analytical chemistry

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Tutorial

Ingestible Smart Capsules for Chemical Sensing in the Gut

The development of novel ingestible sensors can aid physicians and patients in obtaining precise data on the health status of the gut at a local level. This in turn can facilitate earlier and more accurate disease diagnosis, improve the delivery of point-of-care medicine, and allow monitoring of the gastrointestinal (GI) tract status. This Tutorial overviews characteristics of the gut for inexpert readers and reviews emerging chemical sensing technologies for the GI tract from an analytical chemistry viewpoint.

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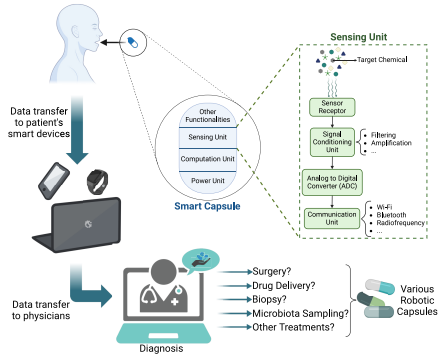

The gastrointestinal (GI) tract of the human body is home to a diverse range of chemical and biological markers that can be used to study and diagnose a human's overall health, stress levels, mood, and behavioral traits[1] through the nonlinear and bidirectional interactions in the gut−brain axis.[2] Furthermore, diseases associated with the digestive system are highly prevalent and account for a considerable number of human fatalities. Consequently, developing monitoring and sensing devices for a wide range of parameters in different gut segments can help medical experts to better assess the patients' health, diagnose related diseases, and plan adequate treatment. Leveraging recent advancements in biotechnology, biomedical engineering, chemistry, material science, electrical engineering, and robotics, new devices are emerging that enable *in situ* sensing of important biomarkers in the gut in a noninvasive manner.

- **Why is it important to study the gut?** In 2019 alone, approximately 8 million deaths worldwide were attributed to digestive diseases, not to mention a further 277 million disability-adjusted life-years (DALYs) lost from these conditions.[3,4] The decline in the global proportion of deaths caused by digestive diseases relative to all causes of diseases from 1990 to 2019 has been marginal, while the prevalence of digestive diseases has increased by around 5%.[4] Consequently, medical experts worldwide must prioritise the diagnosis and prognosis of digestive diseases.

  The GI tract comprises a series of sequential segments: mouth, esophagus, stomach, small intestine, and large intestine. Each segment has distinct responsibilities in the body and any malfunction or physiological variation in any of these segments may result in severe health disorders. Although the gut is mostly associated with food digestion, studies have shown that the gut affects humans' overall health in a number of different ways. For instance, abnormal makeup in the populations of gut microorganisms affect human metabolism,[5] the immune system,[6] and even mood, behavior, and mental health.[7] Therefore, studying patients' gut physiology and the microorganisms contained with the GI tract can give specialists a wide range of fundamental information leading to more accurate early diagnosis of gut-related disorders. The most common gastrointestinal diseases are irritable bowel syndrome (IBS),[8] small intestinal bacterial overgrowth (SIBO),[9] gastroesophageal reflux disease (GERD),[10] and inflammatory bowel disease (IBD),[11] and the best way for early diagnosis of such disorders is regular screening of the GI system.
- **What are the traditional gut screening methods and their limits?** The gut can be physically accessed using analysis of stool samples, tube endoscopy, and colonoscopy. Stool tests have limitations, such as lack of spatial and temporal information,[12] the high dependency on laboratory diagnosis following sample collec-

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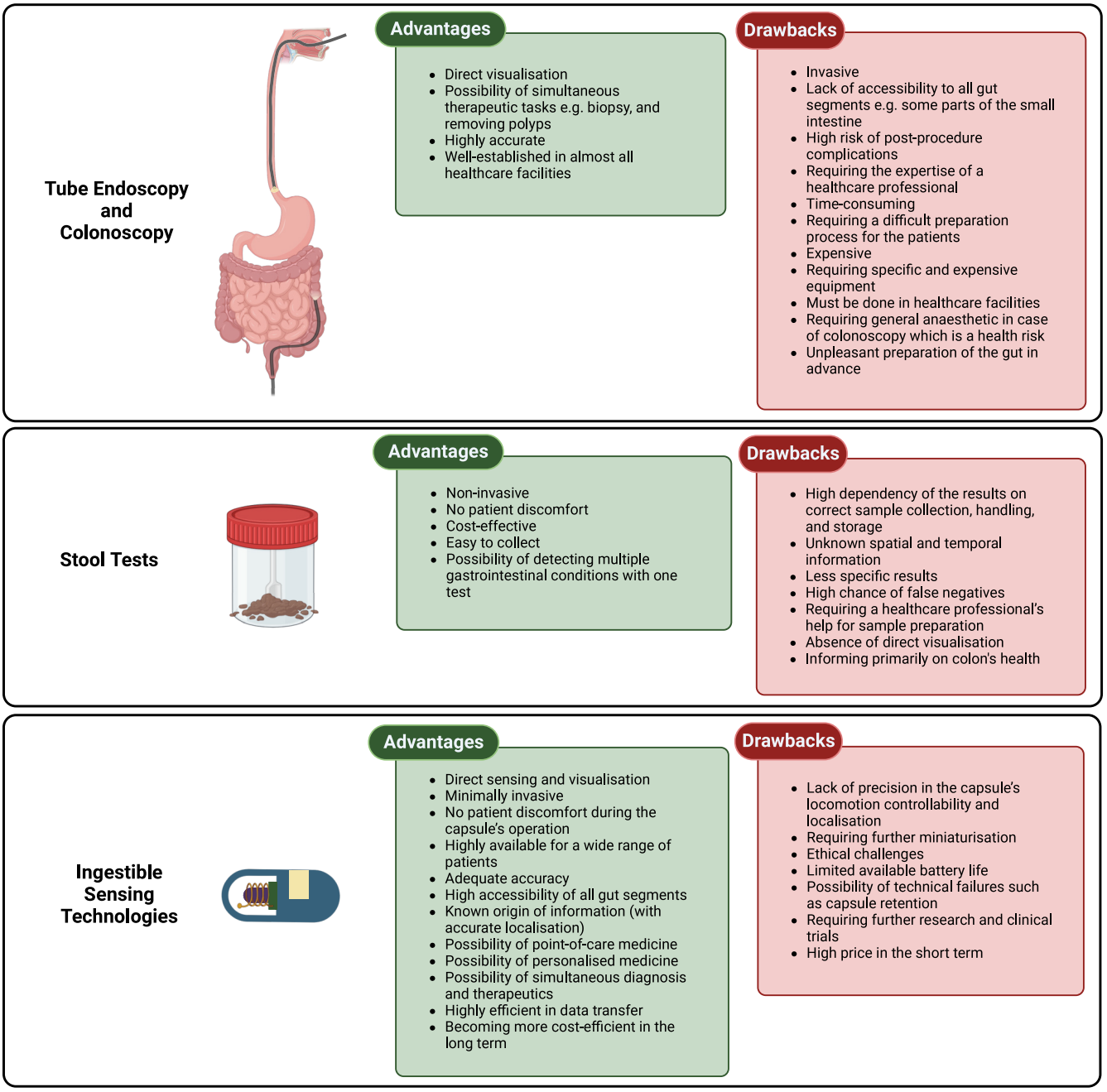

Figure 1. Advantages and disadvantages of tube endoscopy and colonoscopy, stool tests, and ingestible sensing technologies for the GI tract.[12−23] (Created in BioRender. Ghorbani Siavashani, A. (2024) BioRender.com/j97s413.)

tion, handling and storage,[13] and information primarily focused on colon health. Tube endoscopy and colonoscopy are invasive and cause discomfort or require general anesthesia, which results in patient reluctance to undertake regular screening. Furthermore, the human GI tract consists of several distinct segments which are not easily accessible via these conventional screening methods. For instance, some parts of the small intestine cannot be observed via tube endoscopy or colonoscopy.[14] As a result, much effort has been and is focused on developing new GI screening and sensing methods.

- **Why should we focus on ingestible sensors?** Smart capsules are small scale smart devices capable of performing specific tasks in the human gastrointestinal tract after being swallowed. Each smart capsule consists of multiple components depending on its application. These components include, but are not limited to, a power source, microelectronics and a computation unit, sensing units, actuators, and biocompatible packaging. Ingestible GI sensors specifically sense targeted biomarkers in the GI tract. Therefore, they have the potential to add a new dimension to the diagnosis and monitoring of disorders that can manifest themselves via changes in the biomarkers of the gut. They are complementary to the current traditional tube endoscopy and colonoscopy and stool tests. Figure 1 shows the advantages and disadvantages of each of the main

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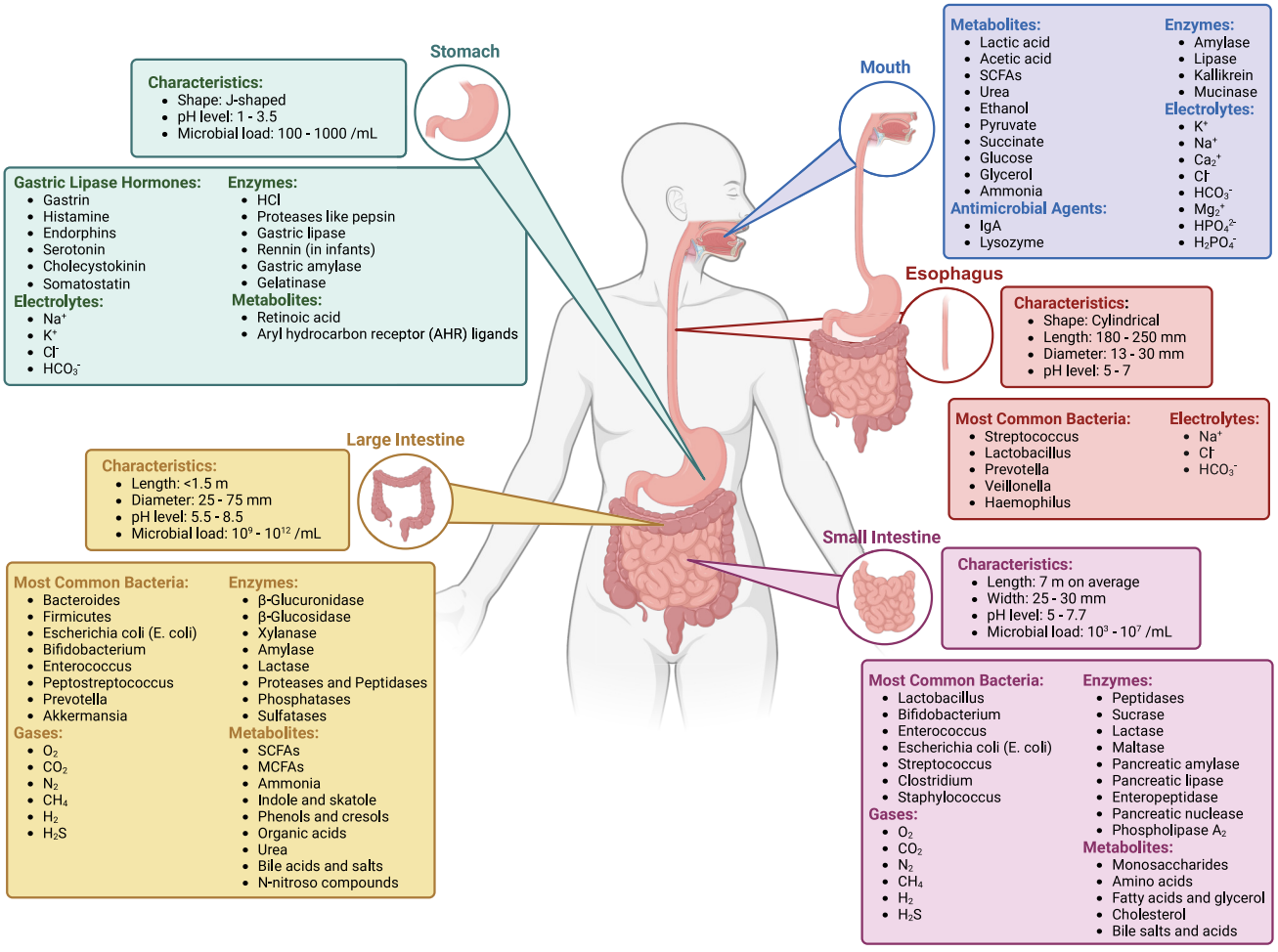

Figure 2. Distinct segments of the digestive tract and their characteristics and chemical contents.[12,27,45,60,61] (Created in BioRender. Ghorbani Siavashani, A. (2024) BioRender.com/p78m550.)

gastrointestinal sensing and screening methods. By comparing these methods, it is evident that ingestible capsule sensors are futuristically the superior diagnosis tools for the gut as not only are they minimally invasive, they also have the potential for simultaneous diagnosis and therapeutic applications. Despite significant progress observed over the past two decades in this field, substantial challenges persist. However, with continued advancements in analytical chemistry, engineering and material science, the future of ingestible sensors continues to hold great promise.

In this Tutorial, the anatomy and physiology of each segment of the gastrointestinal tract are briefly described, related diseases are introduced, and chemical and physiological parameters linked to the diseases which can be sensed are presented. The state-of-the-art GI sensing technologies are reviewed and the existing challenges and future directions in this field are discussed.

THE GI TRACT ANATOMY AND PHYSIOLOGY

The gastrointestinal tract of the human body is mainly responsible for food digestion. The process of food digestion starts in the mouth, continues in the esophagus, stomach, and small intestine, and finally finishes in the colon. Albeit being capable of directly absorbing some nutrients, the role of the mouth in digestion is mainly restricted to cutting or masticating food into smaller pieces, introducing digestive enzymes to it and making it ready for the next stages of the digestive process.[24] The esophagus rapidly transfers the food from the mouth to the stomach, where a major part of digestion occurs over an extended period of time.[25] It is then transferred to the small intestine where the majority of nutrient absorption occurs.[26] The colon is responsible for the final stages of digestion with the help of the gut microbiome, and the absorption of short-chain fatty acids and water from the food, turning it into feces.[27] Any abnormality in the GI tract can lead to serious health conditions. For example, inflammation in the stomach lining which can be treated in most cases if diagnosed early, can cause ulceration and even cancer if left untreated.[28] Hence, it is vital to monitor each segment of the gut. **Table S1** in the Supporting Information presents a comprehensive list of the most common related diseases to each gut segment. There are copious biomarkers in the GI tract that can help physicians gain the necessary information for adequate GI health assessments of patients. However, to develop suitable ingestible sensors, one must first be familiar with the anatomy and physiology of all segments of the gastrointestinal tract as well as the diseases associated with each gut segment.[29] As a result, the important aspects of the gut segments from the perspective of ingestible sensors are described in the remainder of this section. Moreover, Figure 2

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depicts the characteristics and chemical contents of the different gut segments.

Mouth. The role of the mouth in digestion is to prepare food for absorption by the body. This is done by two means: mastication (chewing) and saliva secretion.[24] Mastication physically reduces the particle size of the food and saliva contains various electrolytes and enzymes such as salivary amylase that begin to break down food. Moreover, mucus, white blood cells, epithelial cells and glycoproteins exist in the oral cavity.

- **What are the related diseases?** As the gateway of the body, the mouth can be infected by bacteria and yeast species leading to diseases like Caries and Candidiasis (thrush).[30] Other associated conditions include mouth ulcers, tongue lesions,[31] bad breath (halitosis),[32] dental disease, and cold sores.
- **What can be sensed?** Although the concentration of biomarkers is low in the oral cavity, there are still several biomarkers that can be sensed in this part of the gut. For instance, ulcers, cold sores, lacerations, and inflammation can be visually detected. Moreover, saliva contains various biomarkers that not only enable DNA recognition but also can be monitored for early diagnosis of certain diseases, e.g., diabetes, infections, gastroesophageal disorders, hormonal disorders, allergies, and multiple cancers.[33] The exhaled breath in the mouth also contains gases and volatile compounds that can be associated with various disorders.[34] However, ingestible sensors are not required for sensing biomarkers in the mouth due to the easy access to the oral cavity.

Esophagus. The esophagus is the connection between the mouth and the stomach. It has a cylindrical shape with a length of 180−250 mm and a diameter of 13−30 mm.[35] Food transfer in the esophagus lasts only a few seconds, and nutrient absorption in this segment of the gut is insignificant.

- **What are the related diseases?** One of the most common diseases in the esophagus is gastroesophageal reflux disease (GERD) where the esophagus is damaged by stomach acid.[36] Furthermore, boluses of food transit through the esophagus within a couple of seconds via peristaltic movements of the muscles. Any motility disorder in the esophageal muscles results in abnormally slow or fast transfer of the food. For instance, a common dysmotility of the muscles is called achalasia in which there is insignificant peristalsis in the lower esophageal sphincter.[37] Moreover, diseases such as eosinophilic esophagitis (EoE) cause inflammation in the esophagus disrupting its functionality.[38] Infections and cancer are also among the common diseases in the esophagus.
- **What can be sensed?** Abnormalities in the esophagus such as inflammations and lacerations can be visually detected via tube or tethered endoscopy. The mucosal integrity of the esophagus can also be visually investigated. Moreover, assessing esophageal muscle peristaltic movements and pH levels in the esophagus can present valuable pathological information.

Stomach. The stomach is the most acidic part of the GI tract. Positioned in front of the pancreas and under the diaphragm, the stomach is where food can reside for several hours, allowing initial digestion and enabling the body to control food release to the small intestine for further digestion. The residence time of food in the stomach is highly variable, ranging from 3 to 6 h depending on the type of food and other parameters such as individual metabolism and overall digestive tract health.[39] Moreover, the low pH in the stomach (refer to Figure 2 for numerical values), caused by the secretion of hydrochloric acid (HCl), creates a suitable environment for the chemical digestion of food as well as a reduction in the bacteria load of the consumed food. Furthermore, stomach muscle contraction helps physically break down food particles to accelerate the digestion process.[40] The acidic environment of the stomach can damage the stomach tissues. However, this is inhibited by the mucus layer lining the stomach's inner wall.[41] This mucus also enhances the movement of food particles through the stomach to the small intestine.

- **What are the related diseases?** Bacterial infections such as *Helicobacter pylori* can be common in the stomach.[42] These infections can lead to more severe diseases such as gastric ulcers and eventually stomach cancer. In addition, diseases associated with inflammation in the stomach, e.g., gastritis, can be created from a variety of infection types. Furthermore, motility disorders are prevalent. These diseases consist of gastroparesis (delayed emptying of the stomach) and dumping syndrome (rapid emptying of the stomach).[43] Finally, HCl is vital for enzyme activity and food digestion, so a reduced or absence of secretion leads to conditions called hypochlorhydria and achlorhydria, respectively.[44]
- **What can be sensed?** As food stays in the stomach for several hours for digestion, the acidity of the stomach environment, enzyme levels, gastric emptying time, and mucosal integrity should be carefully monitored for food maldigestion avoidance. In addition, concentrations of metabolites, electrolytes, and bacteria can also be investigated.[27]

Small Intestine. The small intestine is the longest segment of the gastrointestinal tract. It is approximately 7 m long and about 25−30 mm wide and is responsible for the majority of the digestion and absorption of nutrients and maintaining water and electrolyte balance. The small intestine consists of three distinct sections: duodenum, jejunum, and ileum. The innermost wall of all the small intestine segments is the mucosa which is responsible for nutrient and water absorption. The mucosa in all segments of the small intestine is prominently covered with villi and microvilli which leads to an increase in the surface-to-volume ratio and helps to optimize nutrient absorption.[26] The duodenum is the closest segment to the stomach, and its role consists of neutralizing the pH of the digesta leaving the stomach by releasing alkaline bile, by hormone secretion, and also by releasing digestive enzymes. The middle segment of the small intestine is the jejunum, in which specific nutrients such as amino acids, fatty acids, and small chain sugars are absorbed. Lastly, the ileum is the longest segment of the small intestine, connecting it to the colon. Fatty acids, fats, amino acids, and monosaccharides like glucose and fructose along with other nutrients are absorbed in this section. Moreover, the distal section of the small intestine is home to a rich microbial population that consumes nondigested food (fiber) and produces different gases.[45]

- **What are the related diseases?** The distal section of the small intestine is home to a diverse range of bacteria. However, the bacterial population in the small intestine compared to the large intestine is much smaller because the early parts of the small intestine are relatively acidic

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and not suitable for live microorganisms. Moreover, the mucus in the small intestine that expedites food transfer through the intestine hinders bacterial colonisation. Abnormal growth in the bacterial population of the small intestine can lead to SIBO conditions.[46] In addition, a number of diseases are associated with nutrient malabsorption and maldigestion in the small intestine. People with celiac disease are incapable of digesting gluten.[47] Lactose intolerance is another example in which lactose, the major carbohydrate in dairy, cannot be adequately digested,[48] and Crohn's disease is an abnormal inflammation in the last segment of the small intestine, (the ileum).[49] Finally, the movement of food particles in the small intestine depends on the peristaltic movements of the muscles, and a number of motility disorders can occur. For example, postoperative ileus[50] which usually happens after surgery is a disease associated with delayed food transfer. Peptic ulcers and various cancers also exist in different parts of the small intestine.[51]

- **What can be sensed?** There are many visual markers for disorders that can be identified in the small intestine. The quality of the mucus layer, inflammation, and ulceration can be visually observed. Additionally, the density and balance of gases, electrolytes, metabolites, and microbiota (bacteria, fungi, and archaea) are among other important biomarkers of the small intestine.[27]

Large Intestine. The large intestine or colon has multiple sequential sections: cecum, ascending, transverse, descending and sigmoid colon, rectum, and anus. The colon can be up to 1.5 m long, and its diameter varies between 25 and 75 mm in different sections.[52] The colon is responsible for the final stages of digestion by absorbing water and any remaining food nutrients before excreting the indigestible residue and the remnant microbiota from the rectum. The large intestine contains a massive population of microbiota accounting for 0.2 to over 1.5 kg.[27,53] Any dietary alteration leads to a change in the composition or diversity of the colon's microbiota, which can affect human health, mood, and behavior. Furthermore, there is a high concentration of gases in the colon.[45,54,55]

- **What are the related diseases?** Inflammation and infection can lead to various diseases in the large intestine. These diseases include pathogenic bacterial infections, diverticulitis, and IBD, such as Crohn's disease and ulcerative colitis. Certain infections and psychological conditions can lead to IBS which is accompanied by abdominal pain, bloating, and gas.[56] Furthermore, motility disorders, such as pseudo-obstruction in the colon, can lead to improper fecal excretion.[57] Additionally, abnormal softening or hardening of tissues (sclerosis) can also be seen in the colon.[58] Other diseases in the colon include a range from poor nutrient absorption issues to cancer.
- **What can be sensed?** As the majority of microbiota and gas populations reside in the colon, gas sensing and microbiota sampling are now being actively researched.[12,54] Traces of various gases such as oxygen, nitrogen, carbon dioxide, hydrogen, methane, and hydrogen sulfide can be seen throughout the gut. The concentrations of these gases are heavily affected by the composition of the luminal microbiota as well as the ingested dietary compounds. Accurate gas profiling in the gut can lead to precise diagnosis of several common gastrointestinal diseases including IBD and colorectal cancer.[45] Moreover, monitoring short and medium-fatty chain acids and certain nutrients can also give helpful information on the digestion process.[59] Furthermore, the quality of the mucus layer, inflammation, ulceration, and blood traces can be visually detected.

SENSING TECHNOLOGIES FOR CHEMICAL BIOMARKERS IN THE GI TRACT

Sensors are instruments capable of detecting specific analytes in their environment. The detectable substance can vary depending on the sensor's type and functionality. For instance, chemical sensing refers to sensors that are able to detect chemical compounds. Subsequently, sensors can convert what they detect to a measurable and usually digital signal that may need further processing for accurate sensing of the analyte. Interfacing with microcontrollers or other electronic devices as well as calibration are also required for the proper sensor functionality. The overall process of sensing units is schematically described in the graphical abstract at the beginning of the Tutorial.

The first ever reported ingestible sensor, named Endoradiosonde, was developed in 1957 by Mackay and Katchalsky at the Karolinska Institute in Sweden. With a length of 33 mm, this smart capsule was able to measure temperature, pressure, and pH along the GI tract and transmit the data via radio telemetry.[62] Ever since then, much effort has been put into the area of developing ingestible sensors for purposes ranging from capturing images of the gastrointestinal tract to detecting a wide array of physiological and chemical parameters.[12,16,17,27,63]

The commercialization of ingestible sensors of the gut began with putting cameras in ingestible capsules. Such ingestible and wireless capsule endoscopes were first developed by Given Imaging Ltd. in 2000.[64] Since then, advancements in robotics, electronics, material science, and analytical chemistry have propelled the evolution of capsule endoscopy. Other examples of ingestible sensors with cameras have been developed by companies such as Intromedic Co., Olympus Inc., and Chongqing Jinshan Science and Technology Group.[27] Yet, while visual data is valuable, exploring the physiology and chemistry of the gut has emerged as a significant target for diagnosing gut diseases and assessing overall gut health. Consequently, numerous commercial ingestible sensors and laboratory prototypes have been created for a wide range of purposes, including measuring and monitoring physiological and chemical parameters in the gut, each with its own merits and limitations. Chemical sensing technologies in the GI tract can be categorized into four groups: pH sensors, gas sensors, hemorrhage sensors and other chemical sensors.

pH Sensing in the Gut. As depicted in Figure 2, the acidity levels vary markedly throughout the gut. As a result, pH can be a useful parameter for measuring an ingestible sensor's approximate location as well as food's transit time in each segment of the gut.[65,66] However, using pH alone, the exact location of the sensor within each segment of the gut cannot be known, and extra information is required for precise localization. Furthermore, pH sensing can help diagnose certain diseases like GERD[67] and *H. pylori* infection.[68]

The first commercialized ingestible pH sensors were attached to catheters, e.g., Medtronic's Bravo capsule,[69,70]

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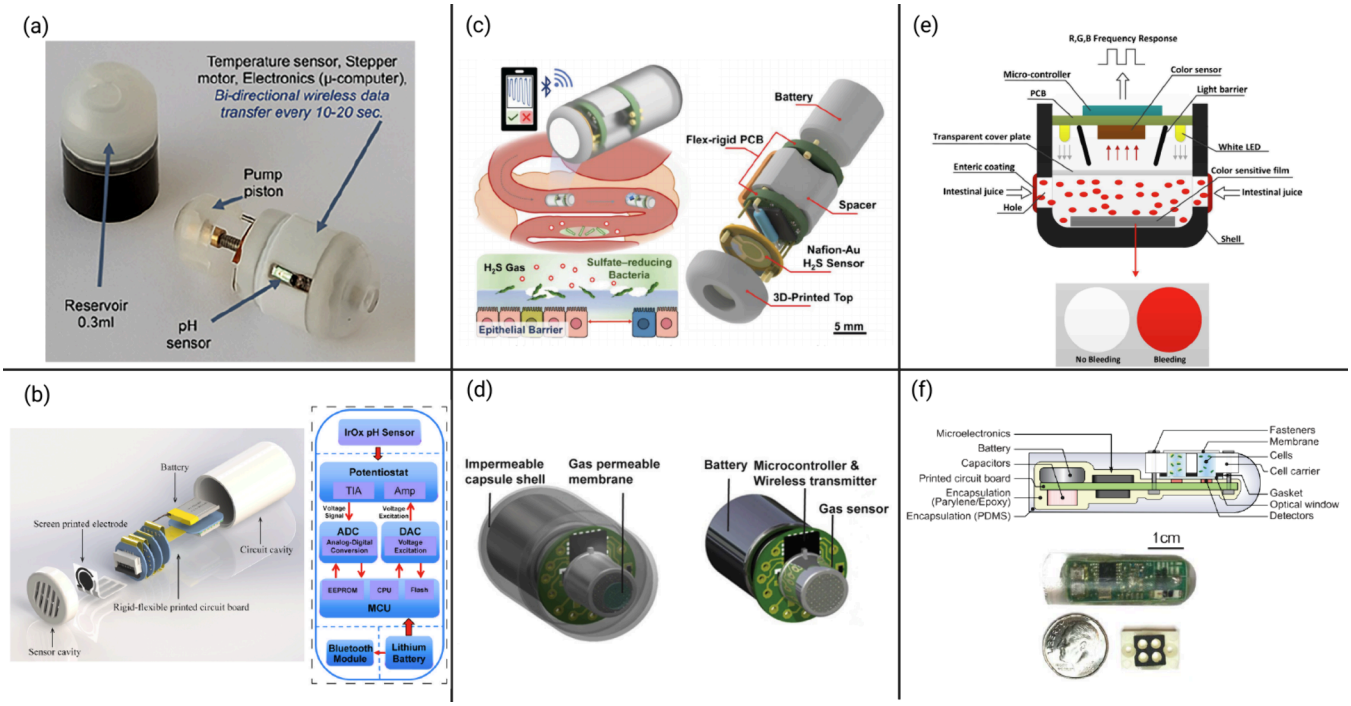

Figure 3. Examples of pH, gas, and hemorrhage sensing technologies. (a) Commercially available IntelliCap for pH sensing in the gut. Reproduced from Dieter Becker et al.,[75] licensed under CC BY. (b) A solid state iridium oxide (IrOx)-based pH sensor embedded in an ingestible and wireless capsule system. Reprinted with permission from ref 76. Copyright 2021 Elsevier. (c) Conceptual overview of the wireless H_2S gas-sensing capsule platform. Reproduced from Stine, J., et al.,[83] licensed under CC BY-NC 4.0. (d) A swallowable gas-sensing capsule capable of measuring methane, carbon dioxide, and hydrogen in the gut. Reprinted with permission from ref 80. Copyright 2016 Elsevier. (e) A schematic figure of a hemorrhage sensor based on HSL color recognition for automated detection of intestinal bleeding. Reproduced from Qiao, P., et al.,[85] licensed under CC BY 4.0. (f) Cross section, electrical system diagram, and front- and back-side photos of an ingestible microbioelectronic device capable of detecting heme. Reprinted with permission from ref 85. Copyright 2018 AAAS.

Jinshan Group's alpHaONE capsule,[71] and the Heidelberg pH capsule system.[72] Moreover, many wireless pH sensing capsules, such as Medtronic's SmartPill (manufacturing discontinued[73]) and Medimetrics' IntelliCap,[74,75] were released commercially for pH monitoring in the gut. Aside from commercialized ingestible pH sensors, there are several laboratory prototypes incorporating pH sensors. Most common pH sensors incorporated in ingestible capsules are chemical or electrochemical sensors, solid-state sensors, and optical sensors. One example of this is a solid-state pH sensor based on iridium oxide incorporated in an ingestible capsule which made real-time measurement of the pH in beagle dogs feasible.[76] Thanks to advancements in analytical chemistry within this research field, numerous *in vitro* tested prototypes have been developed which have demonstrated promising results. A pH sensor based on electrodeposited polyaniline (PANI) on a carbon-coated conductive thread was incorporated in an autonomous adequately sized wireless pill to develop a pH profile along all GI segments.[77] An optical sensor comprising red cabbage-extracted anthocyanins, chitin nanopaper, and various chemical nanoparticles, such as iron oxide, has been recently developed and tested *in vitro* to detect *H. pylori* bacteria as well as for pH monitoring.[78]

Gas Sensing in the Gut. The GI tract normally contains gases, such as hydrogen, carbon dioxide, methane, nitric oxide, hydrogen sulfide, and oxygen. Gases in the gut are either byproducts of chemical and enzymatic activities in the gut (e.g., oxygen and carbon dioxide), caused by air ingestion through swallowing, or produced by bacteria fermentation in the small and large intestine (e.g., hydrogen, carbon dioxide, methane, and sulfide-containing gases).[27] Detecting different gases can be extremely helpful in diagnosing gut-related diseases. Presently, this is achieved via a standard breath test, which lacks precision, or a fecal fermentation test, predominantly focusing on data from the colon.[79] Detecting gases directly at their source in the gut significantly enhances accuracy. Hence, gas-sensing ingestible sensors are gaining more and more attention from researchers. While gas sensing in the gut is a relatively new field of research, notable progress has been made. For example, accurate measurements of methane, carbon dioxide, and hydrogen in pig models have been achieved via a swallowable gas-sensing capsule.[80] In addition, an ingestible capsule capable of measuring hydrogen, carbon dioxide, and oxygen using thermal conductivity and semiconductors has been successfully evaluated by Atmo Biosciences, on human subjects in clinical trials.[54] More specifically, this capsule's performance with human subjects has been compared against a standard breath test, proving its safety and reliability in measuring hydrogen concentration in the gut.[81] This gas-sensing capsule is being commercialized currently.[82] In a more recent study, a Nafion-Au sensor-integrated capsule has been developed that measures hydrogen sulfide which is extremely helpful in diagnosing inflammatory diseases in the gut.[83]

Hemorrhage Sensing in the Gut. Hemorrhage or bleeding in the gut should be detected as quickly as possible because it can increase the risk of infection as well as indicating multiple gastrointestinal diseases such as peptic ulcers, IBD, and colorectal cancer.[63] Gut bleeding is detected conventionally via radionuclide scanning, digital subtraction angiography,

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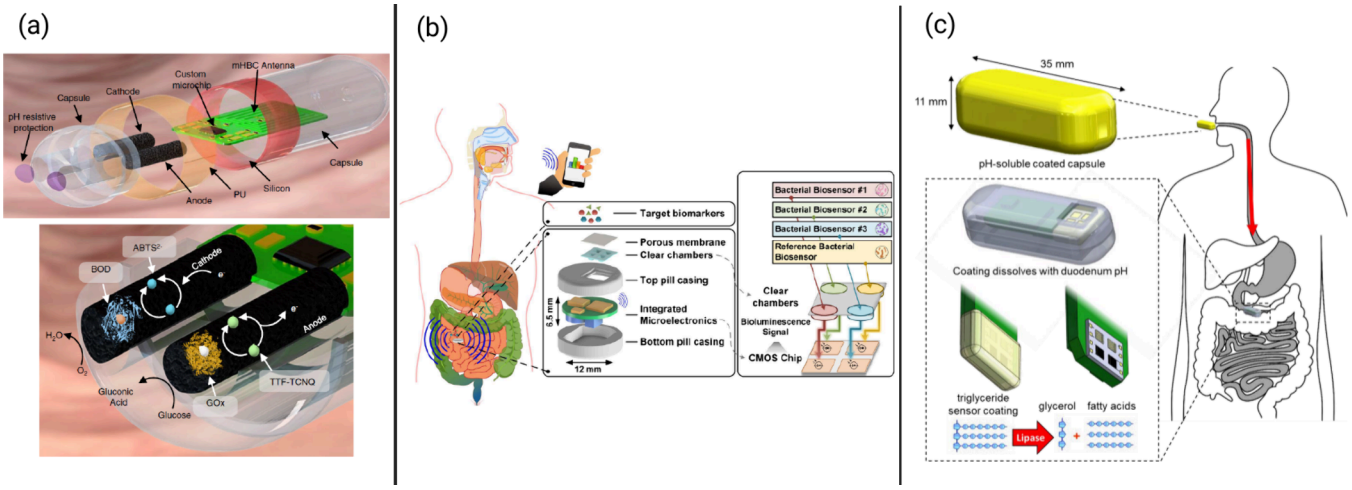

Figure 4. Other chemical sensing technologies for the gut. (a) The schematic layout of an electrochemical sensor embedded in an ingestible capsule for monitoring intestinal glucose dynamics. Reproduced from De la Paz, E., et al.,[100] licensed under CC BY 4.0. (b) A nitrate-responsive genetic circuit which can potentially act as an optical sensor within a smart capsule in the gut. Reprinted with permission from ref 111. Copyright 2020 Elsevier. (c) A capsule system for measuring lipase in the gut with capacitive sensors. Reproduced with permission from ref 116. Copyright 2020 the Royal Society of Chemistry.

and endoscopy, which are all invasive, lack accuracy, especially if the source of bleeding is in the small intestine, and rely greatly on physicians' judgments. Consequently, ingestible capsules have the potential to detect gut bleeding which can be carried out using various methods. Most images extracted from capsule endoscopy can be monitored by a trained physician for visual detection. However, this is not an optimal method, and ideally the capsule should be able to detect bleeding automatically. Optical sensors based on ratiometric intensity measurements of the characteristic optical properties of blood[84] and the hue-saturation-light (HSL) color space of blood[85] have been successfully tested *ex vivo*. Additionally, microbiological-based sensors can be used for this purpose. Genetically engineered bacteria have been used in the framework of an ingestible microbioelectronic device (IMBED) to detect heme, a crucial component of hemoglobin in blood, *in vivo*.[86] Moreover, the integration of chemistry with electronics shows potential in this area. In a recent study, a chemiluminescence sensor has been implemented in a smart capsule for detecting hemorrhage in the stomach. This sensor contains a luminol reagent that produces blue light in the presence of blood. However, additional miniaturization is necessary for the capsule developed in this study to achieve successful *in vivo* implementation.[87] A major advantage of smart capsules is that they have the potential to detect bleeding and treat it, simultaneously. An intelligent intestinal bleeding diagnosis and treatment capsule (IBDTC) system has been recently reported.[88] This ingestible capsule automatically detects blood by means of color recognition and is capable of targeted drug delivery for treating hemorrhage. *In vivo* experiments of this capsule are yet to be performed. Examples of ingestible pH, gas, and bleeding sensing technologies are depicted in Figure 3.

Other Chemical Sensing in the Gut. The human GI tract contains multiple biological chemosensory systems that can send neurological signals to relevant organs in the presence of fatty acids, tastes, and bile acids. The gut's hormone secretion, appetite, immune responses, and motility are all regulated via the gut's chemosensing activities.[89−91] The gut's chemosensory system can be utilized in designing biological chemosensors that can be incorporated into smart capsules. Furthermore, there are an abundance of chemical compounds such as enzymes, electrolytes, metabolites, and reactive molecules in different sections of the gut. These chemicals are currently mostly sensed via electrochemical sensing methods,[92] like voltammetry, optical methods,[92] and capacitive sensors.[14] Figure 4 depicts a few examples of these methods.

Widely used in analytical chemistry, voltammetry measures the current resulting from electrochemical processes that are created by applying potential to an electrode.[93] This method is suitable for ingestible sensors as it can be fabricated on a small scale.[60] The electrochemical behavior of gastric fluids has been successfully characterized using this method both *in vitro* and *in vivo*.[94,95] Moreover, recent advances in developing edible electrochemical sensors that are food-based have added to the existing potential this method has for gut chemical sensing.[96,97] Other examples of gut chemicals measured via electrochemical sensing include protein kinase A (PKA) activity assay[98] and glucose.[99,100]

Most optical methods used for chemical sensing in the gut are based on luminescence.[101] The first group of such methods are fluorescence-based, e.g., measurement of live bacterial count in the gut with the aim of early diagnosis of small intestinal bacterial overgrowth disease[102,103] or enantioselective sensing of D-alanine (D-Ala), a gastric metabolite, in simulated gastric fluid samples.[104] Second, genetically encoded circuits can be incorporated into bacteria to develop luminescence-based sensors for gut chemosensing. For example, genetically engineered bacteria have been successfully used to detect biochemicals indicative of inflammation in the gut,[105] such as tetrathionate,[106−108] nitric acid,[109] nitric oxide,[110] and nitrate.[111] Genetically engineered bacteria for gut sensing have been comprehensively reviewed previously.[112,113] Third, the successful use of silicon-based aptamers in *ex vivo* detection of a target protein in GI fluid has been reported, which can form a basis for capsule implementation in future work.[114]

Capacitive sensors function by measuring the changes in electric capacitance caused by the alteration in a specific substance's concentration.[115] Capacitive sensing technologies

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have been used for *ex vivo* gut chemical sensing. For instance, they have been used for *in situ* measurement of lipase, an enzyme responsible for the digestion of dietary fats (lipids), in the duodenum[116,117] and for *in vitro* measurement of hydrogen peroxide, which is a reactive oxygen species.[118]

Table 1 lists the most common sensor types used for chemical sensing in the gut. It should be noted that sensing is not the only functionality of ingestible capsules. Researchers have worked on robotic capsules capable of performing various therapeutic tasks, such as targeted drug delivery,[119,120] biopsy (tissue sampling),[121−123] microbiota sampling,[124−126] surgery,[127−129] obesity treatment,[130−132] and other interventional functionalities.[19] These robotic capsules have been thoroughly reviewed.[12,16,17,133−135] However, sensing adequate gut-related parameters can be critical to the correct performance of the robotic capsules in each therapeutic task. It should be noted that although remarkable capsule designs have been proposed for the above-mentioned applications,[12,16,17,133−135] none have currently replaced other conventional methods globally from the commercial perspective. However, this will likely change in the future due to the significant potential ingestible sensors have.

Table 1. Gut Chemical Sensing with Smart Capsules and Their Most Common Sensor Types

Biomarker Source	Examples	Sensor Types
pH	–	Solid-state sensors,[76] electrochemical sensors,[77] optical sensors[78]
Gases	H_2, CO_2, H_2S, O_2	Semiconducting sensors,[54,80,81] electrochemical sensors[83]
Hemorrhage	Heme, hemoglobin	Optical sensors[84−88]
Enzymes	Protein kinase A (PKA), lipase	Electrochemical sensors,[98] capacitive sensors[116,117]
Metabolites	D-Alanine, tetrathionate, glucose	Electrochemical sensors,[99,100] optical sensors[104,106−108]
Bacteria	Bacterial counts	Optical sensors[102,103]
ROS	O_2^-, OH	Capacitive sensors[118]
RNS	NO, NO_2^-	Optical sensors[110]

CHALLENGES AND FUTURE DIRECTIONS

Smart capsules have a number of advantages compared with traditional gut-related diagnosis and therapeutic methods. The absence of patient discomfort during the operation of the sensing capsule, the increased accessibility for a broader spectrum of patients, the enhanced precision in assessments, the ability to access all segments of the gut, and the suitability for point-of-care medicine all contribute to the promising future of smart capsules in gastrointestinal health assessment.

However, there are still considerable limitations to the current status of smart capsules. For example, the lack of precision in localization as well as locomotion control for some robotic capsule designs prevents targeted drug delivery and sampling with high accuracy. Moreover, fabrication issues such as the need for further miniaturization and limited available battery life, currently hinder the mass production of this technology. Energy-harvesting systems[136,137] and wireless power transfer via inductive coupling[138−143] have been fruitfully studied to resolve the limited battery life issue. Nonetheless, smart capsule technology still faces significant challenges in this regard and more clinical research is required to be able to transfer the designs in the research facilities into an accessible technology. Personal data ethics-related challenges[19] and technical failures such as capsule inability to move through the GI tract and in some cases, capsule retention, [151] are also among other shortcomings of the current therapeutic robotic capsules. Furthermore, *in vivo* chemical sensing in an intraluminal environment which is highly anaerobic and humid exhibits substantial challenges. For instance, the inhomogeneous nature of the GI tract, with its varying pH levels, enzyme activity, and mechanical movements,[144] creates a complex environment for consistent sensor operation. Cross-sensitivity, where sensors respond to multiple analytes, poses another challenge by reducing the specificity of measurements.[145] Biofouling, where biological materials accumulate on sensor surfaces, further complicates accurate sensing.[146] Additionally, the need for biocompatible and functional packaging[147] of ingestible sensors presents an extra challenge. All these existing issues contribute to the current limited standardization of ingestible chemical sensing technologies in clinical guidelines.

An ongoing multidisciplinary approach is crucial to advancing this research field and addressing the current limitations of ingestible sensors for the gut. For example, the integration of analytical chemistry-based sensing methods with the smart capsule technologies is expected to revolutionize the diagnosis and drug delivery via ingestible smart capsules. The advances in robotics and material science will help to make these ingestible sensors smarter and more automated, as well as safer and more environmentally friendly. In the future, we envision the outpatient clinical use of smart capsule tailored with specific sensors to meet any routine GI screening need. The information from the capsule could be sent to our smartphones as well as to our health system and doctors. Ideally, if any other monitoring or therapeutic task is required, the treatment could be as simple as taking a different smart capsule. These ingestible devices would alleviate a significant burden from healthcare systems by simplifying and automating routine gastrointestinal screening, enabling easier access to gut-related therapeutics and paving the way for personalized medicine. As a result, ingestible sensing technologies for the gastrointestinal tract will play a pivotal role in shaping the future of GI medicine. However, further research and clinical advancements will be essential for the full potential of this field to be realized.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.analchem.4c04683.

A concise but comprehensive list of diseases in the digestive tract, the affected sections of the GI tract, and a short description of each disease (PDF)

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A.G.S. wrote the manuscript. A.G.S., M.R., and E.A. conceptualized the manuscript. A.G.S., M.R., J.T.S., D.T., E.D., J.S., R.G., and E.A. critically revised the manuscript. A.G.S., M.R., J.T.S., D.T., E.D., J.S., R.G., and E.A. approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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