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Capsule robots for the monitoring, diagnosis, and treatment of intestinal diseases

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ABSTRACT

Current evidence suggests that the intestine as the new frontier for human health directly impacts both our physical and mental health. Therefore, it is highly desirable to develop the intelligent tool for the enhanced diagnosis and treatment of intestinal diseases. During the past 20 years, capsule robots have opened new avenues for research and clinical applications, potentially revolutionizing human health monitor, disease diagnosis and treatment. In this review, we summarize the research progress of edible multifunctional capsule robots in intestinal diseases. To begin, we introduce the correlation between the intestinal microbiome, intestinal gas and human diseases. After that, we focus on the technical structure of edible multifunctional robots. Subsequently, the biomedical applications in the monitoring, diagnosis and treatment of intestinal diseases are discussed in detail. Last but not least, the main challenges of multifunctional capsule robots during the development process are summarized, followed by a vision for future development opportunities.

1. Introduction

Intestine is a continuous tubular structure that is responsible for nutrients and water absorption in the body. Moreover, as the largest immune organ, a large body of evidence has suggested the intestine as the new frontier for human health in recent years. *In vivo* [1,2], 70 % of immune cells and immunoglobulins are concentrated in the intestine, which are essential for intestinal homeostasis along with the microbial system. The interplays are tightly associated with a series of physiological functions including immunity, nutrition, digestion, absorption, disease defense, as well as maintaining the balance between the host and external environment [3,4]. Besides, increasing studies have identified that the intestine is connected with other organs and shapes our body all the time, affecting our health and aging conditions [1,5]. For example, the gut-brain axis includes endocrine signals transmitted by intestinal hormones, neuronal information transmitted by the vagus nerve, and immune signals transmitted by cytokines [6]. Thus, gut microbiota contributes to the homeostasis of the central nervous system by mediating immune processes, and thereby expanding the scope of the gut-brain immune system [7]. In addition to the brain, the lung can be linked to the gut through circulating inflammatory cells and mediators, and related dysfunctions include impaired intestinal barrier and immune environment disorders [8,9]. The mucosal environment has been found to vital for the occurrence of lung diseases such as chronic obstructive pulmonary diseases and lung tumors. Overall, it is very important to monitor, diagnose and treat intestinal diseases, potentially avoiding the occurrence and development of many diseases.

Endoscopy is a routine medical procedure to for the monitoring,

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diagnosis and treatment of intestinal diseases. However, traditional endoscopy has its own limitations, such as the risk of perforation, low efficiency and purity of intestinal flora collection, and the failure of biopsy sampling. In regard to drug administration, conventional therapeutic drugs are almost uncontrolled after entering the body, and thereby the drug efficacy is limited. In recent years, multifunctional robotic drug capsule for intestinal diseases is rapidly developing, and the combination of nanotechnology, electric power system, spectrum, biosensor and image analysis makes them the ideal substitute for the monitoring, diagnosis and treatment of various intestinal diseases [10]. Specifically, robotic drug capsule can help doctors see hard-to-reach areas in the gastrointestinal (GI) tract, and collect bacteria and gas samples anywhere in the intestine. By monitoring pH value, temperature and gas, biosensors endow the capsule robot with multidimensional diagnostic capabilities, offering an automated and intelligent tool for GI tract diseases. Of note, nanotubes embedded with nanosensors, named as the intestinal submarine, can target specific cells in the intestine and delivery therapeutic drugs to specific sites. Up to now, robotic drug capsules with distinct functions have been extensively developed in the study and therapy of intestinal diseases, including intestinal bowel infection, colorectal polyps, cirrhosis, GI bleeding, gastroesophageal reflux, obesity, constipation, and so on.

The focus of this review is to highlight the recent progress of robotic drug capsules that have been adopted in the monitoring, diagnosis and treatment of intestinal disease (Fig. 1). We firstly give a snapshot of intestine including microbiome and gas, and highlight the importance the intestinal homeostasis. We then outline the multifunctional capsule robot technology in terms of materials for wireless capsule endoscope, visual system, lighting, image acquisition, capsule locomotion, biosensing, drug delivery, drug monitoring, energy supply as well as information analysis by artificial intelligence. We also describe the clinical applications of multifunctional capsule robots and highlight its great potential in the detection and treatment of various intestinal diseases. Finally, we discuss the future opportunities, challenges and perspectives on how to improve the robot performance and expand the clinical applications.

2. The snapshot of intestine and GI tract endoscopy

2.1. Intestine

The intestine is a vital organ that enables the digestion and absorption of nutrients and excretion of digestive waste, as well as the regulation of immune homeostasis and maintenance of gut microbiota. Structurally speaking, the intestine is composed of four concentric circles: the mucosal layer, the submucosa, the muscular layer, and the serosa or adventitia. The mucosa, the innermost layer mainly containing epithelial cells, plays a role in the absorption, transformation, and secretion of nutrients and protects the body from resident flora and ingested pathogens by limiting their diffusion. The submucosa is a thick layer of loose connective tissue surrounding the mucosa that contains blood vessels, lymphatic vessels, and nerves. The muscular layer is responsible for segmental contraction, thereby enabling mechanical digestion and peristalsis of food along the GI tract. The serosa or adventitia is the outermost layer and its primary function is to lubricate or hold internal body structures together.

At present, increasing evidence have revealed that intestinal microbiome coexists in our intestines, mainly composed of bacteria, fungi, protozoa, parasites, worms, trace elements, etc. With the advent of molecular technologies, intestinal microbiome have been fully identified to be closely related to pregnancy [11], diet [12], host immune response [13], and drug metabolism [14]. In vivo, microorganisms are mainly distributed in the cavity and more than 95 % are accumulated in human colon [15]. Due to the large lumen, intestinal tract creates a permissive microenvironment for the occupation, overlay and adherence of miroorganisms, and contributes to the interaction of microorganisms with the host as well. Via the synthesis and secretion of key elements involved, intestinal microorganisms can affect the regional immune system and even educate immune cells. Abnormal changes in the abundance of certain intestinal microbiomes are defined as ecological disorders, which can destroy the intestinal immune homeostasis and lead to the occurrence of various GI diseases [16] [17]. liver cirrhosis, cardiovascular disease, brain disease, autoimmune disease and alcohol metabolism disorders [18–25] (Fig. 2). In addition to microbiome, intestinal gas accumulates in the digestive tract due to swallowed air when eating and drinking, as well as the byproduct of digesting certain foods [26–29]. Studies have found that abnormal production of intestinal gases such as H_2, CO_2, CH_4, H_2S and NH_3 is often associated with chronic intestinal diseases, such as digestive problems, intestinal infections, motility disorders and even tumors [30–34]. In summary, these studies demonstrated the contributions of the intestinal microenvironment to intestinal homeostasis in physiological and pathological conditions, highlighting the importance of monitoring intestinal microenvironment in diagnosis and treatment of intestinal diseases.

2.2. GI endoscopy

Nowadays, standard endoscopy remains the mainstay of the

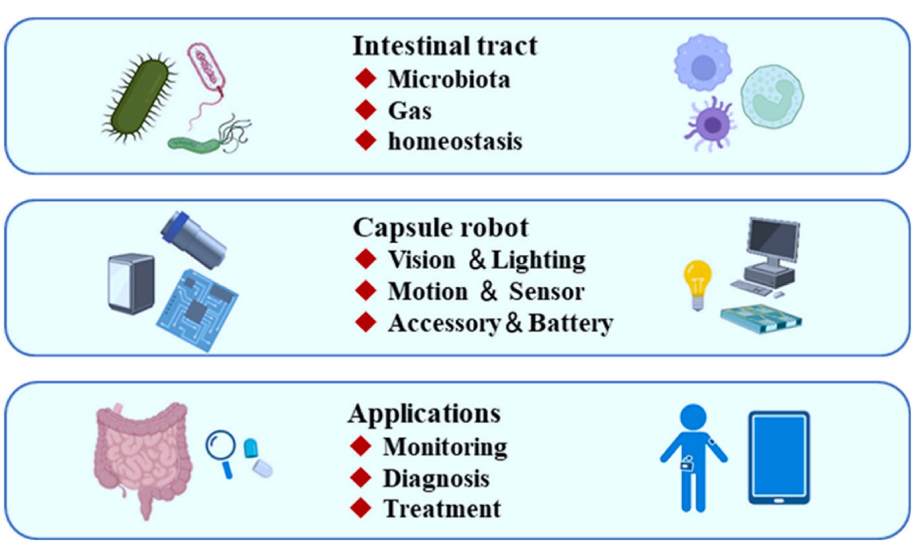

Fig. 1. Schematic for capsule robots, as well as their applications in the monitoring, diagnosis, and treatment of intestinal diseases.

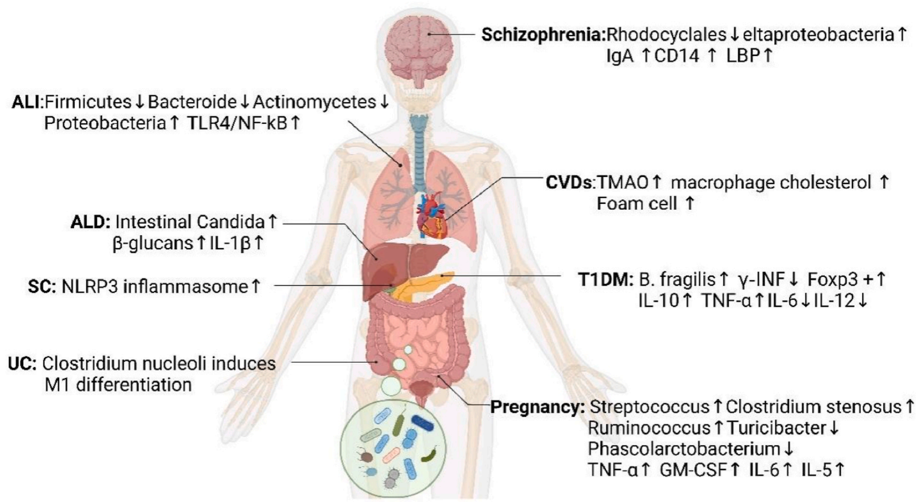

Fig. 2. The role of gut microbiota in human diseases. Intestinal flora is closely related to various system diseases, including metabolic level, antibody level, immune inflammatory state. ALI, acute lung injury. LBP, lipopolysaccharide-binding protein. ALD, alcoholic liver disease. CVDs, cardiovascular diseases. TMAO, trimethylamine N-oxide. T1DM, Type 1 diabetes. SC, sclerosing cholangitis. NLRP3, NOD-like receptor protein 3. UC, ulcerative colitis. Created with BioRender.com.

diagnosis and management of GI disorders. Standard endoscopy involves imaging, biopsy, and treatment of the digestive tract with white-light endoscopy by an experienced physician. The innovative sensors and optical components provide higher pixel density and magnification for endoscopy, facilitating to examine mucosal conditions in detail [35,36]. Thus, standard endoscopy plays an important role in diagnosis and treatment of GI bleeding, intestinal polyps, inflammatory bowel disease, intestinal tumors and other digestive diseases. Despite its critical role, many standard endoscopic examinations often miss early GI lesions, mainly because it is difficult to observe the subtle structural changes of the GI tract under conventional white light illumination. In addition, ordinary endoscopy may cause discomfort to patients who require sedation and monitoring by a clinical team, as well as expensive equipment maintenance. Therefore, the development of new endoscopic technology with minimally invasive, high precision and convenient sampling is highly anticipated to promote the early detection and treatment of GI diseases, and lay the foundation for a new generation of GI endoscopic technology. To support new technologies, the American Society for GI Endoscopy (ASGE) has established preservation and incorporation of valuable endoscopic innovations (PIVI) performance thresholds that should be met before adoption for the evaluation of Barrett's esophagus and colorectal polyps [37].

3. Capsule robot technology

In 2001, Given Imaging, as the first commercial capsule endoscope, revolutionized GI diagnostics with the launch PillCam. It is characterized by simple, noninvasive swallowing of pills without anesthesia, providing a novel alternative to the visualization method of GI endoscopy [38,39]. Today, capsule endoscopy can be widely used to detect diseases in various parts of the GI tract (Fig. 3). With the rapid development of targeted drug delivery, researchers have made great efforts to develop smart capsule robots with multiple functions. Most capsule robots fall broadly into two categories: capsule machines that integrate non-mechanical systems and capsule robots that integrate micro-electromechanical systems. The anchoring of the non-mechanical system is achieved by the interaction between the permanent magnet inside the capsule and the external magnet, which provides remote drive for the controllability of the capsule position and drug release [40]. While microelectromechanical systems (MEMS) can reside in the target area through an anchoring system and control drug release using wireless signals. Generally, these capsules consist of a variety of components to achieve the capabilities of the interventional system such as vision, motion, positioning, sensors, telemetry, biocompatibility, and power supply, as shown in Fig. 4 [10,41–48]. In this part, we will describe the essential elements in the design and fabrication of multifunctional capsule robots.

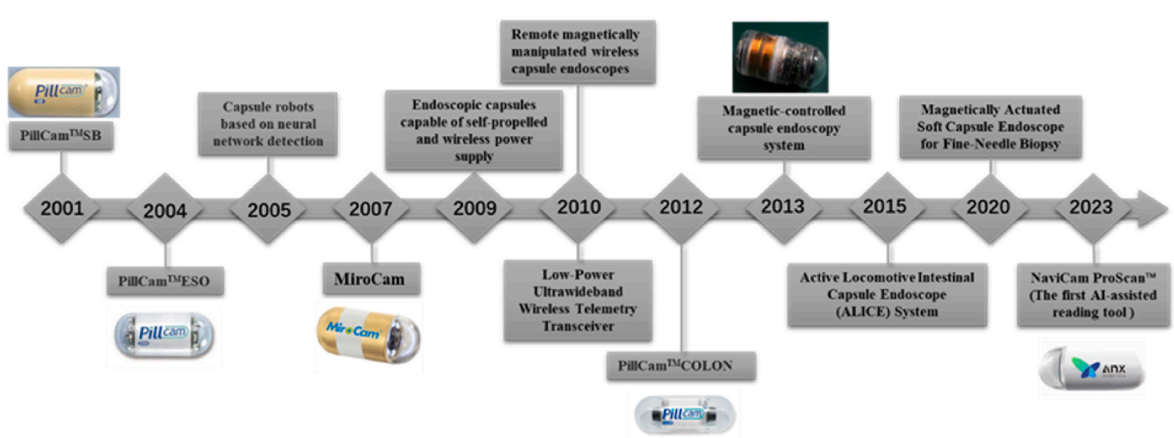

Fig. 3. Timeline of major milestones in the development of capsule robots.

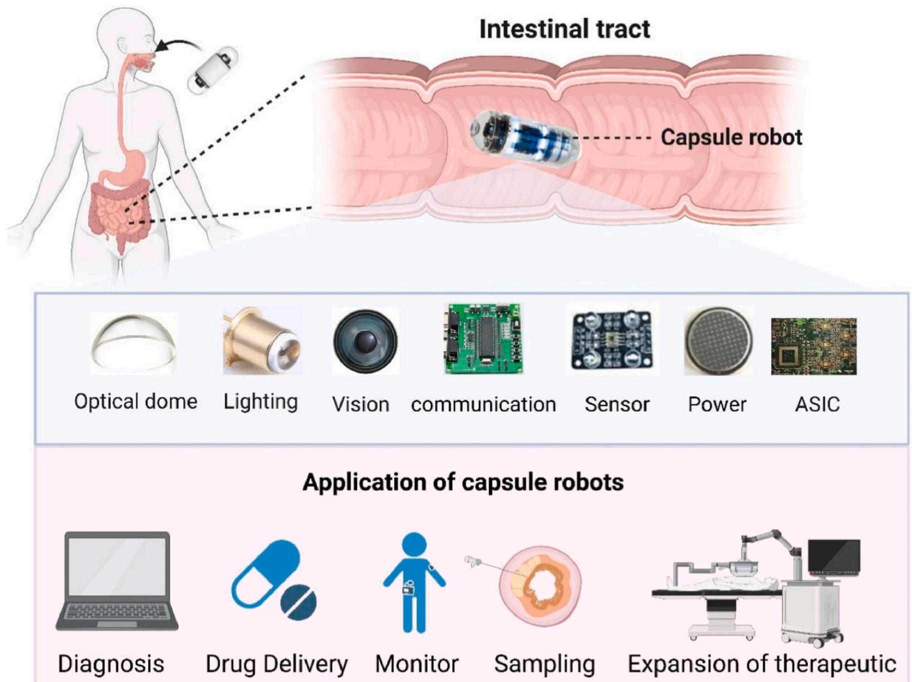

Fig. 4. The basic structure and application of capsule robots. Making a smart capsule requires the corresponding biomaterial and the placement of multiple accessories in a limited space to achieve the functions. ASIC, application specific integrated circuit. Created with BioRender.com.

3.1. Materials for wireless capsule endoscopy

As capsule robots aim to examine the interior of a body, the housing material and optical equipment requirements of the device including batteries are bioinert and compatible. Moreover, the enclosure packaging material should be safe, flexible, easy to swallow, and free of gut microbiota [49–54]. Thus, the shell must be able to resist the extremely acidic pH environment of the GI tract. For optical domes, the shell must also be transparent [55]. Polydimethylsiloxanes (PDMS) and polyetheretherketone are most commonly used as outer coatings for pills due to their biocompatibility and robustness after curing [56,57]. Of note, capsules can be enclosed and encapsulated by 3D printing with biocompatible resins. By using small openings or semi permeable membranes to collect certain chemicals or gases, these ensure that internal electronic components are isolated from the gastrointestinal environment [58]. In addition, the size and shape of the capsule are important parameters. Although larger capsules can accommodate more functional components, they have elevated risk for capsule retention and GI obstruction. To overcome these limitations, several solutions have been developed to minimize capsule size and use partially or fully biodegradable materials [59,60]. It is noted that various edible, biodegradable and transient materials have been established in the previous studies, including biosensors [60], antennas [49], batteries [61], and other structural components [47,62].

3.2. Vision system

Vision system is a major consideration for the capsule robot, which is responsible to acquire clear high-resolution images of the digestive tract. The vision system generally includes an LED, a lens, a vision sensor, and a chip that compresses the images [63], and it often needs a tradeoff between image resolution, frame rate and power consumption. To identify disease signs, more than 60,000 images are typically generated by capsule endoscopes based on light-emitting diodes (LEDs) and X-ray fluorescence photons [64]. Clinically, some lesions, such as tumors, are overlooked at an alarming rate of 18.9 % [65], and thereby it is essential to improve image quality by processing video signals, such as lesion contours, or integrating depth information for 3D video reconstruction.

Currently, the resolution of products on the market ranges from 256 $\times$ 256 to 1000 $\times$ 1000 pixels, and the frame rate is 2–7 frames per second. To convert analog data to digital data, additional chips are required, possibly exacerbating the problem of space constraints. Therefore, it is anticipated to develop new image sensors that can output high-quality images with low power consumption. Vatteroni et al. proposed a monolithic color image sensor with 320 $\times$ 240 pixels, which has lower power consumption and enhanced image sensitivity [66]. The sensor chip includes a pixel array, full readout channels, 10-bit analog-to-digital converter, a series of digital-to-analog converter for internal reference, and a digital module for chip control, offering a more convenient tool for image acquisition. Although this approach simplifies the diagnostic process and improves the accuracy of disease detection, the results of manual video inspection remain barely satisfactory. The advent of AI has significantly enhanced software capabilities, especially in medical imaging analysis. The AI uses an extensive training set of image data to calculate weights based on attributes such as texture, color, and shape to classify lesions. The AI methods has a high sensitivity and specificity for diagnosis of various diseases including, but not limited to, GI ulcers [67], neoplasms [68] and polyps [69]. Current vision systems are already well capable to perform diagnostic activities, and continuous optimization of image resolution, frame rate, compression, and transmission will help to further improve image quality.

3.3. Communication

The data transmission and reception strategy is an important part of capsule robots. The telemetry system of the capsule needs to maintain a high data rate and can provide a large amount of high-resolution images and other sensing data, with minimal power consumption. Capsule robots usually use radio frequency (RF) emission, which can be divided into low frequency, high frequency, ultra-high frequency and microwave according to the frequency range. Low-frequency RF has the advantages of convenient design and good penetration into the skin layer, but it requires large electronic components, which will make capsule robots too large [70]. Therefore, most commercial capsule devices use ultra-high frequency communication, usually around 400 mHz [71]. However, the channel bandwidth allowed in this band is limited in providing the data rate required to transmit high-quality real-time video, hindering the capsule robots transmission technology. In order to reduce power consumption, increase rate, and improve the quality of real-time video data transmission, the ultra-wideband (UWB) communication (the bandwidth <500 MHz) technology is put forward [71]. UWB can achieve more than 100 Mb/s of data transmission with 3.1–10 GHz frequency band. However, it requires higher hardware expenditures, including special UWB chips and antennas, and its widespread use may be limited by regulations in different countries. Despite these shortcomings, UWB still has very promising research prospects in the field of capsule robots [72]. In recent years, the intrabody communication (IBC) technology has been proposed, which is characterized by the use of the human body as an electrical signal transmission medium [73]. As a non-RF communication technology, it eliminates complex RF components and antennas, with lower power consumption and a more compact capsule design. Intromedic's MiroCam, the first device to use IBC technology, transmits electrical signals from the transmitting electrode in the GI tract to the receiving electrode on the skin [74]. By limiting the communication range to a very small area on the surface of the human body, it minimizes interference between various networks to the greatest extent possible [75].

3.4. Localization

An accurate understanding of the position and orientation of the capsule endoscope in the GI tract is critical, as it can provide feedback to control movement and assist the sensing unit to measure important target positions. In addition, probing the position and orientation of the capsule will facilitate wireless power transmission to the device. However, unpredictable GI motion and inhomogeneous media can cause distance measurement errors. Currently, the most direct detection method is based on medical radiological imaging, such as MRI, computed tomography (CT) and other visual localization. Despite with high accuracy, it is expensive, consumes resources and even induces profound radiation sickness. Meanwhile, some novel intake devices have been fabricated to identify the position based on chemical parameters (e.g. temperature, pH, oxygen concentration) without the help of external factors [76]. However, these methods often have too many measurement errors and can only indicate the unclear position of the capsules. Many research groups are actively exploring various localization techniques, including RF localization, ultrasound localization, magnetic localization, and hybrid localization.

RF localization is a sensor connected to the body by wireless transmission of images from inside the GI tract via RF signals. Benefiting from low signal delay, it can use the wireless communication module in the capsule robots, without additional modules and loads, greatly reducing the costs. For RF signals, received signal strength (RSS) and time of arrival (TOA) are two key signal parameters. Early commercial capsules such as Smartpill and M2A use RSS for positioning, but have security risks and bandwidth limitations [77]. Due to the absorption characteristics of human tissue, TOA positioning can provide centimeter-level accuracy only. In addition, current RF positioning cannot clearly determine the direction information of the capsule [78].

Compared with RF, ultrasound has the advantages of harmlessness to human body, good directionality and tissue penetration, so it has been widely used in clinical practice. The ultrasonic localization technique is to estimate the position of the capsule with submillimeter accuracy using the time-of-flight measurement between the signal emitted from outside the body and the reflected signal in the body [79]. However, the accuracy of this method may be affected by other organs in the human body, for example, ultrasound signals reflected by bones can interfere with signal reception and analysis results. Moreover, due to the limited volume of the capsule, the ultrasound signal also has the disadvantage of insufficient bandwidth [80].

Different from ultrasound, magnetic localization can be applied to transmit signals that are not affected by medium and frequency-dependent path losses within the body. The commonly used method of magnetic positioning involves placing an axial magnetic source inside the capsule. Then, the magnetic fields are measured using an array of magnetoresistive sensors mounted on the skin or external surgical platform. The accuracy of magnetic positioning is crucial. Low frequency magnetic fields can pass through the human body with an accuracy of 1.8 mm [80], but this cannot achieve satisfactory accuracy. Recent studies have further reduced the positioning error to a minimum of 1 mm and an angular error of 5.1° by placing two-dimensional or three-dimensional (3D) Hall effect sensor arrays around the capsule endoscope [81]. But further improvement is limited by the earth's magnetic field interference as well as the risk of performation with more than one magnet in the body. Another magnet-based approach relies on a magnetic field generated by an external electromagnet that uniquely encodes each spatial point in the field of view. A magnetic sensor inside the capsule can measure a local magnetic field signal encoded, which is then transmitted wirelessly to an external reader. The advantages of this method include small volume requirements for the capsule, as well as a high accuracy of 1.5 mm [82]. But this technique requires an external magnetic coil with sufficient range and high power consumption, which limits the movement of the carrier. To further improve the accuracy, the sensitivity and power of the system are greatly improved by increasing the frequency of the magnetic coil to 2 MHz, making it miniaturized and resonant with a high quality factor, reaching an accuracy of 920 μm [83]. In addition, it is challenging to obtain capsule rotation angle information related to the internal magnetic axis. Gleich et al. recently proposed the miniature magneto-mechanical resonators, which cover the 3D position and orientation of the capsule and realize a special magnetic positioning method with six degrees of freedom [84]. The device is characterized by small size, real-time monitoring, and high accuracy. However, the positioning accuracy and compatibility of subsequent technologies will be affected by capsule endoscopy containing ferromagnetic metal components.

Because each single localization scheme has its own advantages and disadvantages, the strategy integrating two of them has become a new research hotspot in recent years. Studies have proposed "the RF with vision aware fusion" (RF-VaF) scheme, composed of RF localization, visual localization and fusion-based localization modules [85]. The RF positioning module can infer the capsule position by signal transfer time, RSS indicator and capsule angle. The vision module introduces a novel convolutional neural network (CNN) dedicated to frame registration, correlated image generation, intelligent pixel feature matching, and multi-feature extraction. The fusion module applies a hybrid computing architecture algorithm. Another study is a hybrid localization method known as "MagnetOFuse," which incorporates both magnetic and visual localization methods [86]. It is performed by using nine three-axis Hall-effect sensors for magnetic positioning, coupled with a camera on the side wall of the capsule to observe the movement and improve the accuracy of global positioning. At present, the research on in vivo localization of capsule robots is still in the technical development stage, with aiming to deliver real-time capsule positioning with high precision by maximizing the performance of each positioning technology.

3.5. Capsule locomotion

Natural muscle movements within the GI tract, namely segmentation and peristalsis, can assist the movement of the capsule to the target site. However, relying on GI peristalsis, capsule robot may miss out on the monitoring of key parts, for example, the esophageal transit time is only about 10 s. Thus, active capsule endoscopy has been established to ensure that the capsule was preserved at the target site for sufficient time through mechanical, electronic, and magnetic field control actuators [87].

Usually, actuators are located inside the capsule and drive it to move in the soft body. To adapt the complex environment in vivo, various capsule robots with soft structures have been proposed. Inspired by the movements of a worm, a capsule robot has been fabricated with functions including stretching, shrinking and anchoring driven by Shape Memory Alloy (SMA) actuators [88]. This scheme takes advantage of a low driving voltage, but the motor response of the capsule is delayed. Another option is to use a micromotor to apply fluid pressure to achieve multi-direction capsule propulsion [89]. However, this technique consumes high energy and has low endurance, which makes it difficult to fully explore the GI tract. Electrical stimulation technology can electrically stimulate local intestinal muscles to contract, thereby enabling the movement of capsule in the intestinal lumen. When the stimulus current value exceeds a certain threshold of tens of mA, the device can flexibly move forward and backward. Similarly, due to a high battery capacity requirement, there are still problems in heat dissipation and human safety, which limit its wide application.

To realize the more complex movement of capsule robots, magnetic positioning technology has been developed by generating an external rotating magnetic field with an external electromagnetic coil or a permanent magnet [90,91]. These novel approaches guarantee the precise control of capsule robot positioning without internal batteries. In a recent study, a helical magnetic swimmer confined to a channel enabled a 3D selective spreading motion using a global magnetic field. This provides a basis for realizing the free control of capsule robots in the GI tract [92]. Subsequently, Liu's team proposed a series of self-propelled capsule robots and developed motion control strategies, which made the motion of magnetically controlled capsules more controllable and precise [93–96]. However, magnetic field control also has some drawbacks, such as the risk of causing mechanical damage to narrow intestines. In addition, it is necessary to keep the patient in a magnetic field for a long time, which can cause discomfort. Therefore, magnetic field control needs to address these issues in the future to widen its applications.

3.6. Sampling

Biopsy and sampling of GI tissue are essential for the diagnosis of GI disorders. Although tissue samples can be obtained through gastroscopic colonoscopies, they often cause patient discomfort and carry the risk of anesthesia. Capsule robots offer a promising sampling strategy by scratching soft tissues and collecting the microbiome. In fact, due to the flexibility of the intestine, it is difficult to fix the sampling site. Several attempts have been made. Examples include biopsy capsule robot with a U-shaped clamp that can be folded [97], and magnetically driven fine-needle biopsy capsule robot [98]. However, capsule robots are limited by movement mode, and their sampling rate is low. Kong et al. designed a miniature biopsy capsule robot using a rotating razor for biopsy, and two cylindrical razors were triggered by melting the chip resisters of electric power, but the trigger time was not easy to control [99]. Subsequently, Song et al. developed a new biopsy capsule robot based on high-speed tissue cutting, that is, a tool composed of sharp blades rotates at high speed to cut colon tissue, and can use an external magnetic field to control the movement of the capsule robot under visual guidance, making the sampling efficiency greatly improved [100]. In addition, with the development of simultaneous localization and mapping techniques in the surgical environment, the location and Angle of the biopsy capsule robot can be recorded in the figure. This helps to improve the reliability of the biopsy.

In addition to tissue biopsy, fluid sampling and microbiome analysis are also important. Previous studies mostly analyzed feces to examine gut microbiota and metabolites, which may not reflect the real situation [101]. To obtain fluid sampling from critical GI sites, researchers have developed magnetic control capsules to capture, seal, and safely transport samples [102,103]. Magnetic drive requires a large amount of power and complex electronic components. Therefore, future research needs to address the issues of high energy consumption and high cost. In addition, it is necessary to ensure that samples collected at specific locations are not contaminated by other substances. Despite its shortcomings, the magnetic control capsule sampling method is still a very promising sampling scheme.

3.7. Sensors

Changes in the GI environment are often a sign of intestinal diseases. To monitor these changes, capsule robots need to be equipped with a range of sensors, including mechanical, temperature, gas, electrochemical, and biological sensors. Based on this information, doctors can optimize their diagnosis of gut disease.

3.7.1. Mechanical sensors

Changes in physical parameters of the GI system may indicate pathological changes, which can lead to abdominal discomfort, pain, and altered bowel habits in patients. The current methods to assess intestinal pressure often involves the endoscopical insertion of a manometer, potentially causing discomfort and preventing full examination [104]. The SmartPill is the only FDA-approved wireless capsule device on the market that features pressure sensing. The capsule is equipped with a solid-state microelectromechanical sensor that relies on the piezoresistive principle. Their resistance will change with the mechanical stress of the GI tract, which can achieve high detection accuracy [105]. But it can only measure the pressure inside the intestinal lumen and cannot measure the systolic pressure caused by intestinal peristalsis. To address this issue, Benjamin Terry et al. developed a wireless pressure-sensing capsule that can simultaneously measure systolic and intraluminal pressure through two orthogonally arranged sensors [106]. In addition, a feeding device with a flexible piezoelectric component can be used, which measures the movement and activity of GI muscles by sensing the mechanical deformation in the gastric cavity [107]. Compared to microelectromechanical sensors, piezoelectric pressure sensors can generate charges when subjected to pressure, so they consume less energy, have low manufacturing costs, and are easy to control.

3.7.2. Temperature and gas sensors

Ingestible temperature sensors can serve as a non-invasive method for measuring core body temperature, replacing measurements from the pulmonary artery, esophagus, eardrum, and other sources [108]. It is sensitive to body temperature changes and can help ensure the core body temperature level for human safety. CorTemp® is a core body temperature sensor consisting of a quartz crystal, a circuit board, a communication coil, and a battery. Sensors can send wireless signals to external recorders, achieving transmitting core body temperature data through the GI tract [109]. In addition, monitoring intestinal gas is also very important because abnormal production of gas is often a sign of chronic intestinal diseases. In 2018, Berean and colleagues demonstrated a digestible electronic capsule that employs the structure of a thermal conductivity and semiconductor sensor to adjust the sensitivity to sense O2, H2 and CO2 [110]. The gas distribution of the gut was obtained by altering the intake of dietary fiber to modulate the fermentation activity of the gut microbes. The new capsule collected measurement information every 5 min and transmitted the information to the subject's mobile phone via wireless technology. To date, there are no commercially available gas sensors that can be directly integrated into the capsule.

3.7.3. Electrochemical sensors

Changes in the chemical composition of the GI tract can provide an objective basis for the diagnosis and treatment of diseases. Up to now, various intelligent capsules with electrochemical sensors have been developed to monitor chemical composition. Medtronic Bravo™ can be used to measure the pH value of the digestive tract to monitor gastroesophageal reflux disease and active bleeding. This capsule has high sensitivity, reliability, and no adverse event reports [111]. In addition, conventional and aptamer-conjugated electrochemical sensors can be used to diagnose GI diseases by detecting intestinal fluid [112]. They can even detect some neurotransmitters which play a role in the gut-brain axis diseases [113]. To adapt the highly acidic environment in the stomach, some capsules, such as Proteus Digital [114] and EtectRX [115], use a temporary polymer coating to protect the sensor. When their protective layer is dissolved by digestive juices, a signal can be sent to an external reader indicating successful administration. One issue of this sensor is the measurement drift, which can be avoided by measurement at a specific threshold indoors. In addition, cost and manufacturing time are key factors to consider when selecting suitable sensors [116].

3.7.4. Biological sensors

Biological sensors can use biomolecular components to report the presence or activity of analytes, providing an effective means to collect biological information in the GI tract. For example, researchers have proposed an intelligent capsule that can sample small intestinal fluid to detect bacterial growth by analyzing its metabolites [117]. Recently, edible materials-based sensors such as guar gum have been presented to detect the activity of gut bacteria by measuring the degree to which it is broken down by bifidobacteria [60]. However, the low accuracy of this sensor is a problem that needs to be addressed. Another team has developed a genetically modified biosensor based on bacteria, which responds to NO and H_2S by altering the genome of Escherichia coli [56]. However, this bacteria-based biosensor is highly sensitive to the low pH environment of the GI tract, therefore further research is needed to ensure the survival of bacteria. In short, biological sensors will have a wider range of applications with the advances in high-precision instrumentation and stable sensing elements.

3.8. Energy supply

Energy supply has become a problem with the improvement of video transmission quality and capsule movement efficiency. At present, the main methods to solve power problems are to use batteries, electrochemical galvanic cells, and wireless power transmission. Batteries have become the most common choice due to their stable and reliable power supply. However, the low safety of batteries greatly limits their application in the human body [118]. Therefore, researchers have developed a flexible battery made of biocompatible materials. Such a miniature battery is composed of natural agarose hydrogel electrolyte, which is safer than traditional batteries, but has limited energy reserves [119]. In addition, some researchers have proposed the capsules obtaining energy from the GI tract, for example, piezoelectric materials can provide power for devices when sensing GI movement [120]. Electrochemical galvanic cells use stomach acid as an electrolyte to provide power for capsules, such as Proteus Digital [114] and EtectRx [115] capsules. There are studies suggesting that substances such as glucose and gut microbiota can be used to generate submilliwatt energy [58]. However, additional accessories are required to harvest these substances, increasing the cost of the capsue. Also, these substances-based technologies are hard to provide stable energy supply, further hindering the wide application.

The wireless power transmission system can transfer electrical energy from the transmitter to the receiver, effectively improving the utilization of structural space and playing an important role in battery free capsule robots. There are studies applying sound transmission [121] and RF transmission [42] to power capsule robots, but they are limited by path loss, antenna size, and device orientation in the GI tract, resulting in low transmission efficiency. At present, wireless energy transmission using magnetic fields has become an important research direction. Initially, only 5.4 % power transmission efficiency was achieved by using wearable power transmission coils and 2-3D power reception coils [122]. In order to achieve higher transmission rates, researchers combined Helmholtz coils and birdcage coils into a transmission coil to improve magnetic field distribution, resulting in a transmission efficiency greater than 10 % [123]. Furthermore, a team has proposed a transmission coil with ferrite structure, which improves efficiency to 16.44 % by reducing the negative effects of demagnetization [124]. In addition, it is also necessary to combine the gastrointestinal structure and spatial posture of the capsule robot to further improve energy supply efficiency.

3.9. Image analysis

Image analysis refers to the process of analyzing and processing images captured by an endoscope to extract or enhance information of interest. As lengthy endoscopic images pose difficulties for clinical doctors in analyzing and diagnosing, it is very important to develop an automatic anomaly detection system. The emergence of computer vision and machine learning technologies is expected to solve this problem. The high image processing and analysis capabilities of computer vision can reduce review time and human errors [125]. But as the quantity increases, image classification will become increasingly cumbersome, which requires professional technicians to debug. Machine learning, also known as artificial intelligence (AI), is named as to a model proposed to figure out a specific problem or offer a particular service. In today's society, AI is becoming essential because it can solve complex problems with a highly efficient way [126]. Compared to computer vision, AI can automatically extract the most significant features for the target category. Herein, AI is expected to tackle the problems that hinder the development of capsule endoscopy, such as long reading time (Fig. 5). On average, it takes approximately 30–120 min to read images generated by capsule endoscopes [127]. AI is helping to promote image analysis that can save time, reduce energy consumption and standardize lesion monitoring. Also, AI can assist in capturing transient lesions within 1 or 2 frames that may be inadvertently missed using traditional approaches. So far, AI has been successfully applied to the diagnosis of GI bleeding, tumor and inflammatory bowel disease [128–130]. Based on the 2D to 3D reconstruction images or sensor data [131], can realize 3D visualization of intestinal lesions. In the near future, further research is expected to extend these findings and enhance the clinical utility.

4. Clinical applications of capsule robot

4.1. Disease diagnosis

Compared with traditional endoscopy, smart capsule has the advantages of non-invasiveness and no anesthesia, and its diagnostic accuracy is also satisfactory. In the coming decades, VCE is expected to begin to replace conventional endoscopy as the diagnostic standard for intraluminal lesions. Fig. 6 shows the high value application of Intelligent capsules in the diagnosis of acute GI bleeding (GIB), esophagitis and other diseases, which will be described below.

4.1.1. GI bleeding

Besides the improvements in treatment, the diagnosis of acute GIB bleeding has remained essentially unchanged for a long time [132]. The emergence of wireless video capsule endoscopy (VCE) provides a good guarantee for the diagnosis and risk classification of acute GIB. In a randomized clinical trial, early use of VCE resulted in early discharge of 80 % of patients with hematemesis who underwent endoscopy in the subsequent days and had no safety concerns [133]. In another study, VCE was used to diagnose suspected diverticular bleeding in an efficient and accurate manner, facilitating to detect the location of bleeding [134]. When the source of bleeding is identified, physicians can perform endoscopic treatment immediately or continue to evaluate treatment in the outpatient and emergency departments. In addition, VCE can reduce the risk of exposure in patients with GIB, because it does not produce aerosols, thereby reducing staff exposure to viruses, avoiding cumbersome procedures, and shortening the patient's length of hospital stay

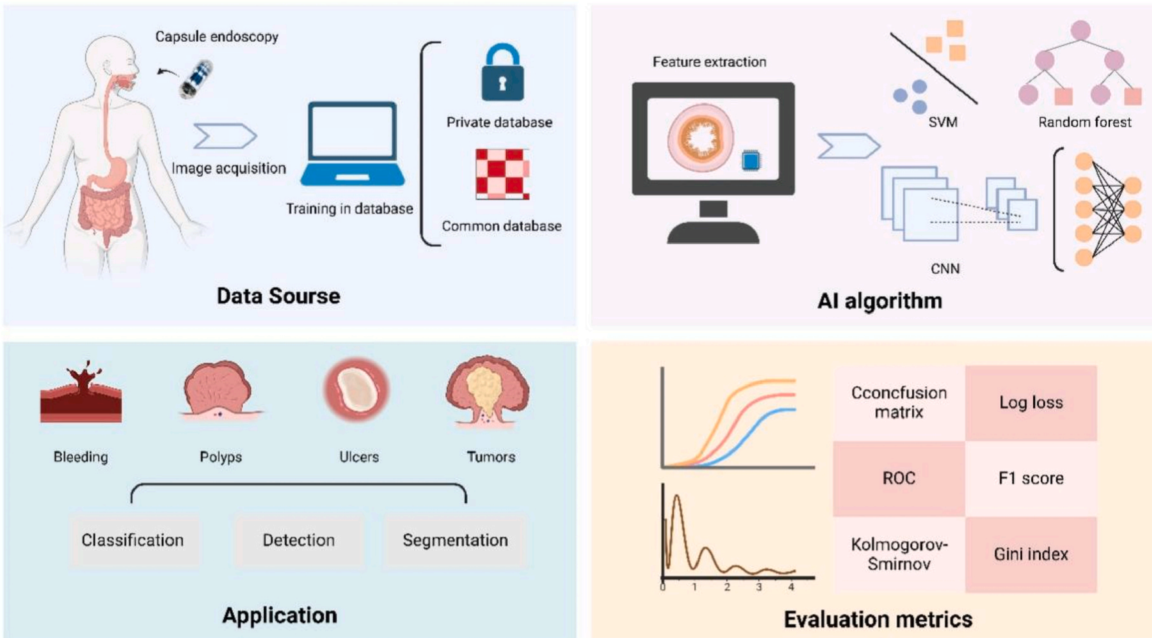

Fig. 5. AI pathological analysis model. The capsule robot captures images of the GI tract, which are then preprocessed and used as input to AI algorithms. Image processing is carried out through different extraction and classification methods combined with the specific application scenarios and analysis tasks of capsule robots. Ultimately, the model outputs relevant metrics to determine its performance. Created with BioRender.com.

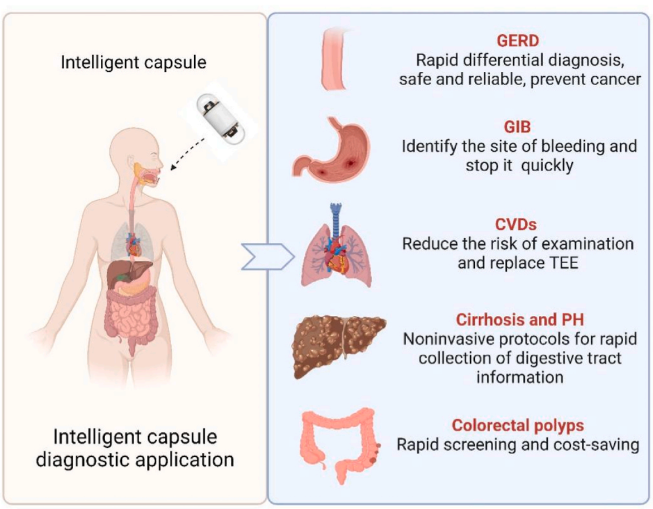

Fig. 6. Application of intelligent capsules in clinical disease diagnosis. Intelligent capsules are widely used in clinical diagnosis, with reliable accuracy and safety. **GERD**: Gastroesophageal reflux. GIB: GI bleeding. CVDs, cardiopulmonary diseases. TEE, transesophageal echocardiography. PH, portal hypertension. Created with BioRender.com.

[135].

4.1.2. Gastroesophageal reflux

It is difficult to distinguish gastroesophageal reflux (GERD) from functional dyspepsia (FD) in clinical practice, which often leads to the inappropriate therapy [136]. Capsule endoscopy has been shown to be feasible in diagnosis of gastroesophageal reflux. In a pilot study of patients with acute chest pain in the Emergency Department [137], 40 % had some form of esophageal diseases, which were consistent with earlier endoscopic data [138]. Timely diagnosis of this group of patients with digestive disorders allows appropriate treatment and reduces the chance of revisiting for noncardiac chest pain. This method is proved to be simple and safe, potentially reducing costs and improving treatment effects. Barrett's esophagus is a condition associated with reflux esophagitis and at high risk for adenocarcinoma. Compared to standard endoscopy, transnasal capsule endoscopy has been evaluated for screening of Barrett's esophagus, showing a high sensitivity (95 %) and a specificity (87 %) [139]. This technique is found to be safe, enabling early and rapid diagnosis, and preventing cancer.

4.1.3. Cardiopulmonary diseases

Patients with cardiopulmonary disease are at increased risk for routine endoscopy due to hemodynamic disturbances and depressed cardiac activity caused by the use of anesthetic drugs. Benefiting from the advantages of capsule endoscopy, it can be applied to evaluate GI mucosal injury in this high-risk group. Preliminary trials of ultrasound capsule endoscopy are currently underway. As an alternative to transesophageal echocardiography in patients with cardiopulmonary disease, capsule endoscopy is optimal compared to the routine endoscopic surgery. GI bleeding often occurs with continuous flow left ventricular assist devices, and capsule endoscopy can be used to diagnose GI bleeding [140]. In a single-center retrospective analysis, positive results were obtained in 19 of 34 CE examinations, with no adverse cardiovascular events, and they could have received timely intervention. Meanwhile, the safety of CE in patients with CF-LVAD has also been confirmed [141]. Nascent experiments into novel capsule endoscopy are ongoing, and are expected to represent more elegant solutions than traditional methods.

4.1.4. Cirrhosis and portal hypertensive bleeding

Patients with cirrhosis are prone to a variety of complications such as portal hypertensive bleeding, and are vulnerable to surgical and anesthesia-related complications. VCE is a noninvasive test with an accuracy of nearly 67 % in detecting varices, thus, it can be widely used for high-risk patients in critical care units in the future [142,143]. Moreover, the application of tethered capsule and magnetically controlled capsule endoscopy will greatly innovate endoscopy in patients with chronic liver disease [144]. For instance, Teflon capsules are used to test for esophageal varices first, followed by gastric varices, gastropathy due to portal hypertension and enteropathy. In 2024, a group from Changhai Hospital, China have carried out a prospective multicentre study to detect oesophagogastric varices in patients with cirrhosis using capsule endoscopy, which have revealed the high safety and diagnostic accuracy [145]. These studies represent a noninvasive approach to collect sufficient GI information from patients with chronic liver disease.

4.1.5. Colorectal polyps

At present, colonic capsule endoscopy (CCE) is mostly used to diagnose diseases, but cannot effectively treat them. The prevalence of colorectal polyps is more than 50 %, and most patients with intestinal polyps may have to undergo a second colonoscopy after receiving capsule endoscopy, so the traditional concept is that colonoscopy should be performed and treated at the beginning. But the latest research shows that not all polyps need to be removed [146]. If capsule endoscopy combined with artificial intelligence (AI) and optical biopsy technology can further determine whether polyps need to be removed, it may reduce the need for subsequent colonoscopy and cost, resulting in a higher benefit of CCE. For example, Mascarenhas et al. developed an AI algorithm based on a convolutional neural network (CNN) architecture. It can automatically detect elevated lesions in images for colon tumor screening with an overall accuracy of 95.3 %. This also suggests that the combination of AI technology with CCE can accurately screen colorectal diseases and provide direction for subsequent treatment [147]. Once brought to clinical fruition, these novel systems would offer a promising strategy in comparison to the cumbersome endoscopically based technology.

4.2. Drug delivery

In addition to endoscopy, capsule can serve as a functional carrier for drug delivery [148]. Theoretically, intestinal drug delivery is the diffusion or expulsion of active pharmaceutical ingredients from internal reservoirs into the GI fluid. Passive drug delivery is to release drugs based on diffusion mechanisms, while active drug delivery is to expel drugs directly from capsules [149]. Regardless of whether the capsule is delivered passively or actively, most capsules are propelled passively by GI peristaltic forces, without the control over the location or speed of drug delivery. Thus, the delivery of therapeutic capsules to specific sites in the gut is challenging and will be described below (Table 1 presents a comparison of the different drug delivery systems.).

4.2.1. Passive drug delivery

Passive drug delivery capsule is transferred from the capsule to the gut by natural diffusion. The high-frequency (HF) capsule developed by Germany in the 1980s became the first attempt in this field. Since then, different passive release capsules have been established using external radio frequency generators and magnetic fields to deliver drugs such as parathyroid hormone, octreotide, insulin, and TNFα inhibitors [150–153]. In 2021, Rani Therapeutics, San Jose, CA, USA [153] explored RaniPill for use in patients with chronic diseases requiring repeated subcutaneous or intramuscular injections. This pill was made of hydroxypropyl methylcellulose with an enteric coating, protecting it from degradation in gastric acid environment. Once reached in small bowel, the coating degrades and the pill inflates the balloon, exposing a dissolvable needle. Drugs loaded inside the needle were injected

Table 1
Comparison of different drug delivery systems.

Capsule	Release Mechanism	Dimensions (mm)	Reservoir Volume	Advantages	Disadvantages
HF [150]	Passive	NA	NA	The external radiofrequency generator heating and melting line, thus with the release of the needle pierced latex balloons containing drugs	External signal instability, poor impermeability, lack of accuracy
InteliSite® capsules [154]	Passive	35 × 10	0.8 mL	The release of the drug from the capsule is activated by heat generated from an external radiofrequency signal	
Enterion [156]	Active	32 × 11	1 mL	Using magnetic field driving internal heating element triggering capsule drug release	Drug release is limited by the battery life and the application time is short.
Intellicap [157]	Active	27 × 11	0.3 mL	It integrates the temperature and pH sensors. It can be controlled manually from a laptop or pre-programmed to release the drug at specific points within the GI tract	Drug delivery was less efficient
SmartTab [230]	Active	N/A	N/A	A new commercial product currently undergoing trials that actively deliver drugs using a smart pill actuated by a smart polymer mechanism	The capsules have a low volume of active pharmaceutical ingredients
RoboCap [161]	Transepithelial	N/A	0.3426 mL	An orally ingestible robotic drug delivery device that locally clears the mucus layer, enhances mixing, and topically deposits the drug payload to enhance drug absorption	Difficult to use in imaging techniques that involve magnets and energy problem
Microneedle Capsule (MIT) [164]	Transepithelial	20 × 10	N/A	Microneedles can be ingested and excreted with good safety. The bioavailability of the drug is improved	The penetrating power of microneedles is dependent on the compression of the intestinal tract by the visual field
LUMI Capsule [165]	Transepithelial	30 × 9	0.3 mg	Microneedles can be loaded with many macromolecular drugs that are not conducive to subcutaneous injection	It may not consistently target the same area of tissue. LUMI metal parts may interfere with magnetic resonance imaging
Rani Therapeutics [153]	Transepithelial	26.1 × 10	3.5 mg	High reliability and high bioavailability.	The drug payload is limited. The exact timing of drug delivery is unpredictable
Magneto microneedling capsules [168]	Transepithelial	27 × 13	N/A	The capsule is manipulated using a magnetic field to achieve a stable drive of the capsule and can be delivered to multiple sites	There may be a lack of sufficient adhesive force between the capsule and the intestine. Capsule ingredients may be intestinal mucous dissolves
SonoCAIT [169]	Transepithelial	30 × 11	External supply	Capsules are loaded with ultrasound transducers that control the required drug dose at the target site by ultrasound and can increase drug absorption to the tissue	It may be affected by the intestinal mucus barrier. A local increase in temperature results in a decrease in ultrasound intensity.
12-legged Endoscopic Capsule Robot [170]	Active	26 × 11	N/A	It is safe to use and can be delivered into the small intestine by active movement, improving the efficiency of the examination.	Making the capsule swallowable requires it to locomote in an uninflated colon

through the intestinal wall. While these systems are appealing, there are some limitations. For example, activation may fail because the inserted tissue attenuates the electromagnetic signal; If the enclosure is not sealed perfectly, the contents may leak; The target positioning before release lacks practicality and precision. InteliSite® capsules, for example, rely on gamma scintigraphy. To address these issues, researchers develop active systems [154,155].

4.2.2. Active drug delivery

Active drug delivery enables to expel drugs directly from capsules at the target sites, which is driven by heat, electricity, gas, magnetic force and so on. By transmitting signals from the capsule, the drug can be released continuously, intermittently, or at different rates via a laptop, or preprogrammed at the intended site within the GI tract. Moreover, by integrating with temperature and pH sensors, capsule robots enable the location imaging without radioactive isotopes. Although some capsules such as Enterion [156] and Intellicap [157] are still in the research and development stage, and are not available on the market, there are capsule robots are currently in clinical trials, such as SmartTab, a new commercial capsule that uses a smart polymer mechanism to achieve active drug delivery [158]. Collectively, these smart capsules can deliver agents to the intestine directly, but they often fail to improve drug bioavailability due to pH conditions, microbiota, gut barrier, and enzymatic degradation [159,160]. To overcome these challenges, smart capsules have been developed in combination with various drug delivery systems, which are simply classified as drug delivery through epithelial penetration or epithelial permeability.

4.2.2.1. Epithelial penetration administration. Intestinal mucus represents the initial steric and dynamic barrier to drug absorption. To overcome this barrier, different drug delivery capsules have been reported. RoboCap, an orally ingestible, robotic capsule, has been developed by Traverso's group [161]. This system was featured with the abilities of mucus-clearing and churning movements, finally promoting insulin absorption. Microneedles, as another main system for epithelial penetration administration, have been studied by various researchers for transdermal delivery of therapeutic drugs, overcoming the limitations of the traditional methods, such as slow onset of action, invasiveness, and pain [162,163]. Langer et al. developed a capsule-based microneedle device that can extend 5 mm radially arranged hollow needles. Animal studies have shown that this microneedle system can be ingested and excreted without causing intestinal perforation or retention. But the penetration of microneedles is dependent on the visual field compression of the intestine; therefore, there is a large variation in the number of microneedles penetrating the mucosa and the penetration depth of each drug particle [164]. Hence, it is difficult to control the dose administered

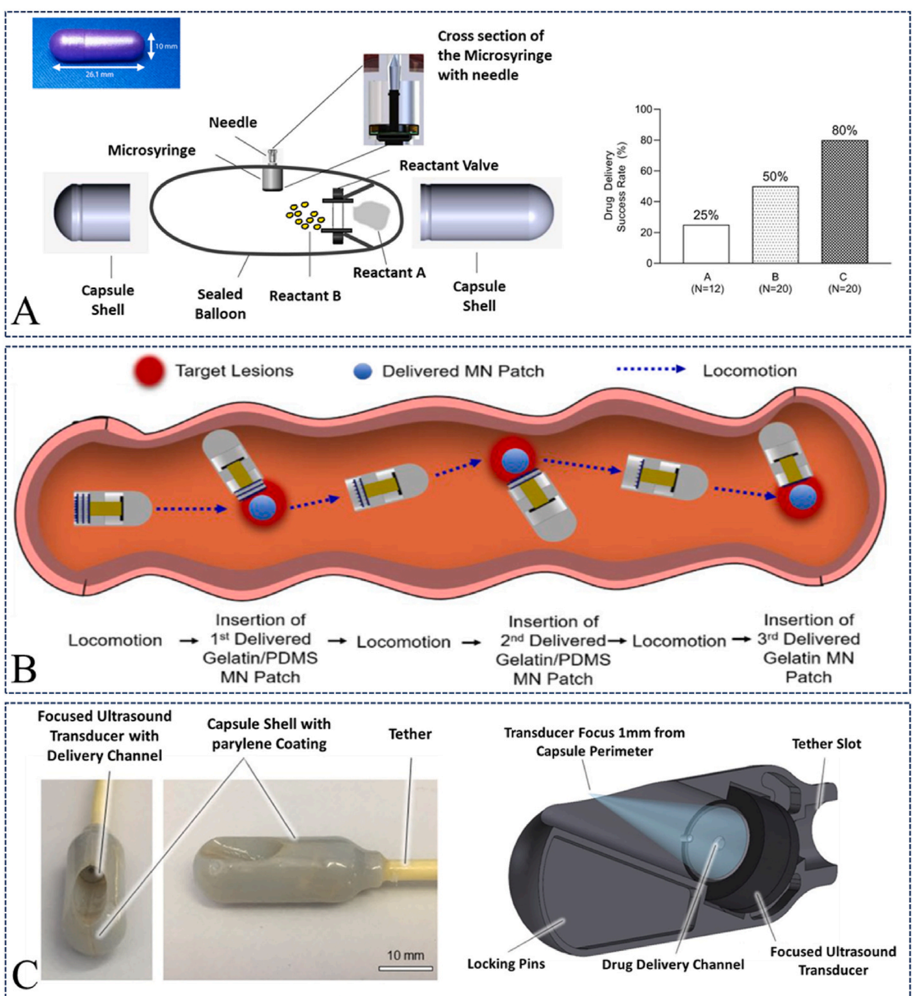

Fig. 7. Drug Delivery Capsules for Biologics. A. A fully assembled, enteric coated RANI therapeutic capsule. Success rate of RANI capsule administration in different balloon sizes. (A, 21 mm; B, 23 mm; C, 25 mm). Adapted with permission [153], copyright Springer Nature 2021. **B.** The process of targeted delivery of drug-loaded MN with magnetically driven capsules. Adapted with permission [168], copyright Elsevier publishing 2020. **C.** Front and side images of SonoCAIT ultrasound capsules and cross-sectional views of the interior of the capsule. Adapted with permission [169], copyright Springer Nature 2021. MN, microneedle. PDMS, polydimethylsiloxane.

due to the complex intestinal environment. Notable, a polymer microneedle-based capsule overcomes this limitation by using a device that exerts mechanical force on the intestinal mucosa [165]. The device consists of a cylindrical tube (length, 30 mm; diameter, 9 mm), coating with a polymer (ethyl methacrylate) that dissolves at pH $\geq$ 5.5. Inside the tube is a spring that can propels a cavity unfolded microneedle syringe (LUMI) as the coating dissolves. Furthermore, as the microneedle degrades, loaded drugs are released rapidly.

In addition, smart microneedles can integrate with other forms of driving force, such as gas pressure. Rani Therapeutics manufactured a hydroxypropyl cellulose capsule consisting of an enteric-coated layer of 0.1–0.5 % Plasacryl-HTP20 and Eudragit L30-D55 (Fig. 7A). Upon entry into the intestine, the coating dissolves and releases the polyethylene airbag device. In the reaction of potassium bicarbonate and citric acid, CO_2 was produced to inflate the balloon, and then soluble drug-loaded microneedles were injected into the intestinal cavity in a directional manner [153,166]. Reassuringly, the product has been clinically tested and the capsules can be effectively administered 80 % of the time and the bioavailability of octreotide administered through the device is 65 %, which is higher than in previous studies [167]. Besides, magneto-microneedling capsules have been proposed by Korean researchers, which enables clinicians to actively control the position of the capsule with a magnetic drive system [168] (Fig. 7B). Specifically, the capsule carries three pyramid-shaped microneedle patches with drug loading, and a magnetic system is used to sequentially release these patches to the target location. These different forms of driving forces can be specifically designed for various microneedle drug delivery, laying the foundation for individualized treatment.

4.2.2.2. Epithelial osmotic administration. Reversible osmosis is another method to increase drug permeability through the intestinal epithelium by using chemicals, electric fields, and ultrasound [159]. Recently, ultrasound has become a research hotspot in intestinal drug delivery. By adjusting ultrasound signal, the absorption of therapeutic drugs was increased in the isolated porcine GI tissues and could be controlled with desired drug dose at the target site. Stewart et al. designed a capsule (length, 30 mm; diameter, 11 mm) loaded with ultrasound transducer (Fig. 7C). The capsules were surgically implanted into the small intestine, and delivered more solution containing fluorescent quantum dots and microbubbles by an external syringe pump [169], as evidenced by the enhanced fluorescent signal in intestinal tissue biopsies.

In order to target a specific region within the gut, peristalsis must be resisted to "anchor" the region. Various mechanisms have been proposed to solve the problem, the most basic of which is that the capsule can be immobilized in the digestive tract, thereby increasing the field of view by preventing too fast transport and allowing the capsule to be removed. A variety of options for anchoring in the cavity include magnetic, balloon-shaped, and "leg" -based designs to maintain capsule position. These designs can provide a strong anchoring force without affecting the weight of the robot. To move within the digestive tract, leg-like devices have been developed, inspired by insect feet. For example, a 12-legged capsule device can be moved within the colon by rotation of two sets of legs [170]. In 2008, researchers designed a three-legged device with a microcolumn adhesive foot that grasps the intestinal wall and withstands peristaltic forces. It has been shown that the anchoring force of the leg device increases in response to an applied magnetic field [171]. Overall, capsule robots are beneficial to eliminate cross-contamination between patients as well as the limitations of repeated sterilization [172,173]. Although further studies should be carried out to prove the feasibility of these smart systems, we can believe they offer a powerful tool for the intestinal drug delivery.

4.3. Drug monitoring

Non-adherence is highly prevalent in patients with drug taking behavior, however, it is estimated that adherence to chronic medications is only around 50 % [174]. Failure to adherence not only affects patients but also increases health care costs [175]. Edible capsules are promising to solve this problem [114,115]. Up to now, two smart capsules have received FDA regulatory approval, Proteus Digital Health's capsule and Etect-Rx pill. When ingested into the digestive tract, the Proteus capsule interacts with gastric acid to emit a radio frequency signal, which is picked up by a wearable patch on the subject and transmitted to an external system, and a mobile phone transmits the data to the clinician [176,177]. Different from Proteus system, the Etect-Rx system is equipped with a lanyard-based reader that receives data signals collected by the capsule rather than a wearable electronic patch [178]. By integrating the advantages of various materials and functions such as mobility, navigation, and communication into the device, capsule robots can penetrate deep into the narrow GI tract and perform drug monitoring for long periods of time under harsh conditions.

Studies have shown that smart capsules can improve medication adherence [179,180]. In a study of patients with hypertension who used Proteus capsules, users had significantly improved clinical outcomes at 1 and 3 months compared with participants who did not use the system [180]. However, unlike those who did not take Proteus tablets, those who took Proteus tablets also received lifestyle guidance. However, adherence to treatment was not measured among nonusers of Proteus pills. Because of these factors, the health improvements observed in patients taking Proteus pills in clinical trials cannot be attributed to the system alone. A randomized controlled trial investigating TB treatment adherence found 92.9 % adherence in samples treated with Proteus compared with 63.1 % adherence in samples treated directly under observation [181]. But statistical analysis suggests that the observed differences may be largely attributable to the Proteus system being able to monitor adherence 7 days a week, whereas directly observed therapies can only be monitored during weekdays. When this factor is considered and compared, the compliance of Proteus is 95.6 %, while the compliance of direct observation therapy rises to 92.6 %. Another study investigating adherence in patients with hepatitis C was a single-group clinical trial, which limited the reliability of its results [179]. In addition, this technique was controversial in a study of the effectiveness of aripiprazole treatment adherence in a population with severe mental health problems [182,183].

4.4. Non-drug treatment

A variety of smart capsules are already available for drug delivery. However, drugs alone cannot achieve effective treatment. The reliability of non-drug treatments has been recognized and integrated into smart capsule forms for the treatment of GI diseases. Fig. 8 shows the non-drug treatments of intelligent capsules, which will be described below.

4.4.1. Obesity

Obesity poses a serious health burden, and many ingestible smart capsules have been used to treat obesity [184–186] (Fig. 9A). Intragastric balloons (IGBs) are widely used to treat obesity. It expands in volume to 250–950 mL in the stomach and resides for up to 1 year. The balloon occupies a part of the stomach space, so that the patient will be full and appetite will decrease soon, so as to achieve the purpose of weight loss [187]. But balloon placement and removal require endoscopic surgery and anesthetic sedation, which is expensive and causes pain for the patients [188]. Integration of such balloons into easy-to-swallow capsules may solve these problems. Researchers from Singapore have developed edible IGB capsules that can be reduced in size by coupling magnets to an external magnetic field, and the bicarbonate inside the capsule can react with gastric acid to produce gas that inflates the balloon [189]. Unlike traditional IGB, the entry of stomach acid into balloons is precisely controlled by wireless communication. After optimization and adjustment, the balloon can be inflated to 120 mL without any adverse reactions. This IGB capsule has been confirmed

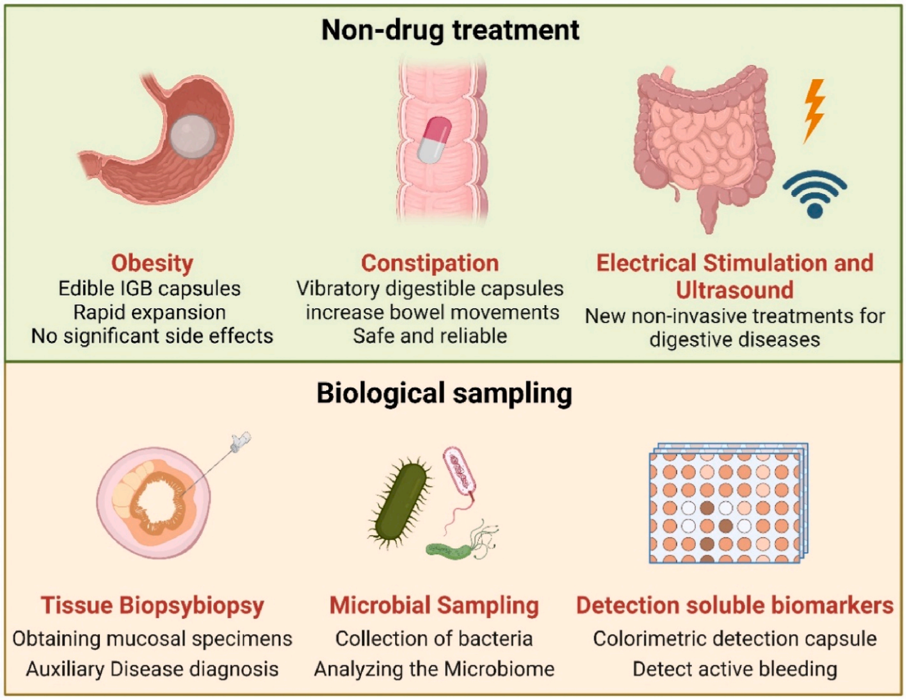

Fig. 8. Applications of smart capsules. The non-drug therapy of intelligent capsules can be used to treat obesity and constipation, and can be used for sampling and detection of various types of specimens. IGB, intragastric balloon. Created with BioRender.com.

to be safe and feasible through human experiments. With further development, we can believe that this device will be widely accepted to alleviate the global obesity epidemic.

4.4.2. *Constipation*

Constipation is a common disorder associated with GI dysfunction. Currently, due to the high incidence of the disease, limited therapeutic effects, poor quality of life for patients, and high medical costs, innovative solutions are urgently needed [190]. Existing research attempts to solve these issues using smart capsules. Vibratory digestible capsules designed by Vitality Limited with a size of 24 × 11 mm [191] (Fig. 9B). It consists of two parts, each of which can move independently and freely. The solenoid valve and spring are connected by a ferromagnetic shaft and control both parts by the duration and frequency of their vibrations in the colon. In an in vivo study in adults, spontaneous bowel movements increased in 23 of 26 patients, with the mean number per week increasing from 2.19 ± 0.67 to 3.79 ± 1.31 [192]. Recently, a large-scale clinical trial confirmed that vibration capsules are highly reliable and safe to treat constipation by enhancing colonic peristalsis rhythm [191]. Future research needs to further optimize the vibration parameters of capsules to achieve better clinical outcomes.

4.4.3. *Electrical stimulation*

Electrical stimulation has been shown to modulate GI motility and may serve as an alternative to drugs for GI motility disorders [193]. Recently, some edible and implantable devices have been reported to treat gastroparesis [194] and obesity [195] by electrically inducing muscle contractions. An electrode stimulator attached to the stomach can apply a series of short pulses that have little effect on gastric motility but can alter hormonal signaling in the hypothalamus, reduce appetite, and produce an early satiety sensation. Of note, a miniature self-powered vagus nerve stimulation device was found to reduce body weight of rats for up to 38 % compared to the control after the implantation for 100 days [196]. In the case of a digestible self-directed system, the device consists of a stainless steel needle whose external electronics are protected from gastric acid by a layer of PDMS, connecting the external microcontroller to the silver oxide cell via flexible twisted wires [57] (Fig. 9C). The microcontroller generated two continuous voltage pulses of 330 μs length separated by 70 ms, mimicking the pulses generated by the gastric electrical stimulation system. The tests were performed on an adult pig model and the stimulated muscles were observed by ultrasound. To prevent corrosion, microneedle fabrication using iridium or platinum is recommended and integrated with current control systems to reduce the effect of tissue fibrosis on electrical impedance [57].

4.4.4. *Ultrasound therapy*

Traditional low-frequency ultrasound is known to promote the treatment of intestinal diseases via the increased uptake of drugs in the GI tract [197], For GI cancers, ultrasound therapy can ablate or mechanically destroy target tissues and enhance anticancer immune responses [198]. Considering the features of ultrasound, Stewart F proposed a capsule robot based on ultrasound in 2021 [169]. Experiments on pigs have shown that focused ultrasound can allow fluorescent markers to penetrate the mucous layer of the small intestine, providing a new approach for drug delivery. As this field is just beginning, future research aims to further improve the efficiency of capsule ultrasound transducers while ensuring safety and energy supply. In this way, the ultrasound-activatable prodrug can be further extended to preclinical or clinical studies for GI disease treatment, such as cancer, GI dysfunction.

4.5. *Tissue biopsy*

Initially, Crosby capsule was made to assist in the diagnosis of celiac disease, and now it is widely used to obtain GI mucosal specimens and become a good tool for the diagnosis of intestinal diseases. Generally, Crosby capsules are stainless steel capsules (length, 20 mm; diameter, 11 mm) and are attached to a polyethylene tube [199]. Negative pressure was generated using a syringe, and mucosal tissue was aspirated through a hole on one side of the capsule, and the comprehensive knife begins to rotate and the mucosal tissue is removed. Although Crosby capsule assists in the biopsy diagnosis of many diseases, it has risks such

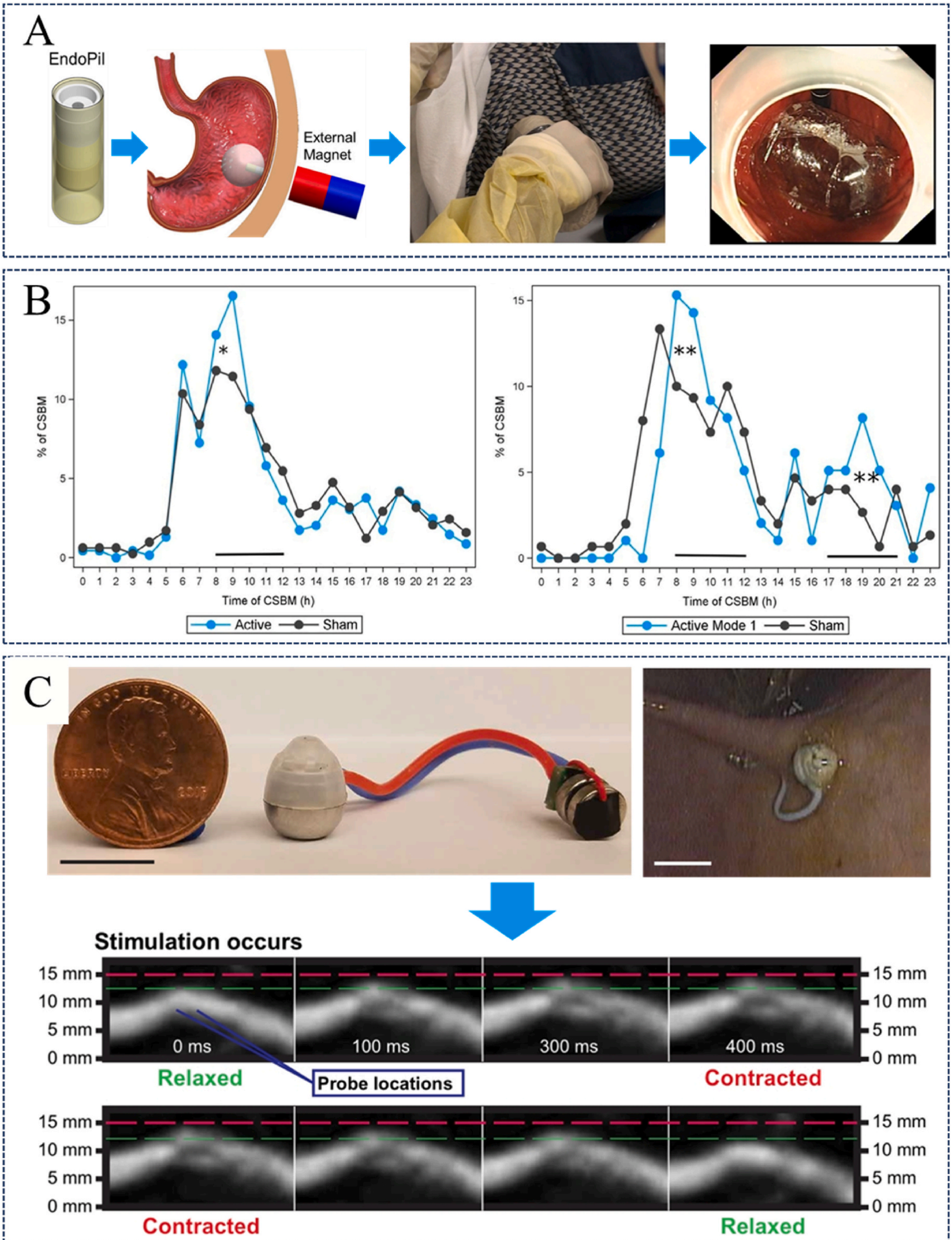

Fig. 9. Smart capsule non-drug treatment. A. Novel magnetically driven inflatable capsules. It can be activated by an external magnet after swallowing and IGB is placed in the stomach. Adapted with permission [186], copyright SPRINGER NEW YORK LLC 2021 **B.** The correlation between the working time of the vibratory capsule and the percentage of CSBM. The black line in the two images represents the cycle of active vibrations. Adapted with permission [191], copyright John Wiley & Sons 2020. **C.** Appearance diagram of the electrical probe and its ultrasound image of stimulating porcine gastric muscles. Scale bars, 1 cm. Adapted with permission [57], copyright AAAS 2020. CSBM, complete spontaneous bowel movements.

as bleeding and perforation [200]. Nowadays, a series of capsule robots have been presented with more powerful features, although most of them are not yet applicable to clinical medicine [98,201,202]. It is worth to mention the wireless capsule biopsy that offers a flexible solution to the diagnosis of intestinal diseases. Although both in vitro and in vivo experiments have revealed the feasibility of this capsule, clinical trials have been limited due to the insufficient power supply. Besides, scientists and engineers have designed and fabricated some biopsy capsule robots based on high-speed cutting tissue [100,109]. These biopsy capsule robots have opened new avenues to revolutionize the traditional ways of gut diagnosis.

4.6. Microbial sampling

The world is gradually realizing the importance of intestinal microbiome to health, and at present, fecal specimens are often used as proxies for intestinal microbiome because it is easy to collect and reproducibly sampled. However, the fecal microbiome is different from the whole microbiome of the GI tract, and cannot represent the whole intestinal microbiome of the individual [203,204]. Current sampling methods for obtaining intestinal microbiome includes intestinal aspiration and mucosal biopsy, all of which have the risk of sample contamination [205,206], or causing changes in microbial composition. To obtain samples that can accurately reflect the intestinal microbiome, several

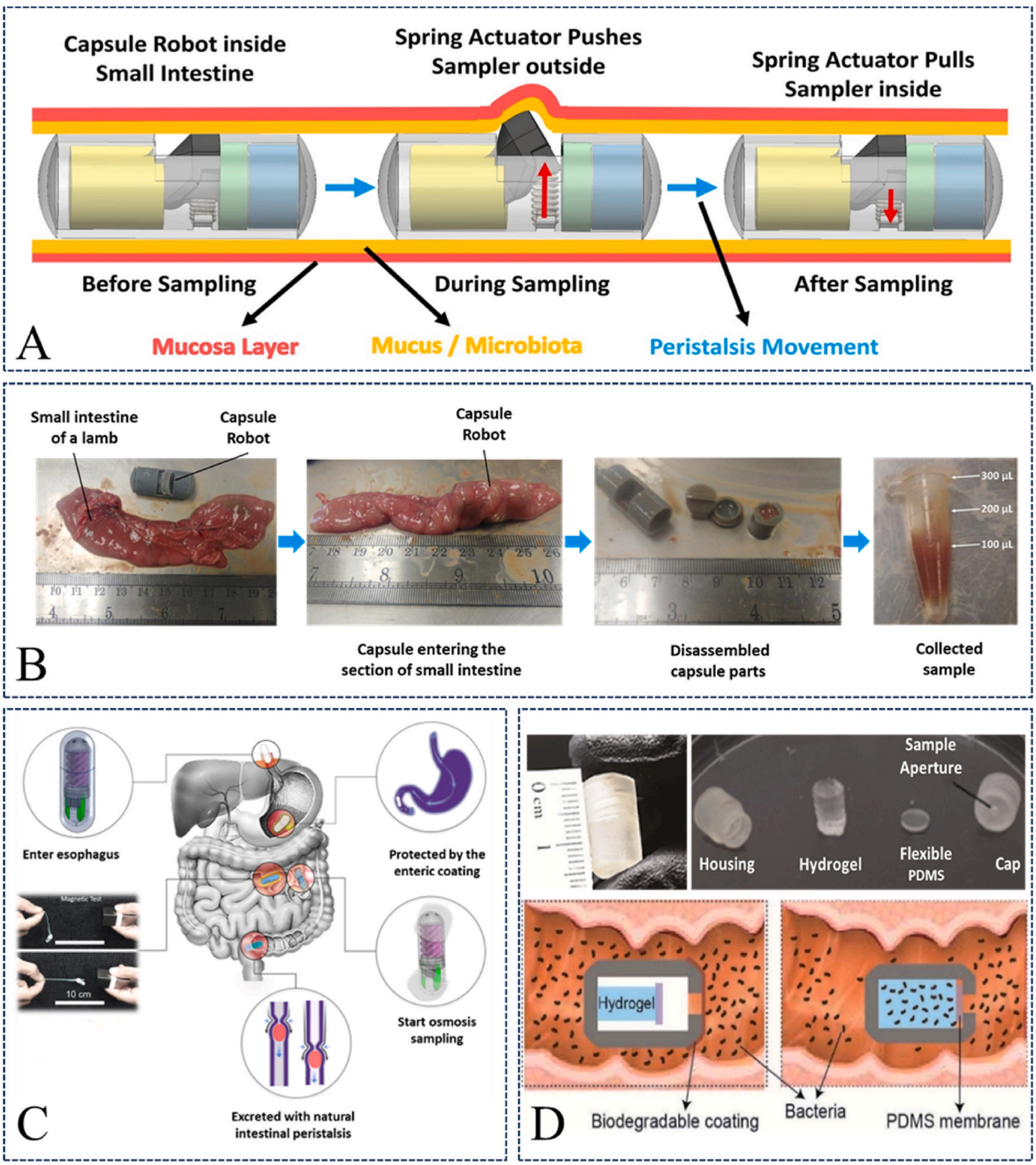

Fig. 10. Microbiome sampling capsules. A. Shape memory alloy spring-based capsule robot. It uses a shape memory alloy spring to achieve driven sampling, collecting the microbiota within the mucosa and storing it in a sampling chamber. Adapted with permission [208], copyright John Wiley & Sons 2020. **B.** Capsule robots with shape memory alloy springs for in vitro lamb small intestine sampling experiments. Adapted with permission [208], copyright John Wiley & Sons 2020. **C.** The sampling process of the osmotic pill sampler in an enteric capsule. Adapted with permission [209], copyright John Wiley & Sons 2019. **D.** Biodegradable coating structure and its sampling schematic diagram. Adapted with permission [210], copyright RSC Publishing 2020.

capsule robots have been explored. In short, these capsules are available for microbiome sampling using as spring and suction core materials [207], shape memory alloys [208], osmotic pumps [209], biodegradable coatings [210] and so on (Fig. 10). However, using these capsules, samples are collected along the entire GI tract but not at a specific site, failing to reflect the spatial distribution of the GI microbiome [211,212]. Taking into account the diversity and spatial distribution of intestinal microbiome, it is necessary to develop more powerful and controllable capsule robots for sampling. Moreover, more continuous studies with support of doctors and nutritionists could be performed based on these smart microbial capsules, aiming to specify the optimal diets for individuals.

4.7. Detection soluble biomarkers

Currently most smart capsules are integrated with sensors to detect soluble biomarkers, such as hemoglobin, as it is associated with intestinal bleeding [213,214]. These capsules work mostly by using optical sensor and enable the contactless detection of analytes. Regular capsules can be used to identify gastric bleeding but cannot quickly distinguish between old and active bleeding. To address this issue, Qiao et al. reported a colorimetric detection capsule that enable to detect blood cells entering the measurement chamber based on hue, saturation, and lightness color space [215]. The measurement chamber includes a white-light LED, a color sensor, and an adsorbent color sensitive film that changes from white to red when hemoglobin is detected. In vitro experiments showed that the method could detect hemoglobin concentration as low as 2.375 mg/mL, which was lower than the hemoglobin concentration in the GI bleeding area. Another capsule, name as HemoPill [213], enable to detect active bleeding by integrating an optical sensor. Experiments were conducted on a healthy volunteer who are regularly ingested 20 mL of blood to simulate GI bleeding. The capsules were able to detect simulated GI bleeding compared with baseline readings, and the sensor signal changes were correlated with increased gastric blood concentration within 10 min ($R^2 = 0.9016$) [216].

In addition, Nemiroski et al. have developed a wireless battery-powered capsule to detect GI bleeding [214], detecting active bleeding by intravenous injection of fluorescein. More specifically, fluorescein serves as a surrogate biomarker to detect GI bleeding as it emits light when it encounters blood. It has been shown that fluorescein as low as 20 nM can be detected by the capsules. But the spectral properties of fluorescein change with the variation in pH, so the measurement may differ after the patient drink the water. Thus, a better understanding of fluorescein properties is needed in the future work. The development of synthetic biology has successfully created a series of chemiluminescent bacteria. Heme, a biomarker of intestinal inflammation, is associated with bleeding and thiosulfate [56]. Optical detection of heme is achieved by precipitating luminescent bacteria in smart capsules. The capsule was successfully used to detect bleeding in a reliable porcine model. In addition to optically sensing samples, there are also studies using electrochemical sensing capsules to detect intestinal fluid. But the response of these sensors will change with time, which may be related to the adsorption of organic materials on the electrode surface [217].

5. Challenges and perspectives

5.1. Diagnostic smart capsules

To help clinicians for more reliable diagnosis, an increasing number of sensors and imaging techniques have been integrated into smart capsules. They help to detect biomarkers in clinical medicine as well as accurately collect location images with higher resolution within the GI tract, contributing to the subsequent treatment including surgery or targeted therapy [218]. However, it is challenging to fabricate chemical sensors that can adapt to the environment of the digestive tract. Moreover, there may be no sensor that can work alone and meet all clinical diagnostic sensitivities and specificities. Hence, the next step is to seek for the best sensor combination according to different clinical diagnosis. Such multimodal capsules will have higher requirements for sensors, integrated electronic systems, miniaturized structures, and power consumption. The large amount of data output from these capsules also have an impact on the communication bandwidth [219–221]. In summary, these techniques still have limitations, and further development and clinical trials are required for the enhanced efficacy and accuracy.

5.2. Therapeutic smart capsules

In order to enhance the therapeutic effects of smart capsules, some technical issues, such as anchoring effects and capsule positioning, need to be addressed. The anchoring effect allows the capsule to attach to a specific location in the digestive tract. In this process, the capsule can withstand the peristalsis and other forces of the GI tract. In addition, efforts should be made to reduce the transit time and fixation time in the GI tract, so as to improve the reliability of capsule therapy. Also, the anchoring effect allow the delivery of a specific amount of drug or non-drug treatment to the target within the desired time, thereby improving the effectiveness of the treatment. There have been a variety of studies to achieve anchoring effects by microneedles [222], magnets [223] and biomimetic adhesives [224]. Nevertheless, it is necessary to confirm the targeted delivery of therapeutics with larger sample size. Prior anchoring physician must investigate fully a suitable anchoring position, referring to capsule localization. Localization is the technique by which a smart capsule discriminates its orientation and position based on an internal or external frame of reference. The internal reference system includes anatomical landmarks and pathological sites. For the external reference system, telemetry antenna is commonly used in clinical practice [36]. Despite that a series of therapeutic smart capsules have been reported, these capsules are not yet widely used in clinical treatment due to some technical challenges. For instance, it is more difficult to accurately locate in the deformable GI tract, hence, both internal or external frames of reference may be required. Another challenge for smart capsules-based drug delivery is the load storage capacity. Due to the space occupied by various electronic devices and material components, most smart capsules now have a storage capacity between 0.3 and 1 mL. There will be implications for vehicle doses with the increased electronic and mechanical integration. It is promising to overcome these challenges by combining with highly potent drugs, micro-electromechanical systems or microfluidics. The third is the high costs and low sustainability, greatly limiting the scale of the production. As the capsules are single-use and can be excreted through excretion, and the resulting increase in e-waste may present environmental challenges. This can be avoided by using biodegradable biomaterials [225], but more studies are needed to prove the feasibility of the use of adopting these materials in the fabrication of electronic components [226,227].

5.3. Commercial feasibility

Given that PillCam capsule endoscopes, a commonly used product in clinic, cost approximately US $500 [228], it is best to set the cost of smart capsules in this price range. But relatively speaking, the cost of multifunctional capsule robots may be higher. Furthermore, there is currently no strong evidence that multifunctional capsules are superior to conventional capsule endoscopes in terms of cost performance. On this account, capsule robots are not yet able to replace existing technological approaches, but we can believe commercially successful capsule robots will be developed as technology advances and costs decrease. It is worth noting that commercially available healthcare systems are anticipated, which enable the individuals to test at home and the doctors to monitor simultaneously via internet connectivity. With support of doctors and nutritionists, these systems can be widely applied in personalized medicine, overcoming the limitations of current endoscopy.

6. Conclusion

Nowadays, increasing evidence have indicated the complexity of intestinal environment including intestinal microbiome and intestinal gas, as well as highlight its significance in the occurrence and development of diseases [229]. Different from traditional endoscopy, capsule robots are very important for early intervention of diseases. Generally, they contain electronic or mechanical components and can pass through the GI tract for diagnostic, therapeutic, sampling or surgical purposes. These capsules are easily ingested and move smoothly through the entire digestive tract with minimal discomfort. The use of innovative sensors and output devices on smart capsules facilitates our exploration of the etiology of GI diseases. In addition, these devices could enable locally targeted or systemic delivery of therapeutic agents. These microcapsules enable easier sampling in the digestive tract compared to more invasive methods.

While these devices have great potential, the development of smart capsules is still in its beginning stages. There have not been sufficient in vivo tests carried out to clearly illustrate the diagnostic or therapeutic efficacy of these techniques. One capsule cannot perform all functions, and each capsule needs to be optimized to perform its own particular function or to work together to ensure the health of the patient. As the procedures for making such devices increase, the high cost may lead to widespread clinical use. To discover their potential for clinical applications, multiple technical challenges, such as localization, navigation, and intelligence, must be overcome in the future. We expect that this review will aid to build a more effective multidisciplinary community to address the challenges describe above. More importantly, we hope the efforts from different specialists could push forward the whole chain of capsule robot-based biomedical application toward being a versatile, reliable, and industrially applicable technique. We also believe that these techniques may open up the door for the smart and reliable monitoring, diagnosis, and treatment of intestinal diseases, potentially improving the public's health.

CRediT authorship contribution statement

Xiangyu Wei: Writing – original draft. **Peipei Xi:** Writing – review & editing. **Minjie Chen:** Writing – review & editing. **Ya Wen:** Supervision. **Hao Wu:** Writing – review & editing. **Li Wang:** Writing – review & editing. **Yujuan Zhu:** Supervision, Conceptualization. **Yile Ren:** Supervision, Conceptualization. **Zhifeng Gu:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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