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Capsule endoscopy of the future: What's on the horizon?

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Abstract

Capsule endoscopes have evolved from passively moving diagnostic devices to actively moving systems with potential therapeutic capability. In this review, we will discuss the state of the art, define the current shortcomings of capsule endoscopy, and address research areas that aim to overcome said shortcomings. Developments in capsule mobility schemes are emphasized in this text, with magnetic actuation being the most promising endeavor. Research groups are working to integrate sensor data and fuse it with robotic control to outperform today's standard invasive procedures, but in a less intrusive manner. With recent advances in areas such as mobility, drug delivery, and therapeutics, we foresee a translation of interventional capsule technology from the bench-top to the clinical setting within the next 10 years.

Key words: Capsule endoscopy; Capsule robot mobility; Diagnostic capsule; Magnetic capsule endoscopy; Therapeutic capsule

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Core tip: Capsule endoscopy is progressing from a mode of passive bowel viewing to active intervention throughout the gastrointestinal tract. This review outlines advances in capsule mobility, *in vivo* position and orientation tracking, drug delivery, and characterization of capsule-bowel interaction that may aid in device development. Recent advances in capsule actuation schemes suggest that magnetic capsule manipulation is at the forefront of endoscopic research. Integration of proprioceptive capsule sensing may enable reliable capsule control with the potential to facilitate development of interventional devices. We expect to see clinical application of these technologies in coming years.

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EXISTING TECHNOLOGIES

In recent history, the standard tool for visualizing the gastrointestinal (GI) tract has been the flexible endoscope. Unfortunately, endoscopy is invasive, cannot visualize the entire GI tract in an easy manner, and requires reprocessing. Due to invasiveness, the procedure usually requires sedation. Capsule endoscopy was introduced in 2000 and has been utilized as a less-invasive mode for screening the gastrointestinal tract^[1]. The most prevalent clinically used capsules today include the PillCam[®] SB 3 (small bowel), ESO 3 (esophageal), and COLON 2 (Medtronic Plc., Minneapolis, MN, United States - formerly Given Imaging Ltd), CapsoCam[®] SV-2 (CapsoVision Inc., CA, United States), MiroCam[®] v2 (IntroMedic Co. Ltd., Seoul, South Korea), OMOM[®] (Jinshan Science and Technology Co. Ltd., Chongqing, China), Hitron[®] (Jinan Nefisa Medical Trade Co., Ltd, Jinan, Shandong, China), and the EndoCapsule[®] (Olympus Corporation, Tokyo, Japan). Each of these capsules, with exception of the CapsoCam, contains cameras at either one or both longitudinal ends. The CapsoCam has a novel approach of a transparent shell and four radially oriented cameras around the middle of the capsule that provide the examiner with a view of the lumen at any given moment (www.capsovision.com). Typical capsule endoscopy systems include the capsule, a wearable data receiver, an image processor, and video viewing software.

Clinical capsules have also been developed for purposes besides visualization. Given Imaging Ltd's Bravo[®] and SmartPill[®] Capsule collect non-visual data from the GI tract. The Bravo[®] adheres to the esophagus by pinning suctioned tissue and remains fixed in esophagus and transmits pH data wirelessly to an external receiver. Such procedure has a duration of 48 h, but can be extended to 96 h^[2]. Similarly, the SmartPill[®] wirelessly transfers motility and pH data from throughout the digestive tract. Medimetrics (a Philips company, Netherlands) introduced IntelliCap[®] which has been developed to study drug absorption in the GI tract. The IntelliCap[®] can control quantity, rate, and location of drug release and has received the CE mark as well as DEKRA certification, but to our knowledge is not yet FDA approved^[3]. The Enterion[™] Capsule (Quotient Clinical, England) is used in assessment of drug absorption in the GI tract (<http://www.quotientclinical.com/enterion/>). The CorTemp[®] (HQ Inc., Palmetto, FL) telemetry capsule, originally developed by the Johns Hopkins Applied Physics Laboratory in collaboration

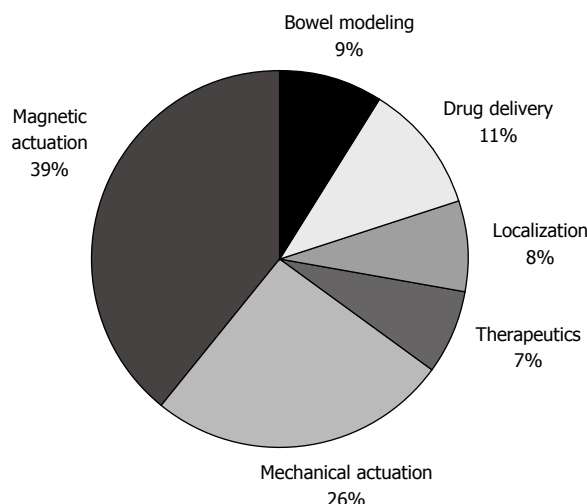


Figure 1 Topic distribution of selected capsule endoscopy publications.

with the Goddard Space Flight Center, is an FDA cleared device that monitors internal body temperature while passing through the digestive system ("CorTemp[®] Core Body Temperature Monitoring Systems" Brochure, www.spinoff.nasa.gov, www.hqinc.net). The capsule wirelessly transmits data to a recorder worn by the patient and has been shown to be a reliable source for intestinal temperature measurement^[4].

These clinically accepted technologies are less invasive than traditional flexible endoscopes, but are still subject to several limitations of which the main can be categorized as follows: (1) Capsules are restricted to passive movement through the GI tract; (2) Capsule endoscopy systems lack position and orientation tracking systems that localize a capsule with respect to both body landmarks and a tridimensional world frame; (3) Effective drug delivery capsules for localized therapy have not yet been developed that enable the transition from research to clinical use; and (4) A unified model of capsule-gut interaction has not been developed.

This review aims to present recent work to address the aforementioned limitation areas. We have selected what we believe to be the most relevant manuscripts and scientific publications from a larger pool of works. The topic distribution of the 142 selected papers is shown in Figure 1. The themes shown are recurring topics of review papers in the field and we believe these to be the most influential subfields^[5-7]. This list does not include information from company websites utilized, though some are specified throughout the text.

OVERCOMING LIMITATIONS

Addressing challenges: Then and now

Several solutions to the aforementioned limitations have been developed in the last ten years, though many of these are limited by system complexity or little possibility of gaining regulatory approval for

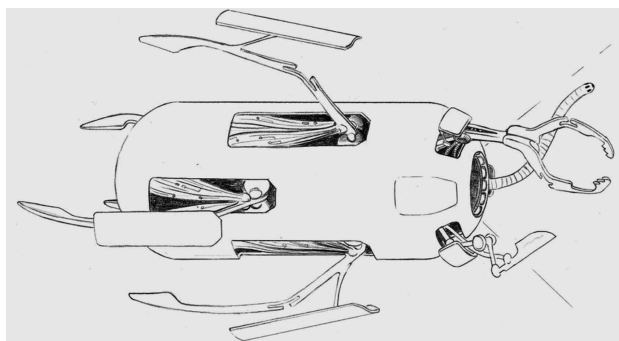


Figure 2 Artistic representation of a robotic capsule from before 2010 (Credit: Virgilio Mattoli).

translating and commercializing the research. A representation of a futuristic capsule robot from before 2010 is shown in Figure 2. This was the vision of Paolo Dario's research team at Scuola Superiore Sant'Anna and served as the ground for the Versatile Endoscopic Capsule for Gastrointestinal Tumor Recognition and Therapy (VECTOR) project. VECTOR was an integrated project funded by the European Union Commission from 2006-2011 that generated relevant momentum in robotic capsule endoscopy in the last decade. Project outcomes such as^[8-12] have resulted in successful, though mechanically complex, systems. Issues in reliability and repeatability accompany mechanical complexity that inhibits the translation of technology from research to clinical use. Magnetic driving of capsules, a more recent focus of research, does not depend on on-board mechanical components for actuation and thus requires less power storage. The extra space and power can be used for integrating interventional tools and sensing systems, or the capsules can be further miniaturized.

In the following sections, we address what we believe are the pertinent developments in capsule technology that either show great promise, or have been relevant steps in bringing technology to where it is today.

Mobilization of capsule robots

Soon after the introduction of capsule endoscopy into the marketplace, researchers began publishing work on methods for enabling active locomotion (as opposed to traditional passive locomotion enabled by physiological peristalsis). The following section discusses mechanical as well as magnetic research approaches for enabling capsule locomotion.

Mechanical actuation

The most explored methods for inducing active locomotion in capsules are crawling through lumens, inchworm-like actuation, and swimming through the stomach cavity. The study of legged capsule locomotion through the GI tract began in 2004 with Menciassi *et al.*^[13] who had a goal of achieving both tissue contact for force transmission and the ability

Table 1 Select mechanically actuated endoscopic capsules

Ref.	Year	Actuation mode	Highest testing level	Speed (cm/min)
Standard colonoscopy ^[28]	-	-	-	7
Menciassi <i>et al.</i> ^[13]	2004	Legged	<i>Ex vivo</i>	NA
Kim <i>et al.</i> ^[14]	2004	Inchworm	<i>Ex vivo</i>	1.47
Kim <i>et al.</i> ^[26]	2005	Inchworm	<i>Ex vivo</i>	13.4
Wang <i>et al.</i> ^[22]	2006	Inchworm	<i>In vitro</i>	NA
Quirini <i>et al.</i> ^[8]	2008	Legged	<i>Ex vivo</i>	3
Quirini <i>et al.</i> ^[16]	2008	Legged	<i>Ex vivo</i>	6
Valdastri <i>et al.</i> ^[10]	2009	Legged	<i>Ex vivo</i>	5
Tortora <i>et al.</i> ^[11]	2009	Swimming	<i>In vivo</i>	90
Kim <i>et al.</i> ^[17]	2010	Paddling-based	<i>In vivo</i>	17
Woo <i>et al.</i> ^[18,19]	2010	Electrical stimulus	<i>In vitro</i>	17.46
Morita <i>et al.</i> ^[32]	2010	Swimming	<i>In vivo</i>	300
Sliker <i>et al.</i> ^[20]	2012	Treads	<i>In vivo</i>	18
Lin <i>et al.</i> ^[23]	2012	Inchworm	<i>Ex vivo</i>	30
Chen <i>et al.</i> ^[24]	2013	Inchworm	<i>In vitro</i>	NA
Chen <i>et al.</i> ^[25]	2014	Inchworm	<i>Ex vivo</i>	2.3

NA: Not available.

to displace these contact points and eventually utilize this combination for both diagnostic and therapeutic purposes. Soon after the development of this field of mechanical capsule actuation, Kim *et al.*^[14] (also 2004) developed a shape memory alloy (SMA) actuated capsule robot that biomimicked micro hooks of an insect and traversed *via* an anchor-and-pull effect.

As part of the aforementioned VECTOR project, Quirini *et al.*^[15] and Valdastri *et al.*^[10] developed prototypes of 4, 8, and 12 legged capsules before 2010. The 4-leg device had a single degree of freedom (DoF) where all legs moved simultaneously and a balloon in the front was used to distend collapsed tissue. The 8-leg capsule had ability to open and close 4 legs at a time (one set in front and one set in back) which allowed for synchronizing motion and preventing back slippage while opening a single leg set^[8,16]. The 12-leg capsule developed in 2009 operated in a similar manner and was designed for generating large propulsive force while maintaining an ingestible body size^[10].

In 2010, Kim *et al.*^[17] introduced a paddling based capsule that traverses a lumen using anchored propulsion. With only one DoF of actuating legs, a linear actuator inside the capsule allows for avoidance of the back slippage problem experienced by Quirini *et al.*^[16] The capsule was able to traverse at a satisfactory rate during *in vivo* porcine trials, as seen in Table 1, though erythematous mucosal injuries were noted. In 2010 and 2011 Woo *et al.*^[18,19] conducted studies on utilizing an electrical stimulus to contract the small intestine. An electrical stimulus applied to the bowel causes contraction and inhibits capsule motion until the electrical potential is released. A 2010 study utilized this phenomenon for resisting peristalsis while the 2011 study targeted active locomotion. During the locomotion study, unexpected contractions were

observed after stimulus application. The authors warned that electric stimulation may cause damage to electrically sensitive organs, such as the liver, and may disturb natural peristalsis^[18,19].

In 2012, Sliker *et al.*^[20] developed a tethered robotic capsule endoscope to enable active locomotion within a collapsed lumen that was able to generate sufficient biopsy forces and reduce chance of capsule retention. The device was composed of a mid-section housing motors, LEDs, and a camera, that was surrounded on four sides by micro-patterned polydimethylsiloxane threads. During *in vivo* testing, the capsule traversed through bowel as well as other tissue surfaces including mesentery, abdominal wall, and liver. This group has continued work to develop a capsule traction force measurement platform for application in developing robotic capsule colonoscopies^[21].

In 2006, Wang *et al.*^[22] developed one of the first capsules to be propelled *via* both internal mechanical system and electromagnetism in the capsule body. In this preliminary study, a capsule that biomimics the motion of an inchworm was presented. In 2012, Lin *et al.*^[23] developed a 3-leg micro robot for actuation and anchoring in the intestinal lumen. This robot utilizes this anchoring to generate an inchworm like motion and is thus able to propel itself. Chen *et al.*^[24] developed a wireless inchworm type colon-traversing robot in 2013 with interventional capability that utilizes a power-transmitting coil for power supply. The robot contains air-balloon anchors that may be safer than previously developed capsule legs, and an extending mechanism to produce forward motion. The following year, this same group developed a robot on a similar principle but utilizing extending spiral legs^[25]. Other inchworm concepts include a piezo-actuated concept from 2005^[26] on which further optimization work was done in^[27].

As seen in Table 1, the works that monitored traversing speed *in vivo* include Kim *et al.*^[14] (1.47 cm/min), Quirini *et al.*^[8] (6 cm/min), Valdastrì *et al.*^[10] (5 cm/min), Kim *et al.*^[17] (17 cm/min), Woo *et al.*^[19] (17.46 cm/min), and Lin *et al.*^[23] (30 cm/min). A standard colonoscopy has duration of 21.1 min (SD, 10.4 min) where a mean total distance of approximately 140 cm must be traversed resulting in a desired velocity of approximately 7 cm/min^[28]. Not all of these devices are targeted for colonoscopy; however, this number is useful as a point of reference for comparison.

In 2008, Kósa *et al.*^[29,30] proposed a miniature swimming capsule endoscope with three tails that utilizes a magnetic resonance imaging (MRI) machine's magnetic fields for propulsion and powering. Power from induction is used to generate alternating currents in three coils on each tail. This device is in a constant magnetic field and thus the alternating currents induce tail movement. Static magnetic field is used for propulsion, while radio frequency magnetic field is used for power transmission. This work was further integrated and developed into a prototype that

generated sufficient propulsive force.

In 2009, Tortora *et al.*^[11] developed a swimming capsule robot for exploration of a fluid filled stomach. The device includes four propellers to be controlled *via* joystick. This system consists of the wirelessly controlled capsule, and triaxial joystick and was tested *in vitro*, *ex vivo*, and *in vivo* using a porcine model. The same approach for locomotion was also tested with a tridimensional inductive link to transmit a 400 mW power supply to operate the four propellers^[12]. Further work on swimming robots was continued by the group into 2014, this time adding a 3.5 mm diameter wireless camera in a capsule that was 22 mm in diameter^[31].

In 2010, Morita *et al.*^[32] developed a self-propelling swimming system. The system consisted of a PillCam (Given Imaging Ltd.) with a fin and a mounted magnetic vibratory propeller at the aft of the capsule. A user's interaction with a joystick changed magnetic field that in turn changed the capsule's velocity and orientation. This disposable device was successfully tested in a dog, clear images were recorded, and a velocity of 300 cm/min was achieved.

Mechanical actuation summary: The majority of legged locomotion work was done before 2011 and this field of research halted owing to on-board power limitations and mechanical complexity. Capsules are generally subject to a size limitation in order to be swallowable. Each mode of locomotion discussed (crawling, inch-worm, and swimming) requires mechanical actuators that take up a large portion of on-board volume that leaves limited space for energy storage, that is needed to drive the actuators. Developments in energy storage technology may resurrect this area of research. Reliability, cost of development, and design hazards such as the need for apertures in the capsule needed for legs or the interaction of legs with mucosa, are all limiting factors in translating legged locomotion technology to clinical use. Other mechanical locomotion schemes that have been developed include rolling on treads that surround a capsule robot, inchworm like capsule motion induced by anchoring mechanisms coupled with on-board linear actuation, and submarine-like motion induced by propellers for gastric diagnostics. None of these technologies has translated to clinical trials so far, and show little promise.

Resisting peristalsis

Peristalsis resistance methods for capsules are generally developed for enabling detailed diagnostic examination of a target site or for enabling therapeutic intervention. This is a subsidiary field to active capsule locomotion - if an effective locomotion method is developed, then that method may be used to inhibit capsule movement. Studied methods that are suitable for lumens include: the use of miniature legs, applying an electric stimulus to artificially induce tissue collapsing, and mucoadhesive

patches. Given Imaging's Bravo pH Monitoring System is widely used but is limited to the proximal part of the GI tract and requires manual insertion with a company-provided tool. The only aforementioned device to undergo human trials is a magnetic sheath that is worn over the abdomen to hold a gastric capsule stationary.

The ability to resist peristalsis is critical for enabling therapeutic intervention in capsule endoscopy. Though most actuation techniques may allow for anchoring, research has also been done on capsules passing through the bowel passively and anchoring only once a target area is reached. Multiple methods for anchoring have been studied, some of which are intermittent to enabling active locomotion (*e.g.*, anchoring legs), while others are developed with the sole purpose of anchoring. In 2006, Karagozler *et al.*^[33] developed a legged capsule with biomimetic micro-patterned adhesives for resisting peristalsis in the small bowel. Also in 2006, Dodou *et al.*^[34] conducted experiments on developing mucoadhesive polymers whose frictional properties may be altered reversibly *via* external stimuli for use in alternative colonoscopic devices. Water and air may be used to detach polymers from the mucosa, but environmentally sensitive polymers are needed to enable repeatability.

In 2008, Glass *et al.*^[35] developed, and tested *in vitro*, an anchoring mechanism that utilizes pulleys for the distension of 4 legs that contain high friction adhesive pads. In 2009, Tognarelli *et al.*^[36] proposed a force controlled stopping mechanism for esophageal capsule endoscopy. The device contains 3 SMA elastic flaps that distend upon wireless triggering. An aforementioned study was done by Woo *et al.*^[18] in 2010 in utilizing electrical stimulus to resist peristalsis. In 2011, this group proposed the use of mucoadhesive films for locking surgical assistive tools inside the gastric cavity. They suggest that this technique overcomes the challenges associated with magnetic coupling: exponential magnetic force relationship with distance, inability to use other magnetic devices in the area, and limitations of use in obese patients owing to larger minimum magnet-tool distance. The authors found that as with most adhesives, a greater application area results in higher detachment forces and thus an ability to hold a larger tool^[37].

A promising concept was presented in 2014 by Kim *et al.*^[38] who introduced a magnetic belt to be worn over the abdomen to restrict movement of a magnetic capsule in the stomach and allow monitoring of gastric motility. This device was tested on a human volunteer using a MiroCam (IntroMedic) capsule that was embedded with permanent magnetic disks. Once swallowed, the capsule was maneuvered to a desired location after which the magnet was fastened by a belt. Without the need for insufflation during this procedure, and owing to the small size of the capsule that does not have significant effect on gastric behavior, motility could be monitored. The magnetic

capsule motility observation was conducted along with cutaneous electroencephalography with a hope of establishing a relation between the two monitoring methods.

Resisting peristalsis summary: Peristalsis resistance methods for capsules are generally developed for enabling detailed diagnostic examination of a target site or for enabling therapeutic intervention. This is a subsidiary field to active capsule locomotion - if an effective locomotion method is developed, then that method may be used to inhibit capsule movement. Studied methods that are suitable for lumens include: the use of miniature legs, applying an electric stimulus to artificially induce tissue collapsing, and mucoadhesive patches. Given Imaging's Bravo pH Monitoring System is widely used but is limited to the proximal part of the GI tract and requires manual insertion with a company-provided tool. The only aforementioned device to undergo human trials is a magnetic sheath that is worn over the abdomen to hold a gastric capsule stationary.

Magnetic actuation

Though the mechanical actuation method of capsules in the bowel has been made possible in research settings, it is accompanied by complexity of mechanical design as well as having large space and power requirements. Implementing magnetic actuation may allow for further miniaturization of capsules by decreasing dependence on internal mechanical hardware for locomotion and minimizing on-board power needs. Researchers are faced with the challenge of developing reliable magnetic actuation techniques that are not trivial owing to the exponential decrease of magnetic coupling force with distance^[39].

Magnetic capsule actuation consists of inducing motion on a capsule with an embedded magnet. Orientation of such capsule may be governed by a uniform magnetic field generated from outside of the patient, while a magnetic field gradient in space induces relative motion. This field may be generated by permanent magnets or electromagnets. In comparing the two, electromagnets provide an additional DoF in varying the magnitude of magnetic field, though the volumetric magnetic flux density generated is lower than that of permanent magnets. Control of magnetic capsule endoscopes has evolved from mobilizing an ingested capsule *via* hand-held permanent magnet, to robotic control in both a static and rotary magnetic field manner.

Hand-held magnet actuation

Carpi *et al.*^[40] published one of the first uses of magnetics in capsule endoscopy in 2007. The group conducted bench trials, using porcine tissue, on M2A[®] capsules (Given Imaging Ltd.) that were coated in silicone elastomer with mixed in magnetic particles. The capsule was driven using a larger external magnet.

This preliminary study was a starting point for years of magnetic actuation research to come.

The first human trial on actuating magnetic capsules *via* hand-held external magnet occurred in 2010 during a study conducted by Swain *et al.*^[41] The compartment for one of the two cameras of a PillCam COLON was replaced by permanent magnets. During this trial, a capsule was moved in the esophagus and stomach and was reported by a volunteer to not cause discomfort. In a similar study by the same group, 10 healthy volunteers swallowed magnetic capsules that were manipulated externally by a hand held magnetic paddle (Given Imaging Ltd.). The authors reported that the esophageal transit time was highly variable and that magnetic forces were not strong enough to hold the capsule against peristalsis near the gastroesophageal junction^[42].

In 2010, Valdastrì *et al.*^[43] developed a method of steering an endoluminal camera mounted inside a capsule that could be manipulated to achieve viewing in a specific direction by use of both an external magnet and an internal motor coupled with a magnet. The external field was generated by a permanent magnet mounted on a passive hydraulic arm that could be manipulated by hand. This device achieved viewing steps of 1.8° and was shown to be feasible during *in vivo* porcine trials. In 2012 Lien *et al.*^[44] developed the magnetic field navigator system that enables button-controlled camera view adjustment as a capsule is actuated *via* a hand-held device. The hand-held navigator contains an embedded motor coupled with a permanent magnet for inducing capsule rotation. Early efforts of magnetic manipulation are starting to be seen in clinic: Jinshan Science and Technology Co. Ltd. (Chongqing, China) has developed the OMOM[®] Controllable Capsule System (<http://jinshangroup.gmc.globalmarket.com/products/details/omom-controllable-capsule-system-4544573.html>). Besides the capsule, image recorder, and image workstation, the system includes a hand held magnetic controller. This system is not available for use in the US.

The SupCam European project is one of the latest developments in hand assisted magnetic capsule control. For use in the colon, Tozzi *et al.*^[45] developed a spherical capsule that contains an internal core and transparent shell that rotate independent of each other so the camera view does not roll. The spherical capsule is actuated *via* a low cost external magnet that is hung from a fixture and contains a handle for easy grip. The group is anticipating testing this in *ex vivo* and *in vivo* settings.

Robotic actuation

Magnetic capsule control consists of actuating a capsule *via* magnetic gradient manipulation, while responding to sensory data. The evolution of magnetic capsule control will be described by four paradigms with progressive computer assistance: [A] - [D] where

[D] is autonomous.

[A] Hand-held magnetic capsule actuation: as described in the previous subsection, consists of a human closing the control loop by receiving sensory feedback by means of vision, and in response, generating actuating movements. This implementation involves qualitative sensory feedback and inaccuracies in actuation *i.e.*, the user has no feedback on magnetic field strength and must move the actuating magnet iteratively to achieve desired motion; [B] An evolution of such control is the use of computer-assisted actuation where magnetic field may be manipulated achieve desired capsule actuation, or a robot is utilized in moving a permanent magnet. A human is a key part of this control loop and has the responsibility of handling sensory (vision) errors and sending commands to an actuator; [C] Introducing a method of closing the control loop without direct human error handling, but rather human assistance, may further improve procedural precision. A final evolution of this control, that we will refer to as closed loop control, would consist of a robot controlled permanent magnet or computer generated magnetic field that is respondent to both sensory feedback in human vision as well as proprioceptive capsule feedback, *i.e.*, magnetic field strengths and localization. A human now directs a capsule in response to visual information, while a range of assistive control schemes such as teleoperation, shared control, or autonomous control may direct a capsule to achieve the user defined motion; and [D] A platform with image processing and aforementioned sensing may someday perform procedures in full autonomy, without a human in the control loop.

In 2009, Ciuti *et al.*^[46] published the first study on *in vivo* actuation of magnetic capsules *via* external robot. The study compared the effectiveness of an industrial robot for holding an external magnet as opposed to the magnet being held by hand. Ten total *in vivo* trials were performed (5 hand-held, 5 robotic). The authors reported an ability to locate a target during hand-held trials, though were unable to approach the target without losing it in view. Using robotic control, more targets were reached (87% ± 13% vs 37% ± 14%) and precision of movement was improved, but mean trial completion time more than doubled (201 ± 24 s vs 423 ± 48 s). The movement precision stems from the ability to adjust the magnet robotically around a particular DoF to tilt or nudge the capsule, while unstable and jerky movements may occur if holding the magnet by hand. Implementing the control scheme as described by [C] above may eliminate such procedural delays. A similar study was conducted using the Niobe magnetic navigation system (Stereotaxis, St. Louis, MO, United States). Carpi *et al.*^[47] were able to drive a modified PillCam capsule around each of the main regions of the GI tract. The group reported omnidirectional steering accuracy of 1° and tridimensional localization with 1 mm accuracy. This

localization was implemented *via* real time fluoroscopic imaging and thus requires exposing the patient to ionizing radiation.

In 2012, Arezzo *et al.*^[48] conducted a study to compare the performance of a robotically-driven magnetic capsule for colonoscopy system to standard colonoscopy. The study included 22 subjects (11 experts, 11 trainees) who were to complete a full colonoscopy on an *ex vivo* swine bowel. Of 672 target pins, 80.9% were detected by capsule procedure as compared to 85.8% by traditional colonoscopy. Detection rate was promising, but the procedure time was nearly three times longer for the capsule procedure (556 ± 188 s vs 194 ± 158 s). The authors also observed that though experts performed better in the traditional procedure, trainees using the robotic platform were able to outperform experts using traditional procedure. Implementing a control scheme as described by [C] may alleviate these procedural delays and potentially eliminate discomfort and need of sedation from the procedure, while maintaining detection rates of standard procedures.

In 2012, Keller *et al.*^[49] presented a magnetic capsule mobility human study on 53 patients and volunteers using a magnetic driving system developed by Olympus Medical Systems Corp. and Siemens Healthcare. This system operates under a control scheme as described in [B], where a human dictates desired motion *via* vision feedback and computer assisted actuation occurs by magnetic field specification. This driving system resembles an MRI machine. The group was able to implement “functions” that caused pre-specified capsule motions, such as “rotation” or “parking” that, in example, resets the capsule in the middle of the stomach to restart the examination. The authors examined which functions were most pertinent for completing a screening. Yim *et al.*^[50] (2012) developed magnet-driven capsules that are made of soft elastomer structures. Specific applications of these capsules will be discussed in the “Therapeutic Capsules” section of this manuscript.

In 2014, Sun *et al.*^[51] presented a novel capsule driving technique that utilizes two actuating magnets mounted on either lateral side of a patient with the magnetic capsule held coplanar. This set-up allows for the use of simpler, and thus less expensive, robotic arms having less DoF. In 2015, Mahoney *et al.*^[52] developed a 5 DoF capsule manipulation method, subject to aforementioned control schema [C], for the screening of a fluid-distended stomach. The group utilized an industrial 6 DoF serial manipulator with a permanent magnet mounted at the end effector for manipulating a capsule that was submerged in a water-filled translucent tank. A vision system was used to obtain 3 DoF position feedback, though this localization method is not applicable *in vivo*. Capsule control was analyzed while the robot was in singular configurations and a control scheme was developed to

maintain capsule position while momentarily sacrificing orientation control.

Spiral capsules and actuation via rotating external magnet

Magnetic capsule actuation by direct magnetic link with an external magnet may be dangerous if the distance between magnets is abruptly decreased and the coupling could potentially cause tissue perforation. The use of a rotating external magnet to induce screw-like capsule motion has been a subject of research for 13 years. In 2002, Sendoh *et al.*^[53] proposed the first work on actuating a magnetic device with embedded spiral threads for converting rotation to linear actuation and soon afterwards, applied the technique to actuate a capsule endoscope. The device consists of a capsule with an embedded permanent magnet and a spiral thread-like structure wrapped around the capsule's exterior. Applying an external rotational magnetic field causes rotation of the capsule that is converted to linear motion *via* capsule threads^[54]. This method showed potential and has been a subject of research since then^[55-60].

In 2011, Mahoney *et al.*^[60-62] proposed a mathematical model to optimize (not necessarily threaded) capsule driving by rotating magnetic field. The motivation behind this work was elimination of potentially hazardous direct magnetic pull that may be experienced by an *in vivo* magnetic device. The group demonstrated that an external magnet rotating at non constant speed according to a specific open-loop rotation trajectory may relinquish direct attractive force while directly applying a nearly constant lateral force^[61]. Later work by this group has investigated the inverse problem of determining necessary axis of rotation of an external permanent magnet to apply a force in a specified direction on the internal magnet.

Magnetic actuation summary: The evolution of magnetic capsule control may be characterized as follows: [A]: Human controlled actuation in response to human sensing; [B]: Human controlled actuation with computer assistance in response to human sensing; [C]: Human controlled actuation with computer assistance in response to computer sensing; and [D]: Computer controlled actuation in response to computer sensing: no human in the loop. The field has progressed to groups having developed control scheme [B]. The first human studies on magnetic capsule actuation were conducted using an external hand-held permanent magnet that is manipulated in response to live video feedback from the capsule. Though hand-held control is simpler to implement, studies have shown difficulty in performing fine movements, such as approaching a particular target site or rotating the capsule about a particular degree of freedom, which may be achieved by use of robotic manipulator. An MRI-like system developed by Siemens and Olympus is the only non-

manual magnetic driving device to undergo human trials. Several groups are developing robotic driving systems that involve either a rigidly mounted magnet at the robot's end effector or a rotating magnet. To achieve control schemes [C] and eventually [D], proprioceptive capsule sensing and integration with actuation modes is critical. The field may then progress to intelligent-assistive actuation. This field shows potential to transfer technology from research field to clinical use in coming years.

LOCALIZATION OF *IN VIVO* CAPSULES

Knowledge of capsule endoscope position can be considered with either a diagnostic or global respect, both of which are crucial for implementing closed-loop magnetic control. Diagnostic localization refers to monitoring capsule position with respect to anatomical landmarks, while global localization (proprioceptive sensing) refers to monitoring position and orientation in a tridimensional Cartesian frame. Fischer *et al*^[63], in 2004, were one of the first groups to develop a capsule endoscopy localization system. This algorithm was developed to be used with Given Imaging Ltd.'s M2A[®] capsule and is based on measuring the received signal strength (RSS) of a capsule's wireless transmission data *via* 8 external antennas. No extra on board hardware is needed and all implementation is incorporated into Given Imaging Ltd.'s existing video processing software (RAPID[®]).

In 2006, Hu *et al*^[64] proposed the first magnet based localization algorithm. This group used a capsule with an internal magnet and 3-axis magnetic field sensors placed outside the body to obtain the capsule's global position and, unlike Fischer's work, implementation required additional hardware.

A localization method based on microwave imaging was presented in 2013 by Chandra *et al*^[65]. The group utilized electric properties of tissue as well as tissue positions to aid in resolving the device's position. Preliminary testing resulted in errors of 1 cm or less and the algorithm is currently limited to 2D application. In 2012, Salerno *et al*^[66] proposed a novel concept of using magnetic field sensors inside a capsule for localization. Using a pre-computed magnetic field model along with the sensor readings, the group reported position errors of 14 mm, 11 mm, and 19 mm in the X, Y, Z coordinate directions.

In 2013, Yim and Sitti^[67] proposed a magnetic localization method that provides 2.0-3.7 mm in 3D position error. The authors developed the magnetically actuated soft capsule endoscope (MASCE) that uses magnet-induced rolling to move through the stomach and is the device on which the localization study is based. The localization system is based on capsule deformation as the external magnet nears the body.

Miller *et al*^[68] (2012) developed a method for measuring the magnetic field produced by an external magnet at the center-point of an internal magnet

embedded in a capsule, without interference of the internal magnet. Knowledge of such magnetic field state allows for manipulating the external field in a controlled manner to achieve a control schema as described by [C] above. Popek *et al*^[69] (2013) proposed a non-iterative localization method that utilizes a rotating magnetic dipole and was shown to produce sufficiently small errors when generating 6 DoF localization data. This method is limited by need of a 30 s post-processing period.

In need of a position and orientation detection method of capsule in presence of a magnetic field, Di Natali *et al*^[70] developed a localization algorithm that employs sensor readings and pre-defined magnetic field maps. This algorithm provides 6 DoF localization data where errors are below 5 mm in position and below 19° in orientation, and allows for real time application during capsule actuation *via* external permanent magnet. To account for magnetic dipole assumption inaccuracies, this group improved this algorithm the following year by utilizing the Jacobian of the magnetic field in relation to capsule pose. This iterative algorithm, operating at faster than 100 Hz, resulted in errors below 7 mm. The authors reported that experimental results suggest that the methodology was effective and reliable at realistic clinical capsule movement speeds^[71].

Capsule localization summary: Capsule position and orientation may be described with respect to landmarks in the GI tract (diagnostic) or by a coordinate position in space (global). Diagnostic and global localization systems that provide both the position and orientation of a capsule endoscopy are vital for magnetic actuation. Current capsule endoscopy systems used clinically rely on RSS measurements on video data that is transmitted, which does not communicate the capsule's orientation. Several research groups are actively investigating global localization methods, though no *in vivo* human trials have been performed.

THERAPEUTICS

Currently available capsule endoscopes are still inferior to traditional endoscopes owing to both passive actuation and inability to conduct biopsies or therapeutic intervention^[5]. Implementing modes of tissue intervention is necessary for moving capsule technology forward. The first biopsy capsule was developed in 1957 by William H. Crosby and Heinz W. Krugler. The Intestinal Biopsy Capsule operated by sucking in mucosa and then releasing a spring-actuated rotary knife^[72]. This work has provided motivation for many of the following devices.

A biopsy module to be used in a capsule endoscopy was developed in 2005 by Kong *et al*^[73]. This device operates similarly to Crosby and Krugler's capsule, *via* torsion spring and rotational tissue-cutting razor. This device was successful in capturing intestinal mucosa of

a cow and rabbit. In 2008, Valdastrì *et al.*^[74] developed an interventional surgical clip capsule for use in both capsule endoscopy and natural orifice transluminal endoscopic surgery (NOTES). The capsule was tested *in vivo* via porcine model and steered to the target lesion site via external magnetic arm and successful surgical clipping was observed. Again inspired by the design of the Crosby and Krugler capsule, Simi *et al.*^[75] (2010) developed a magneto-mechanical elastic torsion spring biopsy mechanism that was driven via external magnetic field. *Ex vivo* trials were performed using excised porcine intestine where the capsule was actuated via hand held magnet from the outside of the intestine. Authors reported that external permanent magnet driving provided stabilization, anchoring, and sufficient torque to acquire biopsies and further *in vivo* testing is needed. Ryou *et al.*^[76] (2011) introduced the self-assembling magnets for endoscopy (SAMSEN) platform for creating a gastric anastomosis to be used in gastrojejunostomy. This device that relies on assembly via laparoscopic graspers provides a simple method for mating tissue walls and has been tested in porcine and human cadaver trials. The same group (Kong *et al.*^[77]) that developed the biopsy module in 2005 went on to develop a robotic biopsy device for capsule endoscopes in 2012. This device consists of three modules: a tissue monitoring module, an anchor module, and a biopsy module *in vitro* testing of this device was successful.

Therapeutics summary: Interventional technology in capsule endoscopy is heavily dependent on development of active locomotion systems for capsules. Nearly all research areas involving therapeutic capsules also involves active locomotion. The rapid development of actuation techniques suggests that applications for therapeutic systems in the capsule will be necessary. This is relevant research, though it has not yet been applied in human trials.

DRUG DELIVERY

Drug delivery capsules have been a prevalent field of study in recent years owing to applications in both treating GI tract diseases and drug absorption studies^[78]. Targeting drug delivery sites in the GI tract may maximize local drug concentration while avoiding drug effects in unwanted areas^[79].

In 2008, Hongying *et al.*^[80] developed a site-specific delivery capsule that utilizes a heating array, elastomeric bellows, and piston to release a drug. The main limitation of this device was a small drug reservoir volume that was limited by large size of internal electrical and mechanical components. Animal trials as well as a study on 12 healthy volunteers suggested this device to be reliable. That same year, Cui *et al.*^[81] developed a microelectromechanical systems (MEMS) microcapsule for real-time drug release and for GI fluid sampling. The hermetic, non-

digestible, and wirelessly controlled capsule was deemed reliable following *in vivo* trials.

In 2009, Groening *et al.*^[82] developed a wirelessly controlled capsule that utilized hydrogen gas production induced by current to activate a piston that dispensed a drug. Preliminary testing of this device was successful and authors stated hopes of making such device biodegradable. Later that year, Pi *et al.*^[83,84] introduced a remote controlled capsule that is actuated wirelessly and utilizes combustion for drug release. The telemetry signal ignites microthrusters that actuate a piston and release the drug. Though the device was tested *in vivo* on beagles, serious safety concerns exist and authors recommend precise calculation of propellant dosage.

Yim and Sitti^[50] (2011) developed a compliant magnetic capsule to be used for drug delivery in the stomach. The device is actuated via magnet induced rolling. The drug release feature is actuated by an external magnet being moved closer to the capsule. Series of devices like this have been developed by this group with focus on the device's shape manipulation, capsule localization, multimodal drug release, and carrying microgrippers for biopsy^[67,85-87]. In that same year, Antipina *et al.*^[88] described possibilities of utilizing physical influences such as magnetic field, ultrasound or light for drug delivery. Laser light illumination on microcapsules can be utilized to open nanomembrane channels for releasing capsule content. Magnetic field can be utilized to both locomote capsules as well as trigger a drug release mechanism. Pirmoradi *et al.*^[89] (2011) introduced a magnetically controlled MEMS device that utilizes an external magnetic field to deform an internal membrane that increases reservoir pressure that triggers drug release.

Dietzel *et al.*^[90] (2012) developed the Magnetic Active Agent Release System (MAARS) for drug delivery that is triggered via magnetic field rather than potentially harmful media such as heating elements or radiation. Magnetic flux forces metallic components of the capsule together and once demagnetized, a compartment is opened and the drug is released. Human trials on 13 healthy volunteers to release a solid drug (acetylsalicylic acid) showed that the technology is safe and the device is well tolerated. In 2013, Woods *et al.*^[91] developed a capsule that housed a rotatable drug injection needle while having capability to anchor in the intestine via mechanical extensions. With video feedback, the operator can approximate a target site for injecting the drug. Preliminary testing has shown this device to be feasible.

To prevent drugs from passing through and being inadvertently affected by bacteria and pH variance throughout the GI tract, Traverso *et al.*^[92] (2014) developed a microneedle capsule that delivers a drug to a mucosal target site. The capsule contains microneedles enclosed by pH-responsive coating that dissolves upon reaching target site. Once the coating dissolves, a drug reservoir is compressed by

peristalsis, which, in turn, releases the drug. *In vivo* studies were conducted successfully and the group intends to investigate the possibility of fabricating the microneedles from biocompatible polymers that can become lodged in the mucosa and slowly release a drug.

Medimetrics Personalized Drug Delivery Inc., a Phillips associated company, has introduced a drug delivery capsule for clinical use. Proclaiming itself as the pioneer and global leader in electronic oral drug delivery, Medimetrics developed the IntelliCap[®] telemetry capsule. The IntelliCap[®] (CE Mark, Medimetrics) is an intelligent oral drug delivery system that contains a microprocessor, employs real-time wireless communication, and contains pH and temperature sensors (www.medimetrics.com). This device has the ability to communicate its approximate location to a physician wirelessly *via* diagnostic localization by tracking variability of pH values^[93]. The Enterion[™] capsule (Quotient Clinical, England) is targeted towards assessing drug absorption in the GI tract and can deliver both liquids and solids. This device underwent 120 clinical studies (4000 capsules) in the United Kingdom (<http://www.ddmag.com/news/2012/05/quotient-receives-enterion-approval>).

Drug delivery summary: A breadth of drug delivery concepts has been developed and human trials were conducted on a piston-based drug release system as well as the MAARS system that utilizes a simple-magnetically driven design and was developed for conducting new drug absorption studies. The IntelliCap (Medimetrics) and Enterion capsules have undergone clinical trials and the former has received the CE mark. Drug delivery via capsules continues to be a thriving area of development and we expect further clinical applications in coming years.

QUANTIFYING DESIGN PARAMETERS FOR ROBOTIC CAPSULE ENDOSCOPES

Robotic capsules for active locomotion or resisting peristalsis may be designed without awareness of the bowel's tribological properties, though this may result in inefficient or inadequate systems. Quantification of mechanical response of the bowel to assist with developing endoscopic devices is pertinent to effective capsule design and has been an area of research since 2000^[94]. Though groups have studied forces exerted by traditional endoscopes^[95], we focus on the mucosal forces relevant to the design of capsule robots. In 2007, Kim *et al*^[96] developed an analytical frictional resistance model for the development of capsule endoscopes to be used in the small intestine, where the main forces applied to the capsule are frictional force owing to capsule weight, stress due to tissue deformation, and peristaltic contractions of the mucosa and the capsule was modelled as a pressure

vessel with induced hoop stress. Results suggest that the frontal shape of the robot was a major contributor in the frictional resistance. Resistive properties of the small bowel were studied in 2010 by Wang *et al*^[97] and the group concluded that the capsule's size and moving speed affect the amount of resistive (traction) force experienced. This traction force may be as high as 8 times the magnitude of a capsule's weight^[98]. To minimize the friction between GI tissue and the surface of a capsule that causes this traction, Ciuti *et al*^[98] (2011) developed a vibratory magnetic capsule with a wireless on-board inertial sensor and reported traction force reduction of up to 30% during implementation.

In 2011, Terry *et al*^[99] quantified the radial (contact) component of peristaltic forces generated by the contractions (migrating motor complex) of the mutually orthogonal circular and longitudinal bowel lumen muscle layers. Previous groups have focused on robot-specific modeling and force quantification and thus the purpose of this work was to develop a unanimous characterization of the bowel to assist in general capsule robot development. The group developed a migrating motor complex force sensor (MFS), a biaxial stress/strain apparatus, an *in vitro* mucous adhesivity protocol, as well as an *in vivo* tribometer. This work experimentally confirmed the previously developed theoretical force values by Miftahof *et al*^[100]. Further *in vivo* studies using the MFS were conducted in^[101].

In 2013, Ze Wang *et al*^[102] developed a frictional resistance determination model for a capsule under radial compression and, as opposed to Kim *et al*^[96] (2007), considered the friction force owing to peristalsis, modeled as a sine wave. Authors report that modeling peristaltic force allows for better observation of influence of capsule radius, length, speed, and contact angle with the mucosa. Zhang *et al*^[103] (2014) developed a capsule resistance force quantification model that where the static and kinetic friction coefficients are analyzed as a stick-slip phenomenon. The group conducted *in vitro* trials and concluded that the model sufficiently predicted experimental results. A further work quantifying force resistance in magnetically rotating capsules can be seen in^[104].

In 2014, Natali *et al*^[105] developed a system to enable tracking of the resistive force experienced by an untethered capsule. The system consists of a wireless capsule with embedded permanent magnet that is manipulated by an external magnetic field.

Force quantification summary: Characterization of tissue tribology and the mechanical interaction with capsule endoscopes is a relevant field of study that has produced models to assist with device design. Past works have shown that the most relevant parameters that affect resistive force in the bowel are the frontal shape and traversing speed of the capsule. Groups have implemented mechanical systems to reduce

resistive force, though none of these systems have yet been applied clinically. Work has been done to mechanically characterize theoretical models of capsule-tissue interaction, though no unified model exists that may be applied for any lumen traversing capsule.

THE HORIZON: FIVE-YEAR OUTLOOK

We have now seen the evolution of capsule technology from a primitive biopsy capsule in the 1950s, to wireless video capsule endoscopes (2000), to robotic capsule endoscopes (mid-to-late 2000's). Currently, the majority of work has been in developing active mobility schemes. In this review, we discussed relevant capsule methods for resisting peristalsis, actuation, drug delivery, therapeutics, and bowel modeling. One of the main ubiquitous challenges has been energy storage on board these devices. Owing to the ability to transfer mechanical force through a physical barrier, magnetics have applications in mobility, therapeutics, study of motility, and bowel force quantification. Development of electronic ingestible devices has also expanded from academic laboratories to corporations. The market for "smart pills" is expected to grow to \$1 billion by 2017^[106]. Studies are being conducted on observing autofluorescence emission from tissue by use of a capsule. This method may be used for detecting diseased tissue without the use of on-board cameras^[107].

A crucial evolution in capsule mobility has been the shift from mechanical actuation techniques, such as legs, to magnetic manipulation which does not consume internal capsule power and does not require internal components for mechanical actuation. Robotic magnetic manipulation seems to have improved precision and reliability when compared to hand-held magnet actuation; however, currently at a cost of longer procedure time^[46]. Capsule actuation schemes range from user dependency in both sensing and direct actuation to fully autonomous robotic control. The near-future direction of the field is to utilize proprioceptive capsule data to assist the user in driving capsules in an intuitive manner. Clinical applications of such technologies seem feasible within the next 10 years.

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