets.[148]

Nokata from Ritsumeikan University (Japan) introduced a new magnetic translation/rotation drive that is very different from other crawling or swimming motion types.[149] It uses a soft or hard hollow shell that holds a liquid suspension with magnetic nanoparticles. The particles (magnetic iron-oxide) have a specific gravity lower than the liquid (kerosene). In Fig. 6(g), the principle of locomotion can be seen together with a simple soft prototype. An externally generated magnetic field can drag the magnetic particles toward its side and can cause the whole robot to roll on a surface. Nokata highlights two other ways of utilizing the force generated on magnetic nanoparticles. First, using cross wheels, where the magnetic particles flow into each of the cavities of the cross wheel, pulling it down. A rotating magnetic field will then induce a rolling motion of the cross wheel.[149] The second solution inspired by a water snake toy consists of a cylindrical water balloon (torus-shaped) filled with magnetic particle suspension. By magnetically attracting the particles to one end of the cylindrical form, the balloon can deform and push itself through a pipe-like structure like the intestine. The work is still at a conceptual phase and currently does not hold any sensors or actuators.

2.B.5. Inductive power transfer

Currently, commercial WCEs use button cell batteries as an energy source. These batteries power the capsular components, such as LED, imaging sensor, ASICs, and radio-transmission electronics; 25 mW was deemed sufficient for the 6 hr operational energy requirements of a WCE.[150] To provide WCEs with multifunctional robotic capability including a locomotion mechanism, additional power is required.[38] Rather than increasing capsular energy storage with additional batteries, an alternative is to use a body-external power source.

While we have previously examined various magnetic techniques to directly propel capsules, alternating magnetic fields can also be utilized to deliver wireless power to charge batteries or capacitors in the capsule. The technology generally employs a pair of body-external transmitting and a capsule-embedded receiving coil assembly. While 25 mW was reported to be sufficient for operating a commercial WCE for 6 hr,[150] power requirements for future WCEs will be much higher. A wireless power supply system based on inductive coupling was demonstrated for powering a swimming capsule with motor-based propellers.[24] The capsule included a ferrite core triple-coil assembly and can capture up to 400 mW of power to power the onboard electronics and motors. The authors further describe an optimized power transmission strategy and a rechargeable WCE system capable of delivery 1 W power in 20 min.[151,152] This is considering that energy levels of up to 5–10 W may be required for future microwave or laser sources embedded in the capsule for photo-dynamic therapy. Yu et al. demonstrated resonant transmission of 150 mW of power which can support an imaging and real-time video (320×240 at 30 fps) transmission system.[152] In addition to energy transfer for powering electronics, a recent result by Boyvat et al.[153] is particularly exciting as he proposes a wireless engine, which uses an external nonrotating magnetic field and couples it directly to motor rotation. The motor consists of two identical LC oscillators, one, which is rotatable, and the other one, which is fixed at a specific angle to the rotation axis of the first one. He proposes a method to control several objects independently by tuning the frequency of an external magnetic field based on the coupled LC resonators. If miniaturized, this technology could find use in magnetically guided WCEs. We think that the current widespread use of wireless charging in electronic devices such as smartphones will lead to further miniaturization of power-transceiver components. These technology developments could be implemented in WCE power modules. The power and frequency ranges of transmission must take into account the medical guidelines set by the International Commission on Non-Ionizing Radiation (ICNIRP) to prevent adverse effects due to induced eddy currents on body tissue and also by nerve stimulation.[154,155]

2.B.6. Capsule localization and imaging

In addition to magnetic maneuverability, the real-time 3D localization of the capsule within the GI tract can improve pathology detection, targeting of therapeutics and surgical interventions. Currently, clinicians find it difficult to determine the location and orientation of the magnetically guided capsule with respect to the anatomy of the patient based purely on the capsular vision system. While a dual camera capsule can alleviate this problem, real-time positional information suitably visualized on a monitor can speed up the intervention process and can also be used to monitor GITT and motility. In addition, real-time localization can be used for robust closed-loop control of magnetic maneuvering of the capsule further increasing the diagnostic efficacy. Some of the nonfluoroscopic and nonmagnetic techniques for real-time localization include monitoring of pH which shows variation across the GI tract,[156] observation of visual landmarks with the onboard camera system, or radiofrequency triangulation as used on the commercially available EndoCapsule 10 from Olympus. A comprehensive review of localization systems for WCE is given in Ref. 157.

Magnetic fields can be utilized for capsule localization, and these techniques may be divided into two main categories. The first kind involves the use of a body-external array of sensors which measure the magnitude and directionality of the field generated by a magnet-embedded capsule.[158] The second kind operates in the reverse manner, which is by using field sensors in the capsule which measure the field generated by field generators placed outside the body.[159,160] The earliest proof-of-concept systems used SQUID technology for sensing, but nowadays the sensors are based on magnetoresistive effects or on the Hall Effect. In combination with magnetic sensors, inertial sensors have also been used in sensor-fusion strategies.[161,162] The localization algorithm generally consists of minimizing the error between a point dipole field approximation and the measurements.[163,164] Recent developments include algorithms for 6-DOF localization,[165] multiobject tracking,[166] and the use of body attached permanent magnets as field references to compensate for unpredictable patient movements.[167]

Motilis Medica SA (Switzerland) offers a commercial localization system, which employs an array of external field sensors to detect the position and orientation of a magnetic capsule. Their first nonambulatory system, the MTS-1, consists of a 4×4 array of 16 sensors placed 5 cm apart. It has shown efficacy of use in studies in healthy adults and young children.[168,169] Gastric emptying, small intestinal, and colorectal transit times can also be calculated. An improved ambulatory and wearable version of the capsular tracking system, named the MTS-2 or 3D-Transit™, was demonstrated validated in healthy patients and those with carcinoid diarrhea.[170]

Another possible nonambulatory system for capsular tracking for GITT investigation could be *Magnetic Particle Imaging* (MPI). MPI utilizes the relaxation kinetics of ferromagnetic nanoparticles exposed to a kHz frequency magnetic field, to generate a tomographic image.[29,171] While there have been no reported demonstrations of such a system, theoretically a capsule filled with a tiny volume fraction of ferromagnetic particles can be visualized by MPI while navigating down the GI tract.

2.B.7. Therapeutics

In addition to guided locomotion and power transfer, magnetic fields can be for operation of therapeutic modalities. The integration of a drug delivery mechanism into the WCE is crucial to advance disease treatment in the GI tract. There are two key requirements for such a drug delivery WCE: first, a mechanism to anchor the WCE to a fixed location, and second, a mechanism to release the drug in a controlled and dose-dependent manner.[172] A variety of capsules which use magnetic fields for anchoring and/or remote triggering to release medications in the GI tract have been reported.[173,174] Yu et al. describe a capsule that releases a drug-filled reservoir when the capsule passes close to an implanted or externally worn magnet.[174] The capsule incorporates a magnetic reed switch, which upon exposure to a threshold field, closes and discharges a capacitor through an intertwined nichrome-nylon wire. Joule heating quickly melts the wire, which in turn breaks its connection to the drug reservoir, releasing its contents. This capsular mechanism is for single use and release of the drug payload.

An interesting concept for controllable drug release utilizing the magnetocaloric effect (MCE) has been recently published and patented.[175,176,177,178] Magnetocaloric materials exhibit internal cooling or heating under the application of a magnetic field. Combining these materials with thermally sensitive drug-loaded polymers, drug delivery platforms with magnetic-field tunable drug release profiles can be developed.[176,178] Another therapeutic capsule for obesity and weight loss management was reported in Ref. 179. The authors propose the use of a magnetically triggered release of an intra-gastric balloon from the capsule to combat obesity in patients. A prototype capsule (9.6×27 mm^2) was developed and experimentally validated in *ex vivo* experiments. In the study by Quaglia et al.,[180] they used a magnetically guided capsule to study the release and adhesivity of a patchwork structure, which has potential to be used as a bioadhesive membrane.

Biopsy sampling for histology is a common diagnostic modality of conventional endoscopy. Even though several *ex vivo* demonstrations have been reported, there are currently no commercial WCEs that offer this capability. Simi et al.[181] report a magnetic field triggered biopsy capsule for tissue sampling in the small bowel. The blind capsule (9×24 mm^2) incorporates a magnetic torsion spring that can be field triggered to release a rotary blade to cut a tissue sample and store it in the capsule [Fig. 7(a)]. The magnetic capsule can in theory be easily integrated with magnetic localization systems which have been described earlier, to for location-specific tissue sampling. A very similar rotary tissue sampling capsule actuated by SMA is described in Ref. 182 [Fig. 7(b)]. Yim et al.[183] describe a multiscale biopsy capsule which can be magnetically guided and incorporates a magnetic latch, which can be opened on command to release an array of thermally foldering micro-grippers for biopsy [Fig. 7(c)]. The capsule additionally contains an adhesive patch to collect the micro-grippers after tissue sampling. A major disadvantage of this design is the low yield (3%) of micro-gripper retrieval.

Deployment of *endoclips*, a metallic device used to bind together mucosal tissue, is a common endoscopic surgical procedure to prevent and stop gastrointestinal bleeding, for closure of leaks and perforations and for anchoring stents.[184] The CRIM Lab demonstrated the magnetic manipulation of a blind capsule and deployment of an endoclip to seal a bleeding colon lesion in a live pig model.[51] The endoscopist used a passive hydraulic arm with permanent magnet tip to guide the magnet-integrated capsule to the desired target site. The capsule included an electromagnetic motor, which could be wirelessly activated, to deploy the nitinol endoclip.

2.C. Magnetic microrobotics

There is no single actuation and locomotion strategy than can be universally applied to miniaturized intracorporeal robotic systems since the body possesses a wide geometrical variety of orifices and biological lumen which are either fluid or air filled, and these pose unique challenges to active locomotion. Lumens like the blood vessels pose additional challenges as the agents have to be small enough that they can move without impeding the blood flow in any health-critical vessels, but simultaneously large enough to be visualized and controlled from the outside. Sufficient blood flow exists for swimming motion, but strong currents are a major concern. Due to the micrometer dimensions of these robots, the flow

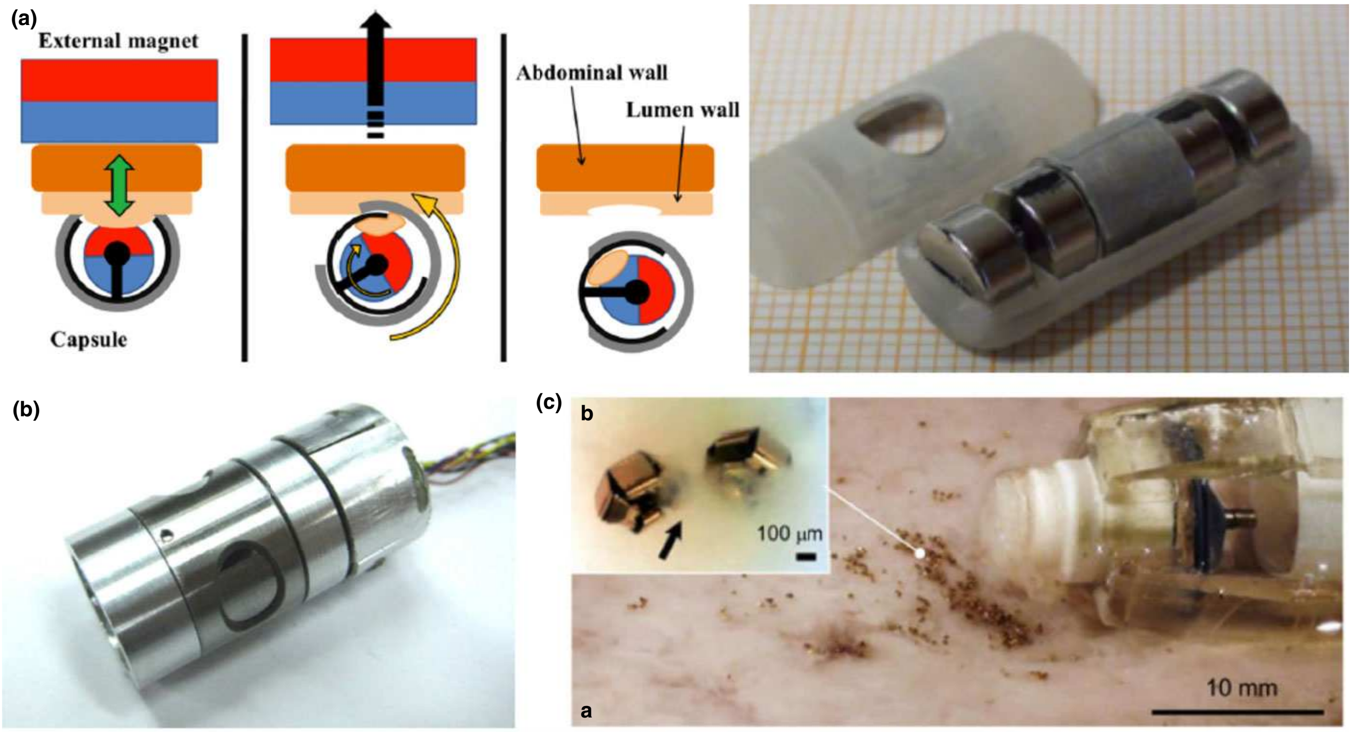

FIG. 7. Biopsy sampling capsules: (a) Mechanism of tissue retrieval developed by Simi et al.,[181] (b) Capsule with rotary blades released using shape memory alloys by Kong et al.,[182] (c) Deployment of magnetic microgrippers for biopsy sampling by Yim et al.[183] [Color figure can be viewed at wileyonlinelibrary.com]

regime is viscous dominated (low-Reynold's number), unlike the motion of millimeter-sized GI robots in the liquid-distended stomach, where inertial-forces dominant the viscous forces and propeller-based locomotion has been found to be useful.[40] Abbott et al.[185] have compared various low-Reynold's number robotic swimming strategies in their article "How should microrobots swim?" In a follow-up article, Peyer et al. reviewed bio-inspired magnetic swimming microrobots for biomedical applications.[186] In low-Reynold's number flows, rotating magnetic field-driven rigid helical propellers are more energy efficient than swimmers employing static magnetic gradient-based dragging motion.

The Multi-Scale Robotics Lab at ETH Zurich (Switzerland) has proposed several different locomotion concepts in the class of magnetic robots called microrobots, a term which refers to submillimeter-sized untethered devices. Kummer et al.[187] described an eight-coil electromagnetic system, the Octomag, which has independent control of magnetic fields and field gradients in all three spatial directions [Fig. 8(a)]. This system allows for 5-DOF manipulation and control of magnetic micro-robots and has been proposed for ophthalmologic applications. A miniaturized eight-coil system (the Nanomag) that can be integrated onto high-resolution inverted microscopes for three-dimensional manipulation of nanometer-sized magnets is presented in Ref. 188 [Fig. 8(b)]. Recently, the group showed the navigation and tracking of a swarm of magnetic helical swimmers in the peritoneal cavity of a mouse, using sub-10-mT rotating magnetic fields.[189] The swimmer was coated with a near infrared fluoropore, which allowed for its tracking in an optical imaging system. In addition, the group has reported two different surface-driven magnetic robots, the MagMite and the RodBot. The MagMite, introduced in Ref. 190, has a submillimeter dimension of ($0.3 \times 0.3 \times 0.07$ mm^3) and consists of two electroplated soft magnets connected by spring, and uses a mechanical-resonant motion for planar locomotion powered by external magnetic fields (flux density 2 mT, kHz frequencies). Speeds of 12.5 mm s^{-1} have been reported for the prototypes. Alternatively, the Rodbot is a rectangular rod-shaped device ($0.3 \times 0.06 \times 0.05$ mm^3) that can be magnetized in a transverse direction.[191] It is a surface walker, and rolls along the surface under rotating magnetic fields, and its motion creates a vertical vortex, which can be used to trap and manipulate micro-objects like protein crystals. The Rodbot can also be used to push micro-objects for remote assembly [Fig. 8(c)]. Scaled up millimeter-sized designs utilizing the magnetics-based motion strategies of the MagMite and Rodbot can be envisioned for locomotion of endoscope capsules in the lower GI tract.

The NanoRobotics Laboratory at Polytechnique Montréal (Canada) have shown the remote manipulation of magnetic bacteria (*Magnetospirillum gryphiswaldense*) using the magnetic torque generated on their internal iron-oxide magnetosome chains. The bacteria were used to push and move 3 μm diameter beads at an average velocity of 7.5 μm s^{-1}.[192] They recently used a combination of magnetic and aerotactic guidance to increase the targeting efficiency of drug-loaded bacteria to cancerous tumor sites.[193] The use of bacterial sheet powered[194] or the use of exogenous biological propulsive systems in the GI tract will be highly unlikely as the gut

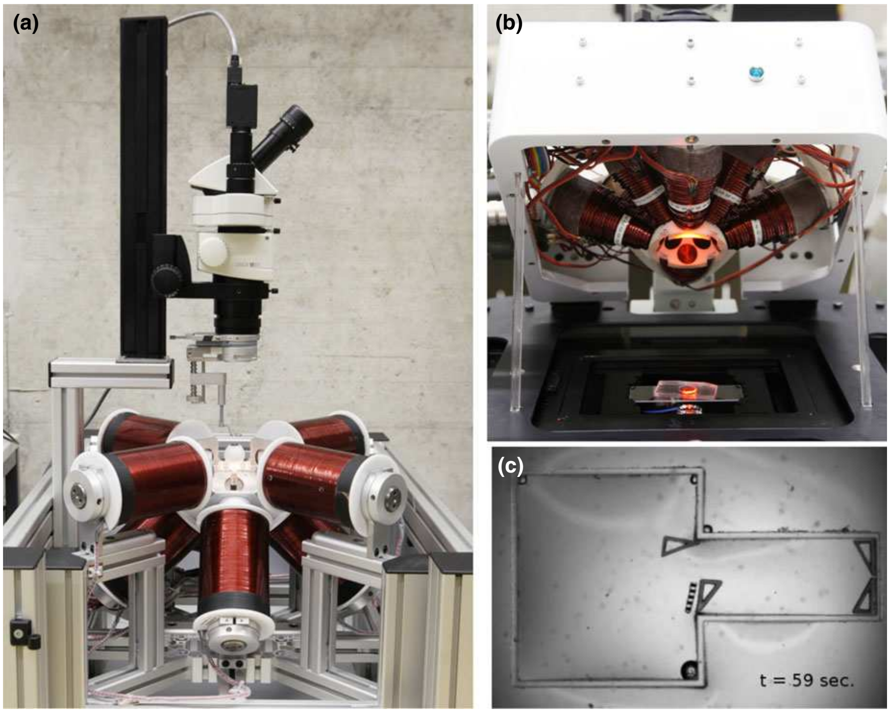

FIG. 8. (a) OctoMag with eight electromagnetic coils. (b) Nanomag electromagnet system mounted on an inverted microscope. (c) RodBot pushing and assembling triangle-shaped micro-objects. [Color figure can be viewed at wileyonlinelibrary.com]

microbiome is vital for whole-body functioning and is extremely sensitive to the presence of foreign biological agents.

In addition to remote-powered propulsion using magnetic fields, magnetic materials can be tuned to exhibit various other physical phenomena for additional on-demand functionality. One such example is the class of magnetostrictive materials that exhibit large strain, when they are exposed to magnetic fields. Micro- and nanometer-sized particles with a core-shell or bilayer structure encompassing magnetostrictive and piezoelectric layers can be used to generate electric charge on demand. Such magnetoelectric micromachines have been wirelessly navigated in fluids[195] and have been used for on-demand release of anti-human immunodeficiency virus drugs in vivo.[196] Larger magnetoelectric cantilever-based devices have also been proposed and patented as cutting and ablation tools for minimally invasive surgery.[197,198] Magnetoelectric and magnetostrictive materials are promising candidates for actuator applications in WCE.

3. CONCLUDING REMARKS AND OUTLOOK

While the use of static (up to several teslas) and slowly varying (less than 1 Hz) magnetic fields and field gradients are generally considered not to possess a health risk,[199] the use of alternating and rotating magnetic fields for imaging and localization, for wireless power transmission, for guidance and locomotion, and for operation of other capsular functions has to be within the guidelines determined for tissue exposure to electromagnetic radiation set by the International Commission on Non-Ionizing Radiation Protection (ICNIRP).[154,155] The maximum permissible amplitude and exposure time of the magnetic field application typically decrease with increasing frequency.[27]

Despite the few proof-of-concept *in vivo* trials of tethered capsules,[200,201] and *ex vivo* trials of untethered capsules, to date there has been no *in vivo* demonstration of an actively guided untethered capsule in the lower GI tract, and correspondingly, there exists no commercially or clinical usage of this technology. We can identify several reasons for this translational gap in technology. The small bowel and the colon provide a complex and variable environment, in terms of diameter, length, and coiling for active capsular navigation. Spiral-type motion or legged-crawling motion could potentially damage the sensitive intestinal epithelium. Swimming motion is not suitable for the lower GI tract, as it is not possibly to completely fill it with external liquid as performed in capsular endoscopy in the stomach.

Magnetic-guided capsule endoscopy (MGCE) has matured tremendously since the very first patent filings for a magnetically driven intracorporeal device in 1963. In the last two years, large-scale clinical trials have been published on the diagnostic efficacy of the three commercial MGCE systems.[83,92,104,202] The systems use different modalities of field generation, namely hand-held magnetic field generator (Intromedic's MiroCam-Navi system), robotic arm with field generator (Ankon Technologies), and electromagnetic coil system (MGCE from Siemens-Olympus). A high degree of visibility and capsule controllability was reported. The difficulty of capsule maneuverability and diagnosis time, both came down with increase in operational experience of the endoscopist. Magnetic capsule endoscopy for diagnosis of the gut and the colon suffer from three main issues: (a) extensive and complicated gastric preparation, (b) lack of biopsy capabilities, and (c) comparatively longer examination time compared to conventional gastroscopy or colonoscopy. The general consensus among clinicians seems to be that MGCE does not offer any particular diagnostic advantages over conventional gastroscopy of the upper GI tract.[203] The efficacy of MGCE has to be investigated for specific diagnosis of disorders.[82] Importantly, volunteers who participated in the trials have clearly indicated their preference for the MGCE procedure compared to conventional gastroscopy. We believe that the noninvasiveness and patient friendliness will drive further research and development and clinical adoption of MGCE technology.

We predict that in the near future, miniaturized modules for drug storage and controlled release, actuators for biopsy sampling, vision, lighting, and minor operations such as excision of lesions, sensors for physiological parameters, software for image processing, and lesion identification will be available as building blocks to build customizable capsules for a particular diagnosis or intervention.[204] Magnetic materials and fields will play a major role in defining several of these capsular components, like propulsion, power generation, and other internal mechanisms. The minimally invasive and patient-friendly nature of MGCE is promising, but its cost and diagnostic efficacy has to be improved for a widespread adoption by medical institutions. A collaborative research and development partnership between academia, clinicians, and industry is necessary for quicker translation of advanced capsular technology to clinical use.

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

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