Techniques and Innovations in Gastrointestinal Endoscopy 2023; 67–81

Current Engineering Developments for Robotic Systems in Flexible Endoscopy

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Abstract

The past four decades have seen an increase in the incidence of early-onset gastrointestinal cancer. Because early-stage cancer detection is vital to reduce mortality rate, mass screening colonoscopy provides the most effective prevention strategy. However, conventional endoscopy is a painful and technically challenging procedure that requires sedation and experienced endoscopists to be performed. To overcome the current limitations, technological innovation is needed in colonoscopy. In recent years, researchers worldwide have worked to enhance the diagnostic and therapeutic capabilities of endoscopes. The new frontier of endoscopic interventions is represented by robotic flexible endoscopy. Among all options, self-propelling soft endoscopes are particularly promising thanks to their dexterity and adaptability to the curvilinear gastrointestinal anatomy. For these devices to replace the standard endoscopes, integration with embedded sensors and advanced surgical navigation technologies must be investigated. In this review, the progress in robotic endoscopy was divided into the fundamental areas of design, sensing, and imaging. The article offers an overview of the most promising advancements on these three topics since 2018. Continuum endoscopes, capsule endoscopes, and add-on endoscopic devices were included, with a focus on fluid-driven, tendon-driven, and magnetic actuation. Sensing methods employed for the shape and force estimation of flexible endoscopes were classified into model- and sensor-based approaches. Finally, some key contributions in molecular imaging technologies, artificial neural networks, and software algorithms are described. Open challenges are discussed to outline a path toward clinical practice for the next generation of endoscopic devices.

Keywords: Flexible endoscopy; Endoscopic imaging; Robotic locomotion; Shape sensing.

Introduction

Statistics regarding gastrointestinal cancer, and particularly colorectal cancer, indicate an increase in cancer incidence among people aged below 50 over the past four decades.[1] In the United States, the number of early-onset cancer cases is approximately 10.5% of the total new cases.[2] Many factors could contribute to this unprecedented rise, such as dietary habits, molecular and genetic profiles, and sedentary lifestyle.[3] Apart from primary prevention strategies such as gene sequencing, regular screening endoscopy of the asymptomatic population can be effective.[4] The benefit of performing endoscopy has been shown by observing a drop in the mortality rate of colorectal cancer from 2015 to 2019.[5] Enhanced therapeutic endoscopy has also contributed to this result. Almost all gastrointestinal diseases originate from the mucosa, the superficial layer of the intestine. For this reason, screening endoscopy is essential, as it can detect cancerous neoplasms at their early stage, when it is still possible to treat them locally. A novel powerful treatment is endoscopic submucosal dissection (ESD), a surgical technique that allows for en-bloc resection of early gastrointestinal tumors. ESD can be executed with standard endoscopes, but it is a technically challenging procedure that requires experienced endoscopists. Other complex therapeutic procedures performed by endoscopic technologies are per-oral endoscopic myotomy, endoscopic pneumatic dilatation, and per-rectal endoscopic myotomy.[6]

As a result of its proven effectiveness and a potential shift in the recommended age for screening,[7] a high clinical demand toward endoscopy operations is expected. However, the lack of skilled health care professionals and the invasiveness and duration of the procedure (that can last more than 40 minutes) limit the use of standard endoscopy.[8,9] Clinicians require long training to master the endoscopy technique, and the procedure's outcome

Abbreviations used in this paper: ESD, endoscopic submucosal dissection; FDA, Food and Drug Administration; MIS, minimally invasive surgery.

Most current article

2590-0307

https://doi.org/10.1016/j.tige.2022.11.006

What You Need to Know

Background

An increase in early-onset gastrointestinal cancer incidence has given rise to a high clinical demand for colonoscopy and endoscopy operations. However, the current limitations of conventional endoscopes necessitate the development of new robotic endoscopy platforms.

Findings

Recent research-level studies in flexible endoscopy are classified into design, sensing, and surgical imaging. To reach the market, several open challenges remain that must be addressed through collaboration between engineers and clinicians.

Implications for Patient Care

Current technological advancements in flexible robotic endoscopy enhance the accuracy of operations and reduce patient discomfort by reducing the invasiveness and duration of endoscopic procedures.

highly depends on their experience. Moreover, they can suffer injuries and high levels of stress due to the excessive workload and lack of ergonomic solutions.[8] Patients often refuse to undergo endoscopy to avoid physical and psychological stress. The application of force to the colon wall can create loops in the intestine, stretching the mesentery and thus causing pain and patient discomfort. In younger patients, pain can be severe, especially in women, as the colon folds around the uterus and the mesentery is more likely to be stretched.[10] Sedation or anesthesia is required to diminish pain, but it can increase the risk of complications,[11] extend hospitalization, and raise the overall costs of the procedure.[12] Abdominal pain after colonoscopy is not rare and can be reduced by avoiding endoscope looping and minimizing air insufflation. The incidence of serious adverse events such as colonic perforation during colonoscopy is very low (~ 0.1%). However, because endoscopy has assumed a more therapeutic role in the treatment of colon diseases, in complex endoluminal procedures such as ESD, the rate of perforation has increased.[13]

The current limitations of conventional endoscopes necessitate the development of new robotic endoscopy platforms. These systems address a series of open challenges in endoscopy by providing more stable and comprehensive visualization, shortening the learning curve for trainees, and improving instrument manipulation.[14,15] In particular, robotic endoscopy enables enhanced triangulation in many ways, such as extending the workspace of the therapeutic instruments, developing collision detection algorithms,[16–18] and reducing surgeons' hand tremors.[19] The incidence rate of looping, as one of the commonly occurring problems in endoscopy, can be minimized if the endoscope is being steered rather than being pushed forcibly.[17] Using telemanipulation technologies for endoscopy is another opportunity offered by robotic endoscopy, which facilitates performing procedures from a remote workstation and has attracted increasing attention from the research community.[20,21] Current trends toward robotic endoscopy are primarily focused on flexible and soft robotic technologies. Soft endoscopes can offer safer navigation through the curvilinear shape of the gastrointestinal tract.[16] In addition, promising locomotion strategies available in soft robotics have the potential to reduce endoscopy procedure time. As a result, a faster procedure, perceived as less painful, could persuade a greater proportion of the eligible population to perform endoscopy regularly. Robotic endoscopy platforms have already been tested in clinical trials and have exhibited promising results in terms of operating time. The mean time for performing ESD using the EndoMaster robotic system was 18.6 minutes.[22] Using Endo-Ease in a study, surgeons succeeded in conducting colonoscopy in 22 patients with redundant colons, with a median time of 14.2 minutes and a high cecal intubation rate.[23] One of the advantages of robotic endoscopy over standard endoscopy is obtaining improved sensory data of the current pose and state of the endoscope. In a study conducted using ScopeGuide, it was shown that providing a shape reconstruction of the colonoscope can remarkably reduce the operation time for cecal intubation.[24]

This review underlines the current engineering developments in flexible robotic endoscopy, with an emphasis on research-level studies regarding gastrointestinal endoscopy. Further improvements and clinical considerations are required to enable ongoing projects to reach the market and enter clinical practice. Technological achievements are categorized into design, sensing, and imaging. Despite major progress achieved in the field over the last decade, several technical challenges have remained. In this work, we aimed to identify the gap in the state of the art and highlight potential research opportunities.

To perform a systematic review of the current literature in the field, a keyword search was conducted on the Scopus database using the key terms in flexible robotic endoscopy. To represent the most current studies, references from 2018 onward were included in this review. It should be noted that Food and Drug Administration (FDA)-approved and Certification European (CE)-marked diagnostic endoscopes such as Invendoscope, Endotics, and Neoguide are not incorporated in this review. Similarly, technical details on therapeutic endoscopes such as EndoMASTER, STRAS, K-FLEX, and CYCLOPS can be found in previously published papers.[16,25–27] Furthermore, the review incorporates capsule endoscopes in addition to conventional continuum endoscopes because the technologies developed for each class are potentially transferable to the other.

Design

The main design requirements that a robotic endoscope should satisfy include: (1) safety; (2) deformability to adapt to the constrained space of the colon; (3) the ability to apply enough force to perform therapeutic tasks; (4) a designated space for the insertion of a camera, light source, waterjet, air insufflation, and surgical tools; (5) an effective locomotion strategy that allows the procedure to be performed in a short time; (6) variable stiffness; (7) a low-cost standardized manufacturing technique; and (8) the possibility to be disposable, to avoid sterilization and the risk of infectious disease transmission. Considering all these functionalities constitutes a real challenge. In this section, we highlight the most recent developments in flexible robotic endoscopy in terms of design, manufacturing techniques, and actuation strategies. The robots are classified into three main categories of continuum endoscopes, capsule endoscopes, and add-on endoscopic devices.

Continuum Endoscopes

Pneumatic soft continuum actuators represent the majority of soft robotic devices designed for minimally invasive surgery (MIS) and endoscopy[28] thanks to their dexterity and manipulability in tortuous environments. Since the first prototype proposed by Suzumori,[29] numerous soft pneumatic actuators have been studied with the same design principle: multi-degrees-of-freedom (DOF) systems with 3 channels and a hollow central operating space to locate the camera and surgical instruments. The STIFF-FLOP manipulator represented a milestone in this research area due to its modular structure and for being the first soft continuum robot in MIS. Recently, the first origami-based soft robotic actuator was introduced for upper gastrointestinal endoscopic applications.[30] The origami-inspired corrugated pattern improves the bending capability of the actuator at low pressures. Most soft pneumatic actuators are made of Ecoflex silicone or Dragon Skin rubber materials and are manufactured using silicone injection molding techniques. In a study focusing on the influence of material stiffness on the mechanical behavior of a 2 DOF soft actuator for endoscopy, Decroly et al proposed a vacuum centrifugal overmolding method that employs centrifugal force to let the silicone flow through the mold from the bottom, followed by a fiber reinforcement step.[31] To achieve commercialization, manufacturing standardization and miniaturization are key challenges yet to be tackled. Different locomotion strategies have been explored, taking inspiration from nature, such as worm-inspired and snake-like robots. A recent example of bioinspired inchworm locomotion is a soft pneumatic inchworm double balloon robot for colonoscopy.[32] Despite the low friction between the endoscope and the slippery mucosa of the intestine, this design provides a stable anchorage by means of two inflatable Ecoflex balloons connected by a 3 DOF soft pneumatic actuator (Figure 1).

A desirable feature of endoscopic tools is variable stiffness to facilitate navigation and apply force during surgical manipulation. Variable stiffness can be achieved through material-based or structural-based stiffening approaches.[33,34] A variable stiffness endoscopic manipulator, which is activated by hot and cold water, has been proposed.[34] The system employs a biocompatible thermoplastic called FORMcard, the stiffness of which is adjustable with temperature.

Alternative solutions to fluidic actuation are tendon-driven and magnetic actuation systems. A novel tendon arrangement was presented in a tendon-driven snake-like endoscope for ESD.[35] The endoscope consists of a passive flexible body and an active snake-like robot with a 7 DOF continuum joint design actuated by the tendons, which are distributed on the outer wall of the joints, increasing the operating area of the central channel. As an example of a magnetically actuated endoscope, a soft-tethered colonoscope actuated by an electromagnet array was shown to achieve active locomotion and orientation in a colon phantom.[36] A soft tether provides a power supply for all the colonoscope functionalities, including illumination, high-quality imaging visualization, irrigation, and insufflation, as well as a safety mechanism to remove the scope in case of malfunction.

Capsule Endoscopes

Non-tethered pill-sized capsule endoscopes are a popular noninvasive diagnostic method for the inspection of lesions and early-stage cancer in the upper and lower gastrointestinal tract. Wireless capsules with integrated cameras are introduced through natural orifices and moved forward by the automatic wave-like contractions of the muscles of the intestine, minimizing pain and improving patient tolerance. However, the impossibility to control the motion of passive capsules leads to an inefficient outcome of the screening procedure, as well as introducing a risk of intestinal obstruction. Therefore, research efforts are pushing toward remotely controllable capsule endoscopes. To address this open challenge, Ge et al presented a capsule robot with an origami inspired design,[37] capable of exploiting the intestinal peristalsis to drive both forward and backward (Figure 2). When squeezed by the colon contraction, the origami structure can deform, assuming two different configurations (folded and unfolded), which enable progressive and retrograde motion. In spite of the promising experimental results, the device still lacks an integrated control system to guide the capsule movement. At present, the most successful solution to provide active locomotion for capsule robots is using an external magnetic field. Such magnetically guided capsule endoscopes have recently been introduced in clinical practice for the diagnosis of small bowel diseases. To improve diagnostic accuracy, a recent study presented a magnetically actuated capsule robot with the enhanced ability to take biopsy samples of submucosal tumors.[38] The capsule robot has an internal permanent magnet that allows for both localization and control of three different motions: orientation control/rolling locomotion, tumor anchoring, and collapsing motion for needle penetration. The system is fabricated using 3D printing and polymer molding techniques, and it has been

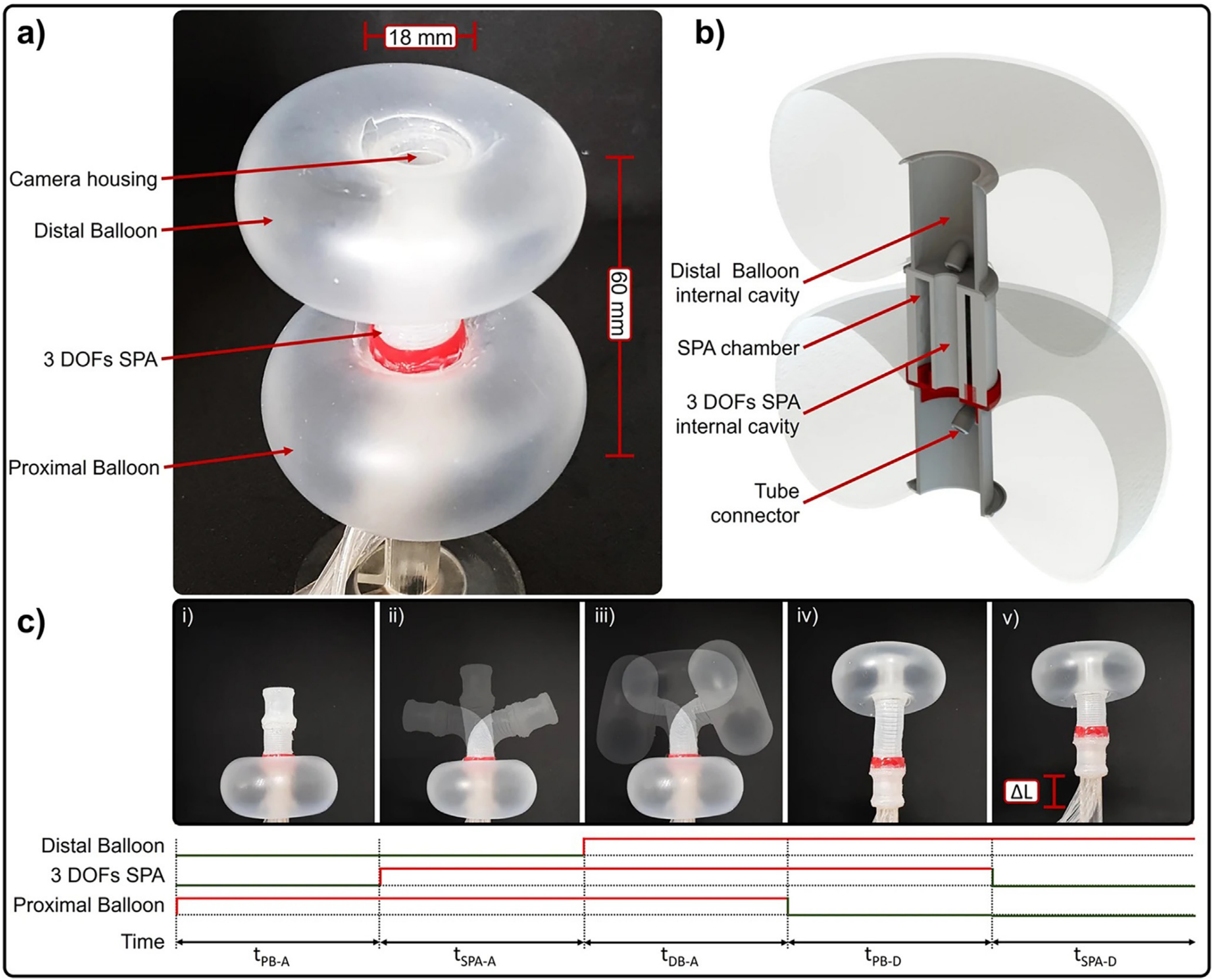

Figure 1. Example of soft pneumatic actuator (SPA): Soft pneumatic inchworm double balloon (SPID) for colonoscopy.[32] (a) Design of the SPID showing the SPA and the proximal and distal balloon inflated. (b) Cross-sectional view of the SPID design. (c) Steps of the inchworm locomotion: (i) tPB−A is the activation time of the proximal balloon, (ii) tSPA−A is the activation time of the SPA, (iii) tDB−A is the activation time of the distal balloon, (iv) tPB−D is the deactivation time of the proximal balloon, (v) tSPA−D is the deactivation time of the SPA. Reproduced under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

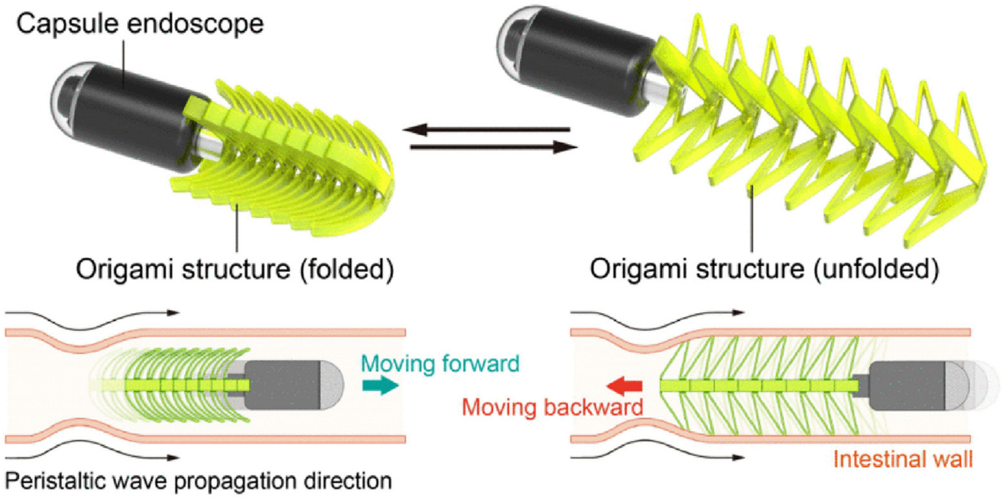

Figure 2. Example of capsule endoscope: origami-inspired design for capsule endoscope to retrograde using intestinal peristalsis.[37] Reproduced with permission from IEEE Robotics and Automation Letters.

tested on a porcine stomach with simulated tumors, demonstrating the feasibility of the capsule endoscope as a platform for both diagnosis and needle biopsy.

Add-on Endoscopic Devices

An additional class of devices that extends the capabilities of commercial flexible endoscopes is external endoscopic accessories. To improve safety and facilitate navigation during colonoscopy, a disposable soft robotic sleeve was developed by McCandless et al.[39] This add-on device is produced flat through a low-cost molding fabrication procedure, and it can be wrapped around the standard colonoscope (Figure 3). It has embedded soft optical sensors and soft actuators, which can detect and redistribute the contact force between the scope and the colonic wall. This system has the advantage of not interrupting the conventional workflow of the endoscopic procedure while reducing the risk of perforation. However, it does not address the challenge of autonomous navigation in colonoscopy because it still requires experienced endoscopists to push the scope through the colon.

Another example of a robotic device created to enhance the performance of flexible endoscopes is a deployable robot made of thermoplastic sheet material for ESD surgery.[40] During navigation, the robot is folded around the scope and then inflated once the target site has been reached, enabling the use of two cable-driven surgical instruments controlled through the platform CYCLOPS. The structure of the deployable robot is a hollow hexagonal prism, designed using a programmatic approach and produced with a rapid laser welding technique, which makes it easy to fabricate and customizable. The device was validated in a preclinical study by performing the three main steps of ESD (marking the target cancerous tissue, injecting saline solution into the submucosa, and removing the tissue in one piece) on an ex-vivo chicken breast sample, and it has been shown to exert forces similar to those of laparoscopic instruments that are manually controlled.

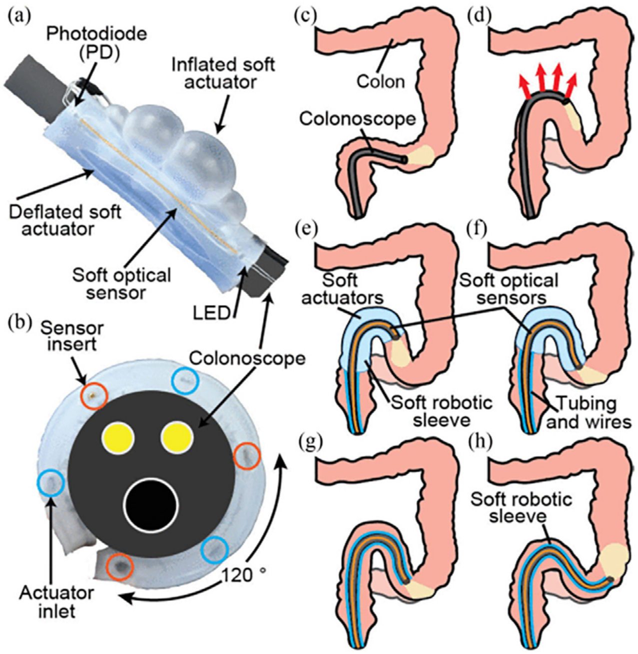

Figure 3. Example of add-on endoscopic device: a soft robotic sleeve for colonoscopy.[39] (a)-(b) Perspective and cross-sectional view showing the design of the soft robotic sleeve, equipped with soft sensors and actuators. (c) Ideal scenario with the endoscope navigating the colon and adapting to its tortuous anatomy. (d) Current limitation: The endoscope applies excessive forces to the colonic wall. (e)-(h) Working mechanism of the soft robotic sleeve wrapped around the scope: The soft optical sensors sense the forces applied to the colon, whereas the soft actuators are activated to redistribute the forces and to improve the navigation. Reproduced with permission from IEEE Robotics and Automation Letters.

Sensing in Current Flexible Endoscopes

Having an awareness of the states of a robotic system and the ability to control them is vital for enhancing the performance of the system. In particular, sensing the states of flexible endoscopes such as shape estimation and distal tip localization is crucial. Accurate sensing and control can reduce safety concerns during operations and result in a less invasive experience for patients. Shape sensing and pose control of flexible endoscopes can help to decrease the pain and damage to surrounding tissues,[41] as well as guarantee the stability of the system.[42] In this section, we review the current developments in sensing strategies for flexible endoscopes, classified into sensor-based and model-based shape-sensing methods, followed by force detection techniques.

Sensor-based Shape Sensing

Sensor-based shape-sensing techniques for flexible surgical devices are mainly classified into electromagnetic tracking, fiber optic sensing, and intraoperative imaging, which were comprehensively reviewed in a paper by Shi et al.[42] Recent studies on the shape sensing of flexible endoscopes are mainly focused on optical sensing, and here, the most salient examples of these studies are highlighted. Fiber Bragg gratings (FBGs) are widely used for the shape estimation of needles[43] thanks to their structural robustness and biocompatibility. This type of optical sensor is composed of a light source, which emits light with different wavelengths, and an interrogator to detect the changes in the wavelength of the reflected light. Mechanical strains, external forces, and temperature changes can contribute to a shift in the wavelength of the emitted light. This shift can be detected by the interrogator and associated with changes in the shape of the optical fiber, and hence the flexible structure in which it is embedded.[44] However, the performance of FBGs in medical applications requiring an extended range of motion has been frequently debated in the literature.[45] Therefore, limited studies have been conducted on the endoscopic applications of FBGs. Roodsari et al.[46] proposed a single-core optical fiber comprising a Nitinol substrate as a shape sensor for endoscopic laser osteotomy. The researchers argued that using multi-core fibers with conventional polyamide substrates contributes to a larger sensor diameter and, hence, limited flexibility. Thus, the use of smaller single-core fibers using Frenet-Serret equations and a kinematic model was investigated. Frenet-Serret equations relate the tangent, normal, and binormal vectors of a particular curve with each other. Using these vectors, any curve can be described in 3D.[47] However, the results indicate that further improvements are needed to increase the shape-sensing accuracy of the proposed sensing method.

The distance between the interrogator and optical cores in FBG sensors has been a factor posing limitations to the use of FBGs in extended flexible endoscopes. This distance directly correlates with the value of the signal-to-noise ratio and can compromise the accuracy of shape-sensing algorithms. To address this issue, Lu et al.[48] proposed a technique to deal with the signal noise based on an extended Kalman filter. The proposed technique incorporates a moving average algorithm into filter-bounded fluctuations in the output signals. The technique was implemented on an Olympus colonoscope using FBGs with 7 cores, which is shown in Figure 4.

Model-based Shape Sensing

As outlined in Section 2, numerous studies related to endoscopy are focused on tethered capsule endoscopes. Shape estimation of the tether in capsule endoscopes facilitates navigation and pose control of their distal tip but requires extensive investigation, as they lack active control and additional space for integrating sensors. Therefore, the shape of the tether in this type of endoscope is estimated using regression and model-based methods. In the study of Li et al.,[36] the deflection of the tether was estimated through a sensorless and regression-based method. Slawinski et al.[49] proposed a shape-estimation algorithm that relies on the position and orientation data of the magnetic tip of the endoscope, which are obtained directly. The shape of the tether is then approximated to a 2-link robot with torsional stiffness at its joints. To estimate the angle between the links and the stiffness coefficients, an extended Kalman filter was utilized. The proposed model was derived considering the Piecewise Constant Curvature (PCC) hypothesis. Constant curvature models describe the shape of a flexible body as a series of tangent arcs, each with a constant curvature.[50] Using this model could pose some limitations where external forces acting on the tether are not negligible.

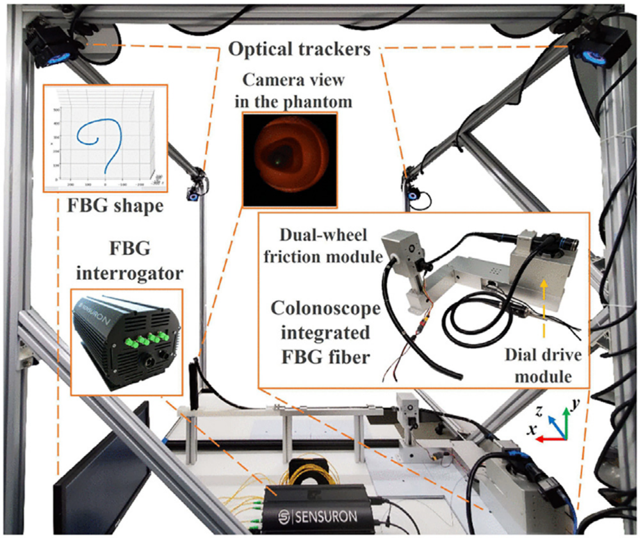

Figure 4. Experimental setup for evaluating the performance of a multicore FBG in shape sensing of Olympus colonoscope.[48] Reproduced with permission from IEEE Robotics and Automation Letters.

Zhou et al.[51] established a tension-deformation formulation for the shape sensing of a cable-driven endoscope composed of rigid articulated links. Knowing the tension in the cables, the model estimates the deformation of the backbone of the endoscope by considering the stiffness and friction between the articulated links of the robot. The coefficients of stiffness and friction were identified through a series of experimental trials. Likewise, Isbister et al.[52] suggested a kinematic model based on Cosserat theory and tension measurements in a 4-tendon-driven robot for endoscopic applications. The Cosserat rod model nonlinearly formulates the effects of external and internal forces on the deformation of an elastic body and accurately predicts the shape even under large deformations.[53] The model proposed in the study predicts the backbone shape of the robot through a hybrid analytical and numerical formulation considering the hysteresis and the friction in the cables.

Force-detection Techniques

Despite the availability of robust and accurate force measurement methods and modalities for robotic systems as shown in a previous study,[54] many of these methods are not applicable to flexible endoscopes. Jin et al.[55] introduced a novel vision-based tactile sensing for endoscopy, where a shape memory alloy probe is mounted on the distal tip of the endoscope. The probe is marked at two points, the distance between which changes when an external force is exerted on the probe. Processing of the scope images to map the distance between the markers provides accurate measurement of the external loads. However, the proposed method can only be applied to limited scenarios where external forces are exerted at the tip of the endoscope alone, with no external loads on the endoscope backbone. Zhang et al.[56] developed a flexible tactile sensor (shown in Figure 5) to estimate exerted forces on surrounding tissues, employing a sensor composed of piezoresistive elements placed on a flexible printed circuit. Originally developed for a tethered capsule endoscope to monitor forces exerted on the colonic mucosa, the compliance of the sensor renders it suitable for soft continuum endoscopes.

A contact-detection algorithm was developed by Campisano et al.[57] to reduce the error in tip position estimation of a 2 DOF water-jet-actuated gastric endoscope by

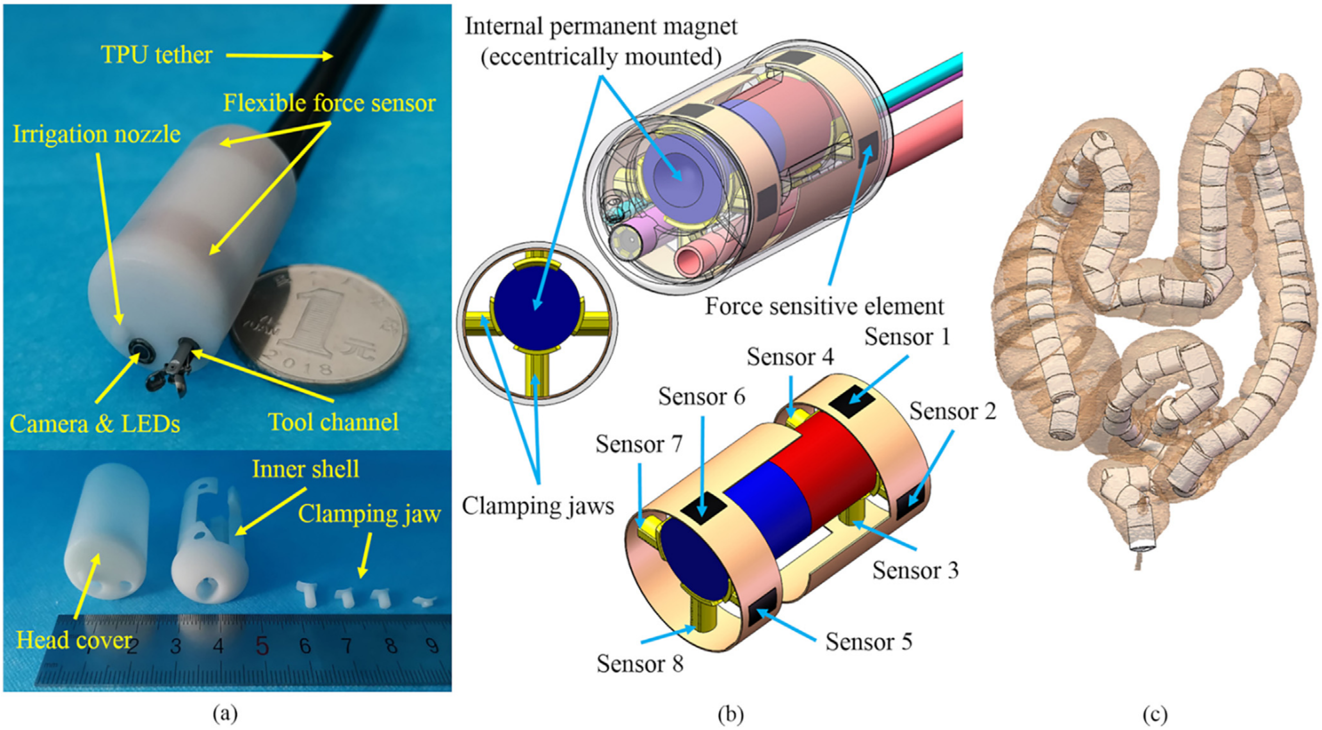

Figure 5. Piezoresistive sensor for a tethered capsule endoscope.[56] (a) Mechanical components. (b) Structure and positioning of sensitive elements. (c) Evaluation of sensor motion in a simulated large intestine. Reproduced under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

detecting the location, but not magnitude, of the external loads. The low-cost sensing unit comprises two inertial measurement units to measure the angular velocity of the tip, which is then combined with a Cosserat-based kinematic model to enable contact detection (Figure 6). However, using velocity measurements in the detection algorithm could prompt erroneous results due to the low signal-to-noise ratio of the velocity signals. The detection performance of the proposed algorithm was evaluated in contact with rigid obstacles, and it is expected that in future studies an investigation of soft contacts will be conducted.

Surgical Navigation and Imaging Technology

Given the elongated, curved, and bent structure of the intestines, the colonoscope has to be pushed through the curved and narrow lumen to reach the targeted surgical site. As the mucosa walls have a similar appearance throughout the intestine, where there are often no obvious anatomical landmarks, it is a challenging task for the endoscopists to locate the tip of the colonoscope with respect to the targeted tumors/polyps, especially for less experienced clinicians. Thus, endowing the robotic endoscopy system with auxiliary localization capability for both tissues and medical instruments can narrow the divide between more and less experienced clinicians. Hence, much research has focused on developing surgical navigation technologies with the aim of assisting endoscopists in gastrointestinal diagnosis.

Generally, the surgical navigation routine involves preoperative planning, as well as intraoperative registration and guidance steps. Although a reconstructed 2D/3D anatomical structure of lesions at the preoperative planning stage is helpful for surgeons to familiarize themselves with the working environment, endoscopic imaging intraoperatively is crucial for carrying out the operations. Once the location of the colonoscope tip, target lesions, and surgical instruments are made available in real time, MIS procedures, such as endoluminal operations, can be performed with higher precision and potentially better patient outcomes. Recently, advances in hardware solutions and software algorithms are enabling progress in the imaging technology of endoscopes. Compared with the widely used white light endoscope (WLE) equipped with higher resolution and increased pixel density, imaging technology in hardware solutions has been developed for visual inspection of finer mucosal details and surface vasculatures, such as the computerized virtual chromoendoscope (CVC) and autofluorescence imaging (AFI), even providing the non-invasive capability to observe histopathological features at the cellular or molecular levels, such as endoscopic ultrasonic (EUS) imaging technology, fluorescence molecular imaging (FLI), optical coherence tomography (OCT), and confocal laser endomicroscopy (CLE). In addition, advanced software algorithms such as artificial neural networks (ANNs) enhance tissue identification and instrument-tracking capabilities, boosting screening efficiency and potentially assisting clinicians. Some of the more salient contributions in this space are summarized in the following sections.

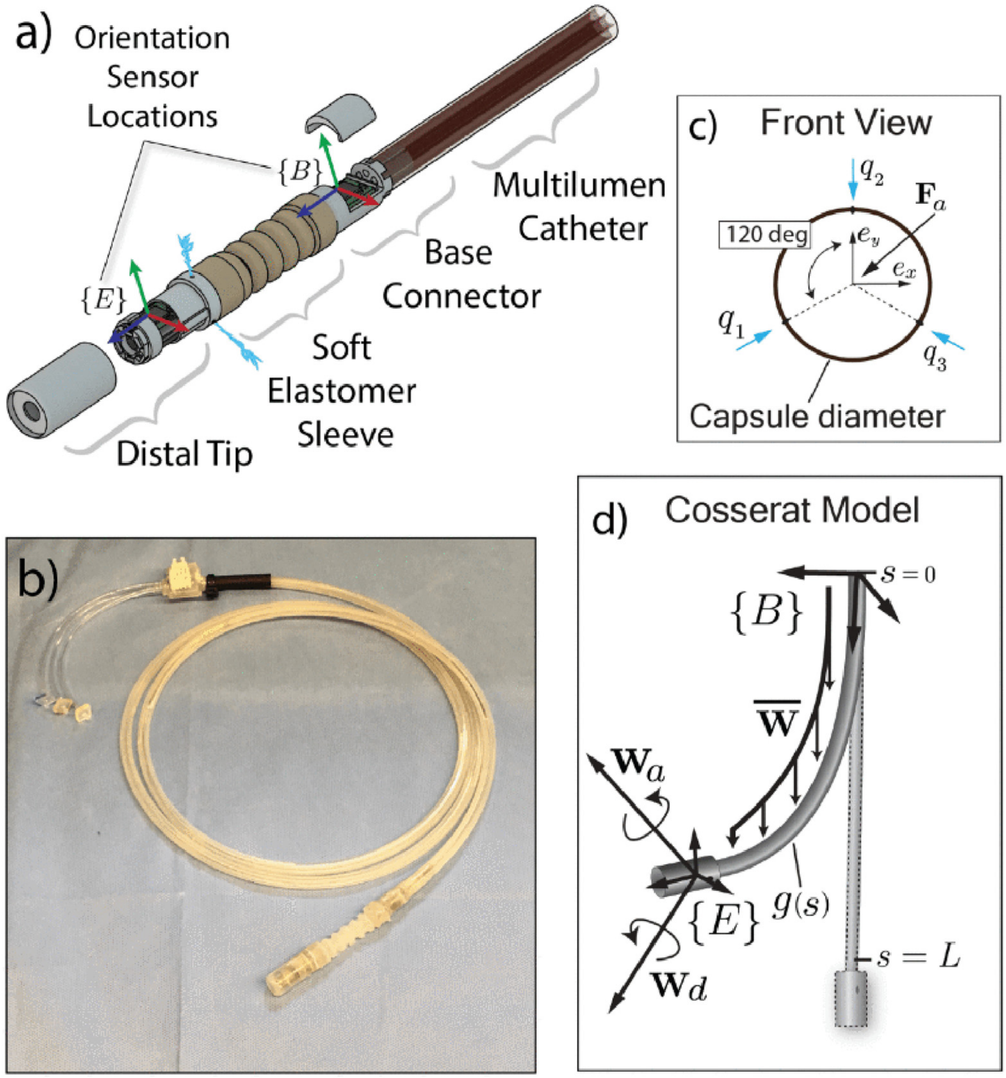

Figure 6. A sensorless approach for force estimation of a flexible endoscope based on Cosserat model and two orientation sesnsors.[57] (a) Mechanical structure. (b) The device used in experiments. (c) Device's tip with coordinate frame and the direction of jet locations. (d) The variables of the Cosserat model. Reproduced with permission from IEEE Robotics and Automation Letters.

White Light Endoscope

Complementary metal oxide semiconductor (CMOS) image sensor-based WLEs are widely used in current clinical practice. Compared with traditional charge-coupled device image sensor-based solutions, CMOS sensors are characterized by high integration potential, compact size, low cost, low power consumption, and fast response capability. One of the evolutionary trends of the WLE is to upgrade to a higher resolution (as shown in Figure 7). High-definition endoscopes, which are widely used in the present day,[58] have 1920 × 1080 pixels with a 4:3 or 5:4 aspect ratio. Recently, ultra-high-definition (UHD) endoscopes with 4K resolution, 3840 × 2160 pixels, and even 8K resolution,[59] 7680 × 4320, are emerging and currently undergoing clinical evaluation. Benefitting from higher pixel density, these endoscopes can capture the finer mucosal details and surface vasculature, which is significant in clinical diagnosis. However, UHD technology has more rigorous requirements for the entire signal chain, including the CMOS sensor, signal transmission cable, video codec chip, and display monitor. All these components must be able to transmit and process the 4K/8K data stream in real time. Furthermore, the optical functions of endoscopes are constantly improving with better optimized optics.

Endoscopic Ultrasound

EUS imaging technology combines traditional endoscopes with ultrasonic probes, which access the workspace through the instrument/biopsy channel and use an ultrasonic transducer as the imaging element. There are different types of EUSs, which include the circular scan type, the linear array scan type, and the high-resolution small probe type. Compared with in vitro ultrasonic examination, EUS significantly shortens the distance

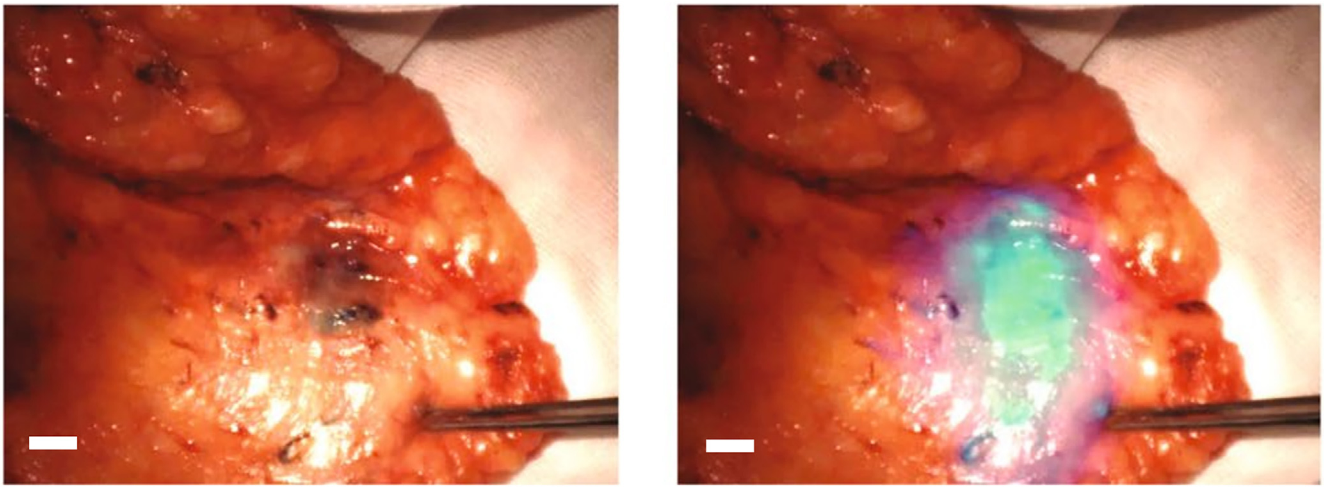

Figure 7. Comparison of WLE and FLI images.[68] Reproduced with permission from Nature Photonics.

between the probe and the target organ and avoids the influence and interference of abdominal wall fat, gas, and bone on the ultrasound signal.[60] EUS can obtain the histological features of the gastrointestinal tract[61] and the images of adjacent organs and can improve surgical performance in polypectomy, mucosal dissection, and endoscopic tunnelling.

Computerized Virtual Chromoendoscopy

CVC, as an image-enhancement technology, uses multiple optical channels to collect, process, and display captured images to record the spatial and multispectral information of the target object simultaneously without any staining agent applied. At present, CVC technologies include narrow-band imaging (NBI, Olympus Corporation, Tokyo, Japan), flexible spectral imaging color enhancement (FICE, Fujinon, Tokyo, Japan), and I-Scan (Pentax, Tokyo, Japan). All of these are led by industries, whereas academic research mainly focuses on assessing the performance of imaging technology and on the visualization of the different wavelengths used in clinical practice to improve screening and treatment efficiency.

NBI technologies replace a broad-spectrum white light source with a narrow-band light source. Using the characteristics of different absorption and scattering coefficients of biological tissues for different wavelengths of light, the surface mucosal texture and blood vessels and other microstructures can be highlighted.[62] However, the additional hardware requirement, poor real-time performance, and low stability have hindered its widespread use. Meanwhile, the transmitted light intensity decreases due to the addition of the narrow-band filter, which limits the viewing depth of the endoscope.

FICE technology decomposes a 400~700-nm broad-spectrum WLE image into a single wavelength spectroscopic image with a 5-nm step through the spectral estimation algorithm and electronic spectroscopic technology. By combining spectroscopic images with different RGB wavelengths,[63,64] a color-enhanced image can be obtained. The entire process is implemented based on software algorithms, so no additional hardware is required compared with NBI. Similar to FICE, I-Scan technology[65] uses S-type or J-type tone curve function to adjust the color component of the image. The CVC plays a positive role in observing the morphology of the gastrointestinal mucosal epithelium and the irregular changes of early tumor glandular fossa. However, some studies have shown that the ability of FICE to screen small polyps and unexplained bleeding is not statistically different from that of traditional endoscopy. Therefore, the current trend is to combine these imaging technologies so that clinicians can freely switch between white light and image-enhancement modes.

Autofluorescence Imaging and Fluorescence Molecular Imaging

AFI, as a variant of imaging enhancement technology, uses different fluorescence spectra generated by endogenous fluorescent substances of the lesions and normal tissues[66,67] to distinguish them with an excitation light source. Similar to the CVC above, an AFI system is frequently equipped with excitation light sources and a white light source to enable fast switching between them. The imaging process unit filters the light and synthesizes fluorescent images based on these received lights. This dye-free characteristic improves the screening efficiency; however, its false-positive rate is relatively high because of its poor specificity, moderate image quality, and interference signal in the presence of inflammation.

In recent years, FLI technology has attracted much attention in the tumor-detection space due to its high sensitivity and specificity, near-millimeter resolution, and real-time characteristics. Unlike the AFI method, the targeted fluorescent reagents are injected into the subject and reach the target tissue/organ (as shown in Figure 7) through the intravenous circulation before imaging.

Subsequently, the imaging system captures the fluorescence generated by the fluorescent molecular probe under the excitation light of a specific wavelength.[68] The noninvasive ability to observe histopathological changes at the cellular or molecular level of this novel imaging technology has made it an interesting topic in recent endoscopic research. The current trend is developing low-toxicity multifunctional fluorescent molecular probes.

Optical Coherence Tomography

OCT uses the principle of weak coherent light interference. This imaging technology reconstructs the plane or the 3D structure image of the sample, utilizing the interference signal obtained from the back reflection or the scattering of weak coherent incident light from different fault planes of the sample. Generally, OCT technology includes both time- and frequency-domain OCT. Time-domain OCT has been abandoned gradually because the scanning along different sample depths is carried out by moving the reference arm, which means the size and the structure of this system are not optimal. In contrast, frequency-domain OCT has a broader application potential because of its compact structure, small size, and fast sampling speed. OCT endoscopes can observe the microstructure at the histological level,[69,70] and their noninvasive characteristics make them more suitable for pathological examination, where resection is not applicable. Minimizing the probe diameter, boosting the scanning speed, and improving the vertical and horizontal resolution remain open research challenges in this space.

Confocal Laser Endomicroscopy

CLE, derived from laser confocal scanning microscopes, is an imaging technology that can obtain the optical cross-section of tissue at a certain depth in real time. Before the imaging stage, fluorescent agents such as sodium fluorescein are injected to contrast cellular, subcellular, and adjacent tissue. During the imaging stage, the incident light emitted by the laser source is focused on the conjugate point, where the sample is fixed, through the optical fiber or objective lens system. At the same time, the reflected light of the sample returns along the original path, passes through the confocal hole, and finally is captured by the photoreplier tube or other imaging sensors to synthesize a high-contrast image. CLE can observe cellular and subcellular structures in vivo without biopsy, such as mucosal cells, goblet cells, and intraepithelial lymphocytes, hence often taking the name of "optical biopsy".[71–73] It realizes real-time histopathological imaging and specific functional imaging and boosts the detection ability from the tissue level to the molecular function level. Currently, probe-based CLE is mainly used in the clinic, and the development trend toward a larger field of view, faster scanning speed, higher resolution, and wider scanning depth is currently underway. Overall, novel imaging technology remarkably improves visual inspection efficiency, even boosting therapeutic outcomes. WLE, as the mainstream method in current clinical practice, supports high-definition video stream transmission and provides finer mucosal and surface vasculature details, enabling the screening of gastrointestinal diseases precisely and quickly; however, novel methods such as UHD introduce a higher hardware cost, which hinders widespread use in the hospital. In addition, CVC technology has gradually become the standard screening routine to compensate for the limitations of the WLE, demonstrating the positive effects in observing some specific morphology changes that can hardly be noticed with WLE and that lead to a decreased procedure time. Meanwhile, the cost of CVC is lower than that of UHD. EUS, OCT, FLI, and CLE are noninvasive technologies that allow for observing histopathological features at the cellular or molecular level, which makes in-vivo pathological examination possible to some extent. In contrast to EUS and OCT, during FLI and CLE procedures, fluorescent agents are needed to improve the contrast between the region of interest and the adjacent tissues, which hinders their use to some extent and results in higher costs. In terms of the complication risk, except for the potential risk of fluorescent agents' usage, imaging technology does not involve any new locomotion strategies and can be seamlessly integrated into the existing clinical workflow; hence, it does not alter the risk of complication.

Software Methods in the State of the Art

The continuous exponential growth of semiconductor and computing technologies and advanced signal-processing methods have led to realization of complex software/algorithms to support endoluminal operations. Among these, the emergence of artificial intelligence technology, represented by ANNs, has greatly enhanced traditional endoscopic technology, providing better imaging and views of the surgical sites and supporting surgeons with better and more accurate patient and anatomical information. ANNs have been widely used in the field of image segmentation for the identification of lesions (as shown in Figure 8) or tracking instruments/objects. Recent research has been focused on the identification of Helicobacter pylori infection[74] and gastric cancer,[75,76] the detection and classification of polyps,[77] and the monitoring of inflammatory bowel diseases.[78] In addition, medical instruments and biological soft tissues can be tracked in real time[79,80] with ANNs to confirm localization orientation and estimate the depth, all of which are crucial components for image-guided navigation during the intraoperative stage. Commonly used ANN architectures include You Only Look Once (YOLO),[81] Single Shot MultiBox Detector (SSD),[82] Faster-Region Convolutional Neural Network (FRCNN), and Mask Region Convolutional Neural Network (Mask-RCNN).[83] Moreover, 3D reconstruction of the gastrointestinal environment[84] is another popular research topic (as shown in Figure 9). The combination of this 3D model and preoperative model will enable surgeons to design the optimal surgery trajectory to avoid tissue damage, meanwhile effectively removing the targeted lesions.

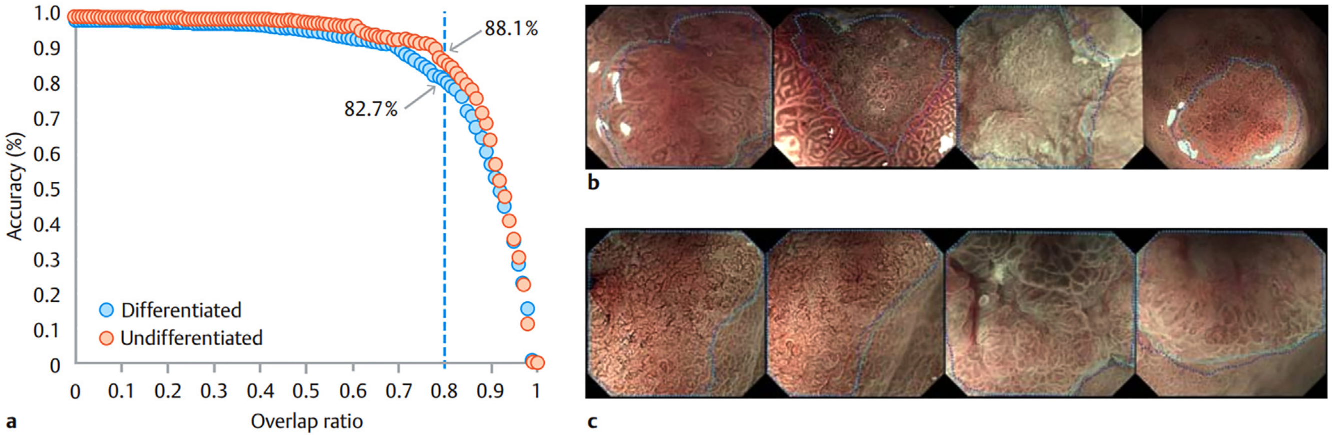

Figure 8. Image segmentation for disease classification.[75] (a) The performance comparison between the differentiated early gastric cancers (EGC) and undifferentiated EGC using a convolutional neural network. (b) and (c), referring to differentiated EGC and undifferentiated EGC, respectively, are several samples for illustrating the classification performance. The green dotted line corresponds to the results of experts, whereas the blue dotted line corresponds to the results of the convolutional neural network. Reproduced with permission from Endoscopy.

Discussion and Conclusion

In this review, current advances in flexible robotic endoscopy were classified into design, sensing, and imaging.

The main actuation methods that have been proposed are fluid-driven, tendon-driven, and magnetic. There is an increasing interest among researchers in the study of soft robotic manipulators actuated by pressurized fluids, as they represent a low-cost and low-risk solution for endoscopy. Thanks to their compliance and stretchability, robotic devices made of soft materials are inherently safe and suitable to interact with the human body. However, they present limitations due to the low speed of locomotion and the limited force that they can apply in surgical tasks. Tendon-driven actuation solves this problem,

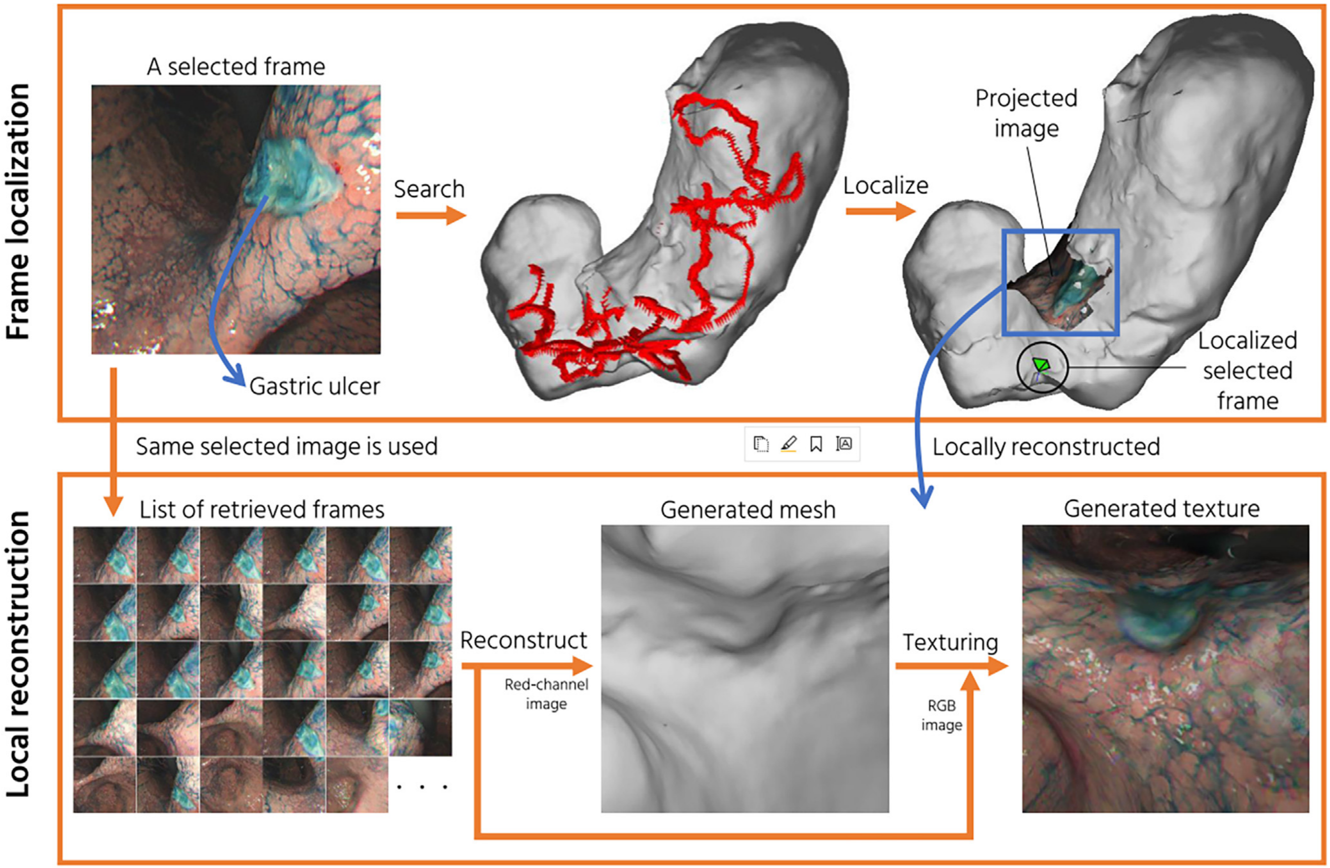

Figure 9. The 3D reconstruction for local lesions using deep learning algorithms.[84] Reproduced under the terms of the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

increasing the force at the distal part of the manipulator. Nevertheless, the presence of cables increases the overall stiffness of the endoscope, and the friction in the cable transmission requires larger actuators. Magnetic actuation requires large and expensive equipment to generate external magnetic fields but provides sufficient locomotion force for colon inspection. The least invasive screening technique is provided by capsule endoscopes, which are better tolerated by patients. The capsule endoscopy procedure has the advantage of not requiring an experienced professional; however, it takes 8 hours to be completed and does not allow therapeutic interventions to be performed. In addition, images are typically captured at preset-time intervals, which limits the amount of information that this approach can provide. Each actuation method has its own pros and cons. To select the most suitable one, the design of a new endoscopic device should be based on the requirements of a specific task. For this reason, collaboration between engineers and clinicians is key to delivering the next generation of robotic flexible endoscopes.

This review highlighted the current distinctive sensing techniques utilized for shape and force estimation of flexible endoscopes, which were classified into model- and sensor-based approaches. In the literature, sensor-based shape sensing is primarily provided through FBGs, which, however, are fragile and have a low signal-to-noise ratio. Conversely, conventional sensing techniques involving electromagnetic trackers and intraoperative imaging are more established; thus, they appear in fewer research works compared with FBGs. The review suggests that model-based methods have predominantly attracted researchers' attention, despite relying heavily on restrictive assumptions such as Piecewise Constant Curvature and a finite number of links in rigid-based models, which can lead to inaccurate predictions in some cases. This shortcoming could be addressed by developing more accurate models, such as using Cosserat's theory, which adds to the computational load. Force and contact detection were investigated in both model- and sensor-based approaches. Whereas model-based force estimation methods are likely to be imprecise, sensor-based methods increase integration costs and might hinder the installation of interventional instruments. In summary, a real-time shape-sensing method compatible with soft endoscopes is still lacking in clinical practice and represents a promising research avenue.

Although there is a large volume of new imaging methods proposed for various surgical applications, most of them can be traced back to previous works. In clinical practice, the most frequently used technology is still endoscopes with a white light source, which have higher resolution, larger field of view, and robustness. Although CVC imaging methods are promising in some specific disease-screening scenarios, recent research has shown that there is no statistical significance in most screening routines, which hinders their applications in practice. Molecular imaging technologies, such as FLI, OCT, and CLE, have attracted increasing attention. Because these methods can provide cellular and subcellular level imaging capability in vivo without the need to carry out a biopsy, they provide the potential for universally accessible real-time histopathological imaging to assist surgery. However, such technologies are yet to be deployed clinically.

As the continuous development of signal-processing methods progresses toward increasingly powerful ANNs, software algorithms play a crucial role in the field of endoscopy and minimally invasive surgery. Given that ANNs can learn and mine information from massive volume of data incorporating high-level contextual information, ANNs have significantly enhanced image-based disease classification, image segmentation, and instrument-tracking capabilities. However, the interpretability and generalization abilities of these methods are critical to their eventual application in clinical practice.

Despite the recent advancements, most robotic flexible devices are not yet commercially available. This is due to the open technological challenges summarized herewith and to the fact that introducing new medical devices on the market following FDA approval takes a long time. Looking at the increasing number of publications in robotic endoscopy, there are reasons to believe that flexible endoscopes will be implemented in clinical practice in the near future. Cost and waste generation in future robotic endoscopes are important factors that require special attention. Although robotic endoscopy can enhance the precision of health care delivery and can lower postoperative complications, the cost-effectiveness of these systems requires further assessment.[25] There are several factors that can make the use of robotic endoscopy justifiable in terms of cost reduction. Introducing artificial intelligence is likely to facilitate the process of training surgeons and reduce their learning curve, which can ultimately lower the cost of operations.[85] A sizeable part of the costs in standard endoscopy stems from the use of sedative drugs, which is associated with constant recording and monitoring of patients' vital signs.[86] The development of robotic endoscopy can lower patients' discomfort, thus reducing the use of sedatives. Additionally, by narrowing the gap between more and less experienced clinicians, robotic endoscopy could enable mass screening programs. In this respect, it has been shown that colorectal cancer screening followed by treatment is cost-effective[87] because the costs of screening are compensated by the reduction of colorectal cancer incidence, which results in a reduction in treatment costs.[88] In particular, delayed colonoscopy contributes to higher hospitalization costs, such as prolonged hospital stay, and the requirement of advanced medical equipment, which can increase the costs by nearly 30%.[89]

Because colonoscopy is among the procedures with the highest waste-generation rate,[90] it is important to consider the role of waste while designing and manufacturing robotic endoscopes. A large number of studies are dedicated to the development of disposable endoscopes as they comply better with sterilization standards and can be cost-effective.[91] However, these types of endoscopes can increase waste generation by up to 19%, which is much higher than the waste generated due to sterilizing and reprocessing of multiuse endoscopes.[92] Another study evaluating the environmental impact of endoscopy waste shows that single-use endoscopes increase waste by 40%.[93] One solution could be manufacturing endoscopes made of recyclable material as only the metal components of current endoscopes can be recycled.[92] Therefore, disposability and manufacturing of future endoscopes require further research to reduce medical waste in endoscopy.

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Article History
Received June 13, 2022. Accepted November 28, 2022.

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Conflicts of Interest
The authors disclose no conflicts.

Funding
This work is partially supported by a research collaboration with the Multi-Scale Medical Robotics Centre, The Chinese University of Hong Kong.

Author Contributions
A.A. and E.Z. conceived the manuscript. A.A., E.Z., and Z.W. wrote the article. A.A., E.Z., Z.W., E.F., J.A., M.R., B.L., F.R.B., and G.M. reviewed and edited the manuscript. B.L., F.R.B., and G.M. provided supervision.

Ethical Statement
The study did not require the approval of an institutional review board.

Reporting Guidelines
Not applicable.