Article:
Barducci, L, Norton, J orcid.org/0000-0001-9981-5936, Sarker, S et al. (4 more authors) (2020) Fundamentals of the gut for capsule engineers. Progress in Biomedical Engineering, 2 (4). 042002. ISSN 2516-1091

https://doi.org/10.1088/2516-1091/abab4c

Fundamentals of the Gut for Capsule Engineers

Lavinia Barducci*, Joseph C. Norton, Sunandita Sarker, Sayeed Mohammed, Ryan Jones, Pietro Valdastri, Benjamin S. Terry

Lavinia Barducci*, M.Sc in Robotics and Automation Engineering, STORM Lab UK, Institute of Robotics, School of Electronic and Electrical Engineering, University of Leeds, Woodhouse Lane, Leeds, UK. LS2 9JT. ellb@leeds.ac.uk

Joseph C. Norton, PhD Mechanical Engineering, STORM Lab UK, Institute of Robotics, School of Electronic and Electrical Engineering, University of Leeds, Woodhouse Lane, Leeds, UK. LS2 9JT. J.C.Norton@leeds.ac.uk

Sunandita Sarker, PhD candidate, Mechanical engineering and applied mechanics, Terry Research Lab, Department of Mechanical and Materials Engineering, University of Nebraska Lincoln, sunandita.sarker@huskers.unl.edu, Postal address: 360 Walter Scott Engineering Center, University of Nebraska, Lincoln, Nebraska, 68588, USA

Sayeed Mohammed, B.Sc in Mechanical Engineering, Mechanical Engineering, University of Nebraska Lincoln, sayeed.mohammed@huskers.unl.edu, Grand Valley State University, 49504

Ryan Jones, BEng, VP, Corporate Development, Progenity Inc., 5230 S. State Road, Ann Arbor, MI 48108, ryan.jones@progenity.com.

Pietro Valdastri, PhD Electronic Engineering, STORM Lab UK, Institute of Robotics, School of Electronic and Electrical Engineering, University of Leeds, Woodhouse Lane, Leeds, UK. LS2 9JT, P.Valdastri@leeds.ac.uk

Benjamin S. Terry, Ph.D., Department of Mechanical and Materials Engineering, University of Nebraska Lincoln, bterry2@unl.edu, Postal address: UNL, 317.4B Nebraska Hall, Lincoln, Nebraska, 68588, USA, No financial arrangements or conflict of interest.

*Corresponding author

Abstract

The gastrointestinal (GI) tract is a complex environment comprised of the mouth, esophagus, stomach, small and large intestines, rectum and anus, which all cooperate to form the complete working GI system. Access to the GI using endoscopy has been augmented over the past several decades by swallowable diagnostic electromechanical devices, such as pill cameras. Research continues today and into the foreseeable future on new and more capable miniature devices for the purposes of systemic drug delivery, therapy, tissue biopsy, microbiome sampling, and a host of other novel ground-breaking applications. The purpose of this review is to provide engineers in this field a comprehensive reference manual of the GI environment and its complex physical, biological, and chemical characteristics so they can more quickly understand the constraints and challenges associated with developing devices for the GI space. To accomplish this, the work reviews and summarizes a broad spectrum of literature covering the main anatomical and physiological properties of the GI tract that are pertinent to successful development and operation of an electromechanical device. Each organ in the GI is discussed in this context, including the main mechanisms of digestion, chemical and mechanical processes that could impact devices, and GI motor behavior and resultant forces that may be experienced by objects as they move through the environment of the gut.

Keywords: digestive system, capsule endoscospy, gastrointestinal anatomy, gastrointestinal properties.

Introduction

The digestive system is made up of the gastrointestinal (GI) tract, liver, pancreas and gallbladder. The GI tract is a large, hollow, tubular organ system that extends from the mouth to the anus. It is a complex environment that comprises the mouth, esophagus, stomach, small and large intestines. These organs have specific functions and they cooperate in order to form a complete working GI tract. The coordinated contractions of muscles, along with the release of hormones and enzymes facilitate the digestion of food, the absorption of nutrients, and the elimination of waste so that the body can carry out its functions of metabolism, growth, and repair (1).

The inspection of the GI tract is fundamental for the early detection and diagnosis of GI diseases, of which there are many. In the last decade, miniaturized robots for gastrointestinal inspection have been investigated with the aim of developing innovative, more sophisticated, and minimally invasive technologies to access this part of the body. Despite the progress achieved so far, the need for innovation is still present and stronger than ever due to the combination of a growing disease prevalence and the harsh, difficult-to-access environment of the gut.

According to the National Institutes of Health (NIH), more than 34 million Americans are suffering from diseases of the digestive system, 20 million of which have chronic disorders (2). Digestive diseases encompass more than 40 acute, chronic, recurrent, or functional disorders. The most common digestive diseases are irritable bowel syndrome (IBS), inflammable bowel disease (IBD) (i.e., Crohn's disease (CD) and Ulcerative colitis (UC)), celiac disease, diverticulosis, and acid reflux. It is estimated that 8% of the U.S. population have chronic digestive diseases, 6% have acute episodes of digestive diseases, and 43% have intermittent digestive disorders. Only 43% are

unaffected. As a group, digestive diseases account for 8%-9% of total U.S. mortality, of which 60% is due to malignant neoplasms and 40% due to non-malignant causes (3).

According to International Agency for Research on Cancer (4), cancer is the leading cause of death in the 21st century. The statistics present some important data about the spreading of cancer worldwide in 2018. Regarding colorectal cancer, the percentage of new cases was 6.1% and the percentage of deaths was 5.8%, while rectal cancer had a 3.9% incidence of new cases and 3.2% of deaths. Considering the stomach, the percentages were 5.7% and 8.2% of new cases and the number of deaths, respectively, while esophagus cancer counted 3.2% of new cases and 5.3% of deaths in 2018. The International Agency for Research on Cancer (4) also reports statistics about the estimated number of new cases (incidence rate, IR) and estimated number of deaths (mortality rate, MR) of each type of gastrointestinal cancer in different countries in 2018. These are reported in Table 1, where the estimated number has been rounded to the nearest one hundred for the sake of clarity.

Table 1: Incidence and mortality of gastrointestinal cancer in 2018 (4).

	North America		**Europe**		**Asia**		**Africa**	
	IR	**MR**	**IR**	**MR**	**IR**	**MR**	**IR**	**MR**
Colon	179 800	64 100	499 700	242 500	957 900	461 400	61 800	40 000
Stomach	29 300	13 400	133 300	102 200	769 700	584 400	31 100	28 700
Esophagus	22 700	18 200	53 000	45 100	444 600	397 700	28 500	27 700

Different procedures are used for examining the GI tract: capsule endoscopies are used to inspect the entire GI tract because of their small size, while other types of endoscopic procedures

are used to inspect a particular organ. For example, gastroscopy is employed for the inspection of the esophagus and stomach, colonoscopy for the colon, sigmoidoscopy for the sigmoid colon and small bowel enteroscopy is used for the examination of the small intestine. The purposes of the devices are typically for both diagnosis and therapy, however, some lack therapeutic capabilities because of device size constraints. Despite the ubiquity of these procedures, they can be stressful and painful for the patient (1,5) due largely to the construction of the endoscopes, which consist of semi-rigid tubes that are pushed and twisted through the body of the patient by the physician, causing discomfort as the instrument deforms the sensitive GI tract.

According to the Center for Disease Control and Prevention (6), only 66% of Americans comply with screening guidelines, and therefore, an estimated 23 million people in the United States avoid these procedures. This lack of intervention increases the risk of developing a cancer (7). Introducing a less–invasive procedure could increase patient compliance to the endoscopic procedure by reducing procedural discomfort (and the associated anxiety), risk of adverse events, and the potential need for sedation (8,9). This has motivated many to develop new technologies to replace the standard flexible endoscope (10).

To develop new and more sophisticated devices, capsule engineers need to understand this complex environment. Therefore, the purpose of this paper is to provide a summary of the critical information regarding the anatomy, histology, physiology, mechanics, and chemistry of the gut as it pertains to medical device engineers. Providing a comprehensive primer of the GI tract can help engineers in this field to speed the development of innovative technologies.

The paper will describe the characteristics of the esophagus, stomach, small and large intestines – the regions of primary interest to engineers that develop capsule endoscopes and similar devices. Given that capsules are typically designed to travel the GI tract, the liver, pancreas

and gallbladder are not the main focus of our research but are described briefly since their enzymatic secretions help with the digestion of the food. Although, focus is placed on providing a comprehensive description of the healthy GI tract, the most common ways disease impacts its properties and function is also discussed briefly.

The paper is organized as follows. In Section 1 we briefly summarize the current non–invasive technologies and we discuss their main limitations. In Section 2 and Section 3, we first provide a general description of the anatomy and histology of the GI tract. In Section 4 and 5 respectively, we present the chemical and mechanical properties of the GI tract, and in Section 6 we investigate the motor behavior of the gut. In Section 7 we summarize all the forces that act on an untethered device in order to understand the capsule dynamics within the GI tract. Section 8 considers the possible physiological alterations to the GI tract from the most common and severe digestive diseases. Finally, in Section 9 we summarize the work, and we briefly discuss open challenges about medical robotic devices; more detailed discussions related to each topic of the paper are included throughout the article.

1. Current non–invasive endoscopic technologies

Conventional flexible endoscopy (e.g. colonoscopy) has been widely used to inspect the entire GI tract. However, despite the widespread adoption of endoscopes, issues around their invasiveness lead to limitation in their ability to diagnose and treat GI disease. Therefore, the demand for new, less invasive and more sophisticated procedures has increased. In the last decades, completely minimally invasive methods have become commercially available for diagnosing the GI tract (11) and researchers have studied appealing non-invasive alternatives to

155 traditional diagnostic techniques. The new technologies are briefly discussed in the following,
156 highlighting the major advantage and disadvantages of each technique.

157 Virtual endoscopy is a technique based on computed tomography (CT) or on magnetic
158 resonance imaging (MRI), and is used to inspect the GI tract (10,12,13). Despite it being
159 completely noninvasive and almost comparable to standard endoscopy in terms of diagnostic yield,
160 its main drawbacks are an inability to biopsy, impossibility to deliver in-situ therapy and limited
161 accuracy, particularly with small or very flat lesions.

162 Similarly, in the last 20 years, swallowable capsule endoscopes (CEs) have been developed
163 and commercialized to facilitate minimally invasive exploration of hard–to–reach regions of the
164 GI tract. To date, the most prevalent clinically used CEs worldwide are reported in Table 2 (10,14–
165 16).

166 Table 2: GI capsules in clinical use today (10,14–16).

	PillCam ESO3	**PillCam COLON 2**	**Endo Capsule**	**Capso Cam**	**Miro Cam**	**OMOM**	**Navi Cam**
Purpose	Esophageal imaging	Colon imaging	Small bowel imaging	Small bowel imaging	Small bowel imaging and navigation	Small bowel imaging	Stomach imaging and navigation

Dimension (mm)	26.0 × 11.0	31.5 × 11.6	26.0 × 11.0	31.0 × 11.3	24.0 × 11.0	27.9 × 13.0	28.0 × 12.0
Weight (g)	3.4	2.9	3.8	4.0	3.4	6.0	5.0
Frame rate	Adaptive Frame Rate (AFR): 2–6 images per second.	Adaptive Frame Rate (AFR): 2–6 images per second.	2 fps	4 high resolution camera: maximum of 20 frame per second (5 fps per camera)	3 fps	0.5–2 fps	2 fps
Angle of view	160°	160°	160°	360°	170°	140°	140°
Illumination	2 x 6 white LEDs	2 x 6 white LEDs	6 white LEDs	LEDs	6 white LEDs	6 white LEDs	LED
Recording time	30 min	10 h	9 h	15 h	11 h	7–9 h	8 h

Regulatory approval	Yes	Yes	Yes	No	Yes	Yes	Yes

Despite encouraging results obtained by current CE technologies, their main limitation lies in the fact that their sensitivity (the proportion of positive cases correctly identified) is not yet comparable to the sensitivity of the standard endoscopes. For example, the sensitivity of the PillCam, the most advanced capsule developed, is still less than 90%, while standard endoscopes can reach in excess of 95% sensitivity (10,17). Other important limitations are (10,14):

- Passive locomotion: the physician is not able to control the pose of the capsule (or orientation of the camera) which leads to inadequate inspection of the organ in some cases.
- Minor interventions (e.g. Biopsy collection) are the main advantage of standard endoscopes and are not currently possible with commercial capsule endoscopes. This is largely due to a lack of device position control, limited on-board space (or payload), and the absence of a stable platform.
- No means of insufflation: the inability to distend collapsed tissue may lead to reduced visibility, particularly in the cavernous environments of the stomach and colon.

Several solutions have been developed for enabling active locomotion capsules and thus overcome the main limitations of passive locomotion. Fundamentally, two major solutions have been exploited to address the active locomotion problem: onboard locomotion (generally this is referred as a mechanical approach) and an external locomotion technique (whereby forces and

torques are transmitted to the capsule from outside the body, generally via magnetic fields) (10,18–20).

In the last decades, a new category of flexible endoscopes has been explored by researchers. These advanced flexible endoscopes, or soft-tethered capsules, are designed to preserve the major functionalities of conventional endoscopy that are familiar to physicians. At the same time, the flexibility of the endoscope body permits it to conform to the shape of the bowel, reducing tissue stretching and the associated discomfort for the patient (21,22).

Advanced flexible endoscopes have the advantage of overcoming the main limitations related to the CEs (23–25). The advantage of an actuation mechanism, such as the magnetic field, is the ability to pull and steer the endoscope inside the body and so completely inspect the organ. Moreover, the tether (with cables and lumen) allows the physician to use the endoscope both as a diagnostic or therapeutic instrument, and with all the typical auxiliary functions such as insufflation, irrigation and suction. However, the presence of the tether (although soft and flexible) creates friction in the environment and makes locomotion challenging (5). Other research has addressed the problem of drag on the soft tether by modifying the locomotion strategy (26).

Aside from standard diagnostic routine, capsule robots are being used as a platform for versatile applications such as drug delivery, biosensing, and active diagnostics and intervention (27). Researchers have measured pH, core body temperature, oxygenation, electric conductivity and, also, blood inside the intestine via capsule robots. These have extended the boundary towards intervention and therapeutic manipulation (28). Clip deployment for stopping bleeding, systemic and topical drug delivery, biopsy tissue collection and microultrasound imaging are some other applications being investigate. Even though interventional capsules are mostly at

the proof-of-concept stage of development, in-vivo animal studies, and benchtop experiment results are encouraging (29–32).

Despite the advance in current technologies the need for novel designs and innovative strategies to enhance the physician's ability to diagnose and treat GI diseases is still present. Miniaturized, capsule-like devices with advanced locomotion techniques and sensing technologies have been at the forefront in achieving this. For this reason, an adequate knowledge of the entire GI tract is mandatory for all the engineers in the medical and endoscopic field.

2. Anatomy and physiology of the GI

The human GI tract is a series of multilayered, tubular organs which extend from the oral cavity through the esophagus, stomach, small and large intestines and terminating at the anus (Figure 1). The GI tract has a total average length of 795 ± 128 cm, it decreases with age and is significantly longer in men (33). The GI tract is one of the most dynamic organ systems (34); muscular contractions, along with the release of hormones and enzymes, enable the digestion process (35,36). In this section, the anatomy of the GI tract will be discussed, focusing on the esophagus, stomach, small and large intestine and the mesentery. The liver, gallbladder and pancreas, are not the focus of this work but will be discussed briefly for the sake of clarity.

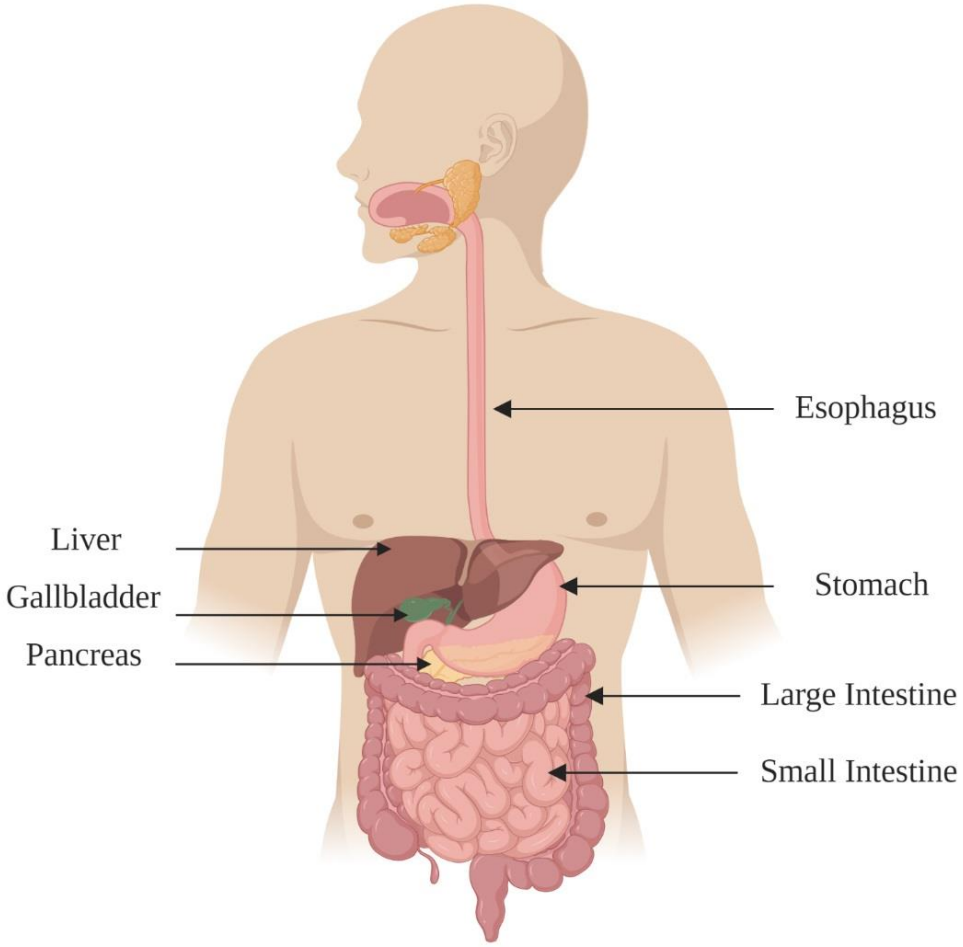

Figure 1: Anatomy of the digestive system, showing all organs.

2.1 Esophagus

The esophagus is an 18 to 25 cm long muscular tube that connects the oral cavity to the stomach (36–38). It is a dynamic tube which serves to propel food, via active peristaltic contractions, toward the stomach for continued digestion and absorption of nutrients. When empty, the esophagus is a collapsed lumen, but it can distend to approximately 2 – 3 cm to propel a food bolus (38,39) .

In general, the ease of passage of a body through the esophagus and into the stomach depends on the length and diameter of the ingested object. Bodies longer than 60 mm and with a

diameter more than 25 mm make the passage difficult and objects can become lodged; in these cases an esophagogastroscopy is necessary (40–42). However, the current swallowable capsules approved by the FDA present smaller values for diameter and length and give a more ideal target size. These values are presented in Table 2.

The passage of food through the esophagus is regulated by two principal high-pressure valves: the upper and the lower sphincter. These two valves are located at the beginning and at the end of the esophagus, but there is not a clear anatomic demarcation that defines the two zones (39). The upper esophageal sphincter controls the movement of food from the pharynx into the esophagus, while the lower esophageal sphincter (also called gastroesophageal or cardiac sphincter) lets food pass into the stomach; the latter can also contract to prevent stomach acids from backing up into the esophagus (39).

The normal esophagus has a wall thickness of 4.7 mm (range 4.44 – 4.95 mm) during contraction and 2.11 mm (range 2.00 – 2.23 mm) when the esophagus is dilated. The thickness of the esophageal wall depends also on the sex and age of the patient (43,44).

2.2 Stomach

The stomach is a dilated and J-shaped organ that rests on the left of the central region of the abdomen at the level of the first lumbar vertebra (35). The main functions of the stomach are the temporary storage, mixing, breakdown, and digestion of food (45).

As shown in Figure 2, the stomach has two openings (esophageal and the duodenal) and five major regions, including: the cardia, fundus, body, antrum and the pylorus (38). The cardia is the point where the esophagus connects to the stomach. The fundus is dome shaped and locates inferior to the diaphragm, above and to the left of the cardia. Below the fundus is the ‘body’, the main part of the stomach. The pylorus is a funnel-shaped valve which connects the stomach to the

duodenum (45). The pylorus has two parts: the pyloric antrum, which is connected to the body of the stomach, and the pyloric canal, which is connected to the duodenum. The smooth muscle pyloric sphincter is located at this latter point of connection and controls stomach emptying. The pyloric diameter is controlled by the contractions of the sphincter and this determines the flow resistance (46).

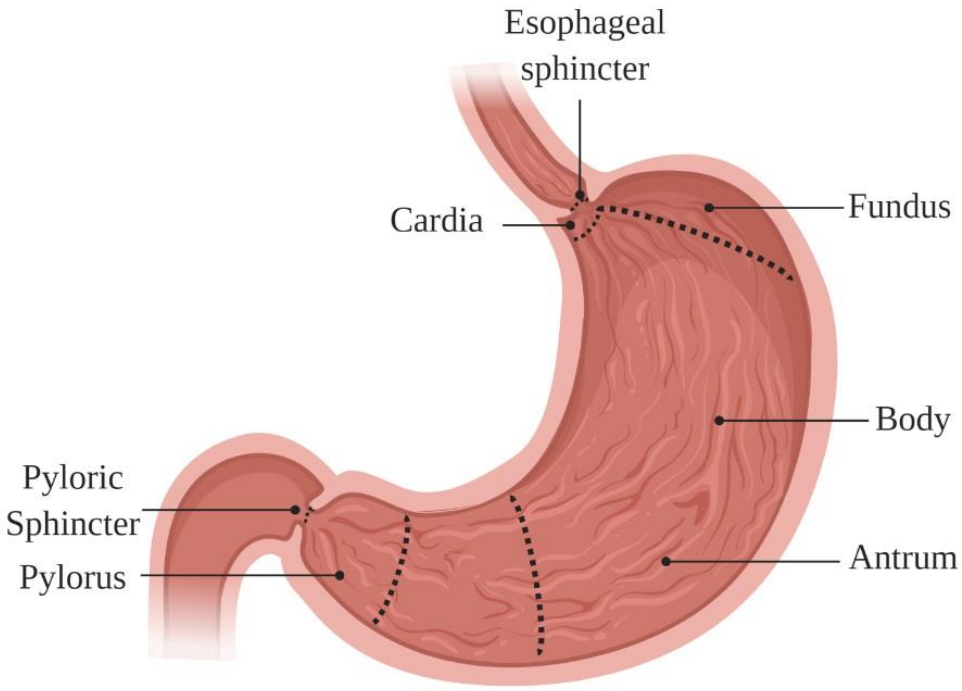

Figure 2: The functional regions of the stomach.

Each region of the stomach has a different function: the fundus can relax to accept large volumes of collected digestive gases; the gastric chief cell in the stomach secretes pepsinogen and hydrochloric acid, produced by gastric parietal cells, to break-down and mix the food and liquid; the pylorus is responsible for mucus, protein-digesting enzyme (pepsin) secretion, and handles the emptying of the stomach through the duodenum (45).

Stomach emptying is an essential factor that capsule engineers should consider. Although the stomach volume is only 0.8 L when empty, it can expand up to 1.5 – 2 L for a typical male and up to 0.9 – 1.5 L for women and children. The emptying rate is affected by meal composition and consistency (47), body position (48), smoking (49) and gender (50). On average, women have a slower gastric emptying compared to men (74 minutes vs. 63 minutes) and smokers have a significantly faster gastric emptying compared to non-smokers (56 minutes vs. 67 minutes). Age, body mass and alcohol consumption habits are not known to affect gastric emptying times (51).

The mean thickness of the gastric wall was measured as 4 mm when distended and 5 – 10 mm during fasting (52). In studies done by Huh et al. (53) endoscopic ultrasound was used to acquire in–vivo data on wall thickness of the stomach when it was waterfilled (i.e., distended). The measurements were taken in a group of ten and five measurements in different locations were obtained resulting in a mean thickness of 3.92 ± 0.16 mm.

2.3 Small intestine

The small intestine (or small bowel) is a crucial component of the digestive system and is responsible for the absorption of important nutrients (38). Here, most of the chemical and mechanical digestion is carried out (54). It is a long, approximately 6 m, continuous, and highly tortuous tube running from the pylorus of the stomach to the ileocecal valve where it meets the large intestine. There are three main sections to the small intestine: duodenum, jejunum and ileum (38). These sections, described below, are shown in Figure 3.

The duodenum is the first section of the small intestine and forms a 'C' shape around the head of the pancreas. Its main function is to neutralize the acidic gastric contents (called 'chyme') and to initiate further digestion (55). Brunner's glands in the submucosa secrete an alkaline mucus which neutralizes the chyme and protects the surface of the duodenum. It is about 25 cm in length

294 in adults, beginning at the pylorus and ending at the ligament of Treitz, which is the junction
295 between the duodenum and jejunum (duodenojejunal flexure) (55,56) (Figure 3). The duodenum
296 is largely retroperitoneal and has an anatomic relationship with the pancreas. It has four sections:
297 bulb, descending, transverse, and ascending. The bulb section begins at the pylorus, which is
298 approximately 5 cm in length for adults and demarcated by the pre-pyloric vein. The descending
299 section is retroperitoneal and is approximately 10 cm in length. The transverse section is also
300 retroperitoneal and is bordered by the pancreas superiorly and the hepatic flexure of
301 the colon anteriorly. The fourth portion of the duodenum courses in a cephalad direction to the left
302 of the aorta and inferior to the neck of the pancreas. The duodenum contains a slender band of
303 skeletal muscle and a fibromuscular band of smooth muscle in the horizontal and ascending parts.
304 These can contract to widen the angle of the duodenojejunal flexure and allow movement of
305 intestinal contents (56).

306 The jejunum and ileum lie within the peritoneal cavity and are the most tortuous parts of
307 the small intestine. Together, they are approximately 4 – 6 meters long comprising approximately
308 40% jejunum and 60% ileum (55) with no clear junction between the two sections. Generally, the
309 jejunum has a thicker mucosal lining (i.e., thicker wall), larger diameters, redder color, and less
310 fatty mesentery than the ileum. Moreover, the mesentery of the jejunum is attached to the left of
311 the aorta while the mesentery of the ileum is attached to the right (57). The mucosa of these
312 sections is highly folded. These folds, called plicae circulares, slow the passage of the partly
313 digested food and increase the surface area (by 1.6 times) to aid absorption of nutrients (37). The
314 majority of plicae extends transversely around the small intestine for about 50% – 65% of its
315 circumference while some of these form complete circles and others are spiral. The largest folds

are about 1 cm in depth at their broadest part and usually the large and small folds alternate with each other (57).

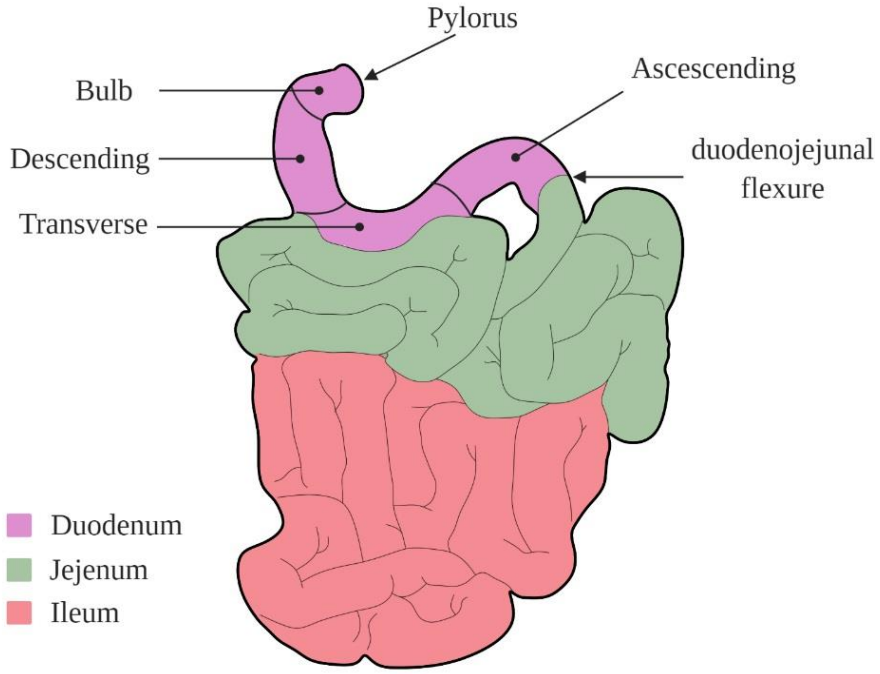

Figure 3: Small intestine.

The total length of the small intestine varies with age (58). Mean length at 1 year is 3.8 m, at 5 years is 4.5 m, at 10 years is 5 m, and at 20 years is 5.75 m (37,58,59). It becomes longer when the bowel is empty and after death; thus, use of cadaveric tissue for capsule development should consider this fact. It is approximately 15 mm in diameter after 35 weeks of gestational age (60) and 25 mm in adults (37,61).

The mean values of small intestine parameters are outlined in Table 3 (61). There is no statistical difference in these bowel parameters over an age range of 17 – 73 or between men and women, while some pathological effects can cause changes in these parameters (61).

Table 3 : Mean and standard deviation values for the small intestine parameters (diameter, wall thickness, fold number per 2.5 cm, fold thickness) (37,61).

	Diameter (mm)	**Wall thickness (mm)**	**Fold number per 2.5 cm**	**Fold thickness (mm)**	**Interfold distance (mm)**
Duodenum	24.8 ± 4.5	1.5 ± 0.6	4.5 ± 0.7	2.1 ± 0.6	4.7 ± 1.54
Jejunum	24.5 ± 4.2	1.5 ± 0.5	4.6 ± 0.8	2.2 ± 0.7	4.59 ± 3.56
Proximal ileum	19.5 ± 3.6	1.6 ± 0.4	1.8 ± 0.6	1.9 ± 0.5	16.8 ± 6.75
Distal ileum	18.9 ± 4.2	1.4 ± 0.5	1.6 ± 0.5	1.8 ± 0.5	18.5 ± 7.18
Terminal ileum	18.7 ± 3.6	1.5 ± 0.4	1.5 ± 0.6	1.8 ± 0.4	17.91 ± 7.86

As shown in Table 3, the duodenum and jejunum have similar bowel diameter, wall thickness, fold number, and fold thickness. The interfold distance gradually decreases in size to its smallest measurements in the terminal ileum. The bowel diameter, wall thickness, interfold distance and fold thickness of the proximal ileum, distal ileum and terminal ileum are similar. The parameters used in Table 3 are illustrated in Figure 4.

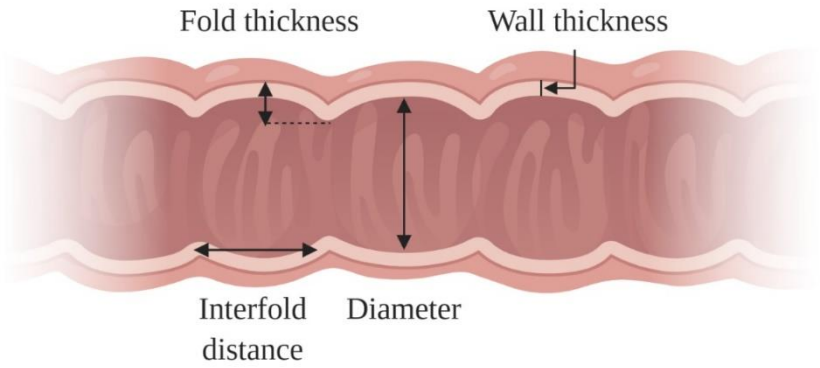

Figure 4: Main parameters of small intestine.

2.4 Large intestine

The large intestine (colon or large bowel) is the last part of the GI tract and, like the small intestine, is tubular and tortuous in shape. It is shorter at approximately 1.5 m, has more pronounced folds and a larger diameter. By the time digestive products reach the large intestine, almost all the nutritionally useful products have been removed; therefore, it does not play a major role in absorption of nutrients. Instead, the main purpose of the large intestine is the absorption of water (approximately 1.5 L of water arrive in the colon each day), Na^+ and other minerals, and the collection and excretion of waste (stool) via the anus (38,62).

The large intestine has six sections, as shown in Figure 5: the cecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum. The first and middle parts of the colon are called the proximal colon. This includes the cecum, the ascending colon, and the transverse colon. The last part of the colon is called the distal colon and includes the descending colon, the sigmoid colon, rectum and anus. The ascending colon, descending colon, and rectum are retroperitoneal and fixed in location while the other two sections are intraperitoneal and therefore mobile (38,62).

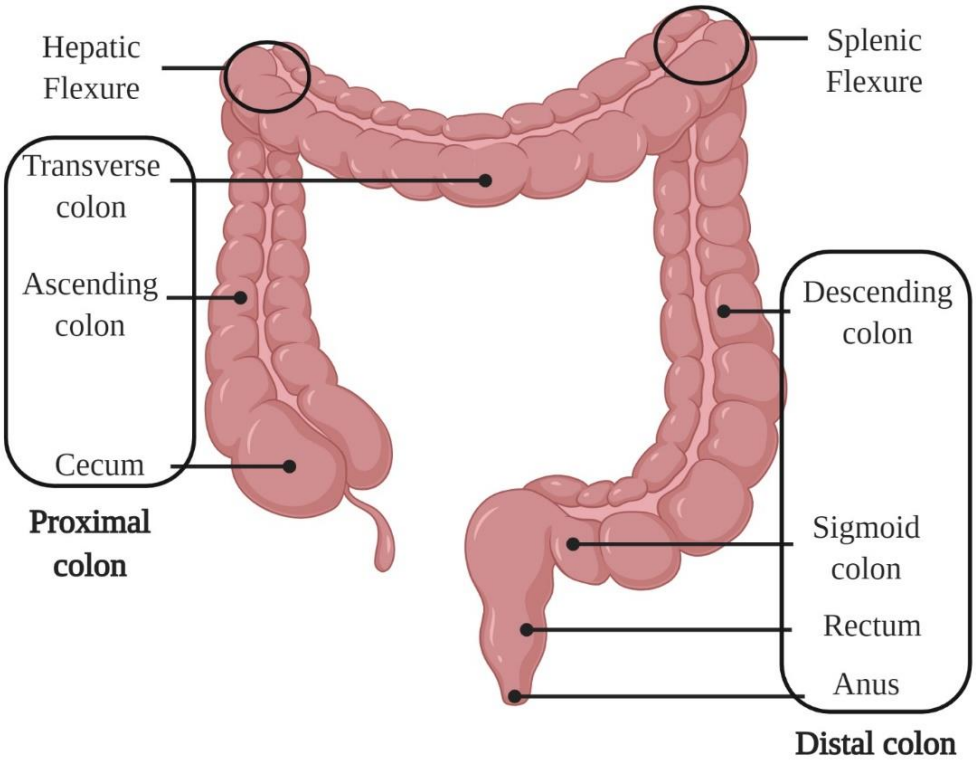

Figure 5: Large intestine.

Eickhoff et al. (63) used a CT colonography in order to obtain more information about the number of colonic flexures (defined as an acute angle < 90°), and degree of tortuosity (judged on a 10–point visual analogue scale (VAS)). They found that the average number of flexures in a colon is 9.6 ± 2.4, and the VAS was found to be 3.7 ± 1.9. Cases with a major number of flexures and an increased degree of tortuosity are difficult to access and increase the chance of incomplete colonoscopy. Moreover, Alazmani et al. (64) demonstrated that the tortuosity of the colon when the patient is in supine position is higher than in the prone position.

Table 4 reports the diameter of the large intestine described by Sadahiro et al. (65), focusing on the difference between male and female. The diameters of the descending colon, sigmoid colon, and rectum are larger in males than in females.

Table 4: Diameter (cm) of distended large intestine (37,65)

	Male	**Female**
Cecum	4.7 ± 0.9	4.8 ± 0.8
Ascendant colon	4.8 ± 1.2	5.0 ± 2.0
Transverse colon	4.2 ± 1.2	4.2 ± 0.7
Descendant colon	3.4 ± 1.2	3.2 ± 0.6
Colon sigmoid	3.4 ± 0.6	3.2 ± 0.6
Rectum	4.0 ± 1.0	3.5 ± 1.0

Table 5 and Table 6 report the diameter and length of the large intestine, considering the supine and prone position of the patient. The research by Alazmani et al. (64) demonstrates that the diameter is governed largely by intra-abdominal compression and pelvic motion. Therefore, changing the position of the patient from prone to supine affects the position of the internal organs, and thus, the compression of the colon (64).

Table 5: Comparison of the colon diameter (cm) in supine and prone positions (64).

	Supine	**Prone**
Rectum	3.6 ± 0.8	3.7 ± 0.7
Sigmoid	2.6 ± 0.4	2.6 ± 0.3
Descending colon	3.3 ± 0.6	3.2 ± 0.5
Transverse colon	3.7 ± 0.4	3.6 ± 0.5
Ascending colon	4.5 ± 0.7	4.3 ± 0.7
Cecum	4.4 ± 0.7	3.8 ± 0.6

Proximal colon	4.2 ± 0.4	3.9 ± 0.5
Distal colon	3.1 ± 0.5	3.1 ± 0.4
Total colon	4.7 ± 0.5	3.5 ± 0.4

376

377 Table 6: Comparison of the colon length (cm) in supine and prone positions (37,64).

	Supine	**Prone**
Rectum	23.4 ± 6.7	23.1 ± 3.9
Sigmoid	50.6 ± 13.9	49.9 ± 11.7
Descending colon	24.2 ± 7.8	26.0 ± 7.8
Transverse colon	57.2 ± 9.3	57.3 ± 10.9
Ascending colon	21.7 ± 4.2	19.7 ± 4.0
Cecum	7.8 ± 2.9	6.9 ± 2.3
Proximal colon	86.6 ± 9.7	84.0 ± 10.2
Distal colon	98.3 ± 14.7	99.0 ± 11.8
Total colon	185.0 ± 18.3	183.0 ± 16.9

378 The mean values of the length of the entire intestine are summarized in Table 7. The study
379 by Hounnou et al. (33) shows the length of the whole intestine is longer in men than women and
380 the length decreases with age, and increases with weight while it does not vary with height.

381 Table 7: Mean and standard deviation values of the length (cm) of the intestine [17], [21].

	Men			**Women**		
	Avg ± std	**Min**	**Max**	**Avg ± std**	**Min**	**Max**
Duodenum (1)	27.8 ± 6.8	17	56	25.2 ± 5.4	17	48

Jejunum-ileum (2)	643.9 ± 110.8	365	1 000	573.8 ± 97.1	280	840
Small Intestine (1+2)	670.7 ± 113.1	390	1 030	599.2 ± 98.2	298	860
Right Colon (3)	74.1 ± 17.4	40	146	71.9 ± 16.5	40	125
Left Colon (4)	94.2 ± 27.2	33	220	82.9 ± 20.1	34	123
Colon (3+4)	166 ± 36.2	80	313	155 ± 28.6	80	214
Whole Intestine (1+2+3+4)	836.7 ± 132.1	550	1 316	754.2 ± 111	378	1 013

Regarding the thickness of the colon wall, the studies conducted by Wiesner et al. (66) report a correlation between wall thickness and colonic distention. A normal wall thickness is ranged between 0.2 – 2.5 mm if the colon is distended and up to 6 mm if the colon is contracted.

2.5 Liver, pancreas and gall bladder

One of the primary functions of the liver, pancreas, and gall bladder is to assist the GI tract in breaking down food into its component nutrients by secreting enzymes. These organs are illustrated in Figure 6.

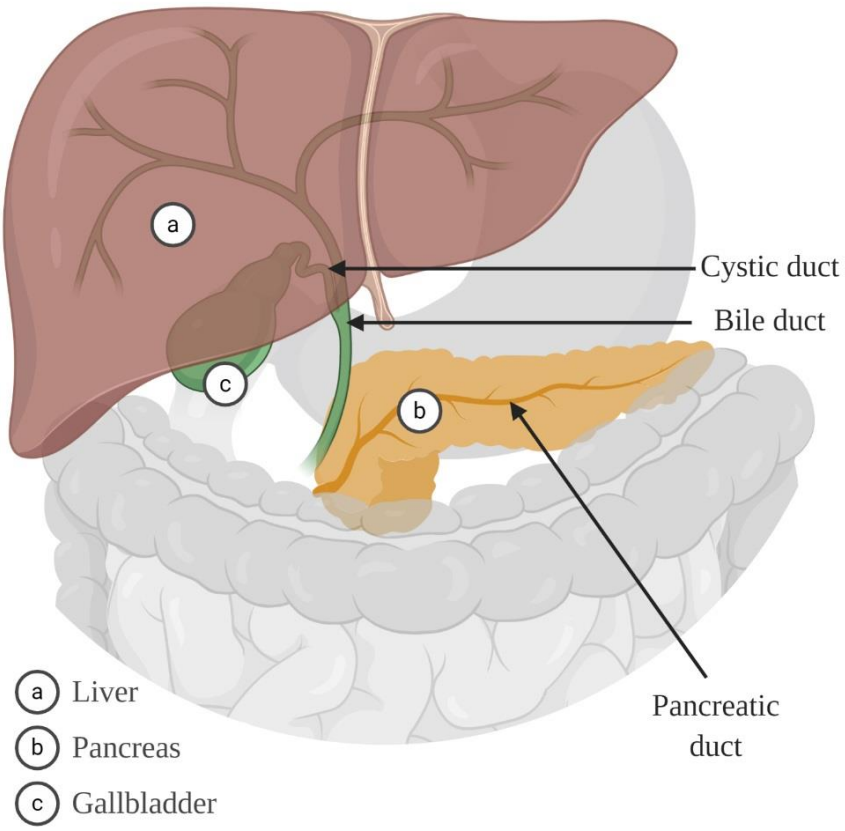

Figure 6: Liver, pancreas and gall bladder.

The liver is situated in the right upper quadrant of the abdomen and is divided into two primary lobes: a large right lobe and a smaller left lobe. The liver has an important role in digestion; it produces bile, a thick fluid which contains enzymes that help to dissolve fat in the intestines, and metabolizes nutrients that are absorbed by the intestines (67).

The gall bladder is a hollow, pear shaped, 8 – 10 cm long organ that is posterior to the liver. It is composed of three sections: fundus, body, and neck. Its main function is storage of bile which is then released via the cystic duct, a 1 – 2 cm long canal, into the biliary duct system linked to the duodenum (68).

The pancreas is a lobular organ that lies posterior to the stomach. It secretes fluid rich in carbohydrates and inactive enzymes which become active once they reach the duodenum. The

hormone secretion is triggered by the duodenum in the presence of chyme. The fluids secreted by the pancreas are then released into the duodenum via the pancreatic duct. The particular enzymes produced by the pancreas are discussed in Section 4 (69).

2.6 Mesentery

The mesentery is a continuous set of ruffled and folded tissues that extends from the base of the stomach down to the rectum. It suspends the intestines from the abdominal wall in multiple regions (70). Its main functions are to fix all abdominal digestive organs, connect them to the other systems and to store fat. It also helps the lymphatic system to transport lymph (fluid containing white blood cells) throughout the body (71).

Knowing how the mesentery is organized and attached to the abdominal wall is necessary in order to understand how it may impact the mechanical properties of the bowel and to quantify the sensitivity of each region of the GI tract. In the study of White et al. (72) the failure stress values for the mesentery in porcine models was characterized.

Most of the small intestine is not attached to the abdominal wall and so is mobile; however, the large intestine is more fixed (where the anchorage system is deficient, the organ is mobile and prone to twisting around the attached region of the mesentery). The right mesocolon is the continuation of the small intestinal mesentery. The transverse mesocolon starts at the hepatic flexure and this continues as the left mesocolon at the splenic flexure. The right and left mesocolon are similar and both are attached to the posterior abdominal wall. The mesosigmoid comprises two regions: the medial region is attached to the posterial abdominal wall while the lateral region is mobile. The mesorectum terminates proximal to the pelvic floor (71). The main regions of the large intestine where the mesentery is attached to are shown in Figure 7.

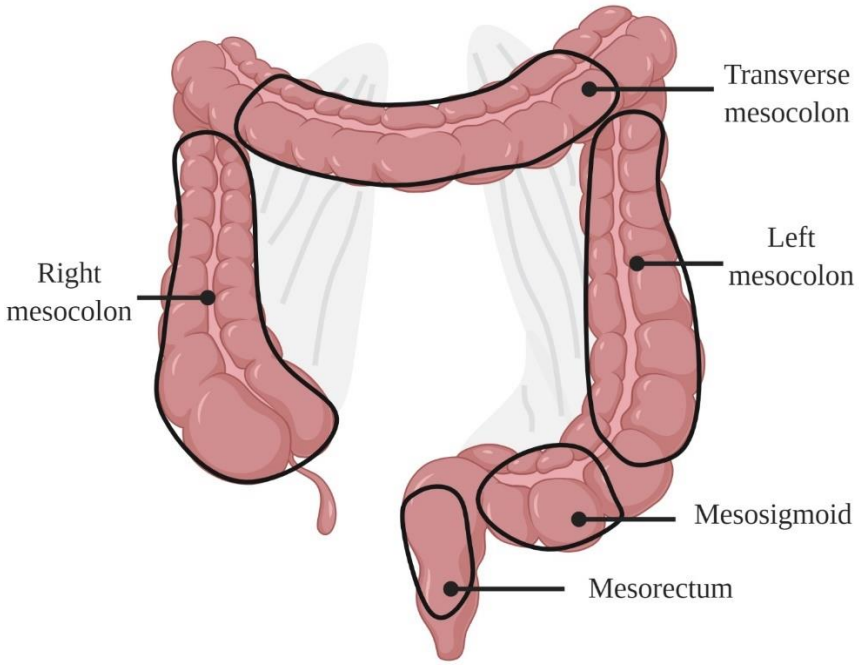

Figure 7: Colon regions where the mesentery is attached to.

3. Histology of the GI

Histology is the study of the microanatomy of tissues. Knowing the composition of tissue is necessary in order to understand how its characteristics can affect the function of a device (e.g. the surface texture) and how specific cells (or regions) can be targeted for drug delivery. In this section, the histological properties of the tissues of the GI tract will be summarized. The most common layers of a digestive tissue are shown graphically in Figure 8; however, subtle differences between organs are elaborated on in subsequent paragraphs.

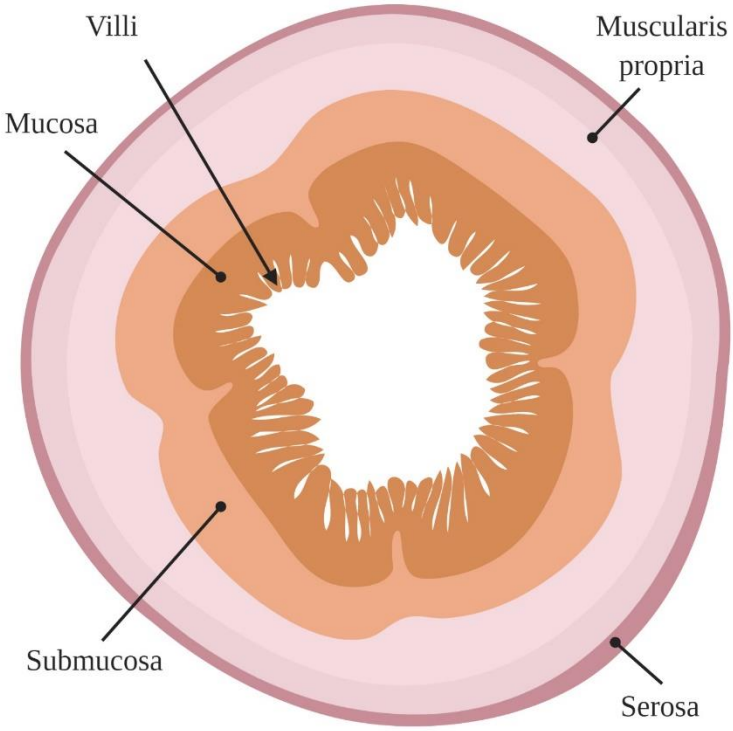

Figure 8: The tissue layers of the GI tract.

3.1 Esophagus

The wall of the esophagus is composed of four layers: mucosa, submucosa, muscularis propria, and adventitia. With respect to the other organs of the GI tract, the esophagus is the only one that does not have a serosa layer. The missing serosa layer allows esophageal cancer to spread easily and for this reason the surgical treatment is more challenging. Without a serosa layer, possible luminal disruptions are also more difficult to repair.

The mucosa is thick and red at the beginning and paler at the end of the esophagus. Longitudinal folds are present in the mucosa but they disappear when the esophagus is distended. The mucosa consists of three sublayers: mucous membrane, lamina propria and muscularis mucosa. The submucosa is made up of connective tissue, cells such as lymphocytes and plasma, and mucous glands. The secretion of these glands is important for the clearance of the esophagus

and for tissue resistance to acid. The muscularis propria, which is responsible for motor function, is composed of striated (skeletal) muscle in the upper part and of smooth muscle in the lower part of the esophagus. The middle area, called the transition zone, is a mixture of both muscles. The adventitia is the external fibrous layer and connects the esophagus with the surrounding environment. Therefore, it is composed of connective tissue, small vessels, lymphatic channels, and nerve fibers (39).

3.2 Stomach

The wall of the stomach consists of four layers: mucosa, submucosa, muscularis propria (or muscularis externa), and serosa (73). The mucosa is relatively thick and contains numerous gastric glands and pits. The mucosa of the stomach has a mean thickness of 1.26 ± 0.07 mm and accounts for about 32% ± 7% of the total thickness of the stomach (53). It has a prominent layer of smooth muscle called muscularis mucosa, which helps to expel the contents of the gastric glands. The mean thickness of the muscularis mucosa is 0.17 ± 0.09 mm (74). The submucosa, made up of connective tissue and lymph vessels, separates the mucosa from the muscularis externa. The muscularis externa consists of 3 layers of smooth muscle: inner oblique layer, middle circular layer, and external longitudinal layer. The three layers are not always visible but have different functions: the inner oblique layer helps to mechanically break down food; the middle circular layer of the muscularis is thick and forms the pyloric sphincter; and the external longitudinal layer is responsible for moving the bolus towards the pylorus of the stomach (74). The serosa is the outermost layer that covers all the stomach wall (73).

3.3 Small intestine

The small intestine also has four tissue layers: mucosa, submucosa, muscularis propria, and serosa, as shown in Figure 8. The mucosa secretes digestive enzymes and hormones, and has many protrusions called villi. These dramatically increase the surface area of the small intestine (by 60 – 120 times) helping the absorption of the digested food (37). This layer is the thickest and can make up 35% – 40% of the overall wall of the small intestine. The submucosa is the layer of dense, irregular connective tissue or loose connective tissue and contains mucous glands, blood vessels, lymph vessels, and nerves. It supports the mucosa and joins the mucosa to the underlying smooth muscle. The muscularis propria is a region of muscle nearby the submucosa membrane. It usually has two distinct layers of smooth muscle (circular and longitudinal) and is responsible for peristaltic movement. The serosa is the outermost layer of the intestine: it is a smooth membrane consisting of a thin layer of connective tissue and a thin layer of cells that secrete serous fluid (73).

The three main sections of small intestine are similar at a microscopic level. Therefore, it can be assumed that the previously mentioned sections of the small intestine have layers of the same thickness. The mucosa and the submucosa have a thickness of 0.4 ± 0.1 mm while the thickness of the muscularis propria is 0.4 ± 0.2 mm (75). The three sections have slightly different functions. For example, unlike in the jejunum and ileum, the submucosa in the duodenum has Brunner's glands whose main function is to produce a mucus-rich, alkaline secretion to neutralize the acidic content of chyme introduced from the stomach and to provide an alkaline condition for optimal intestinal enzyme activity for enabling absorption. On-the-other-hand, the ileum has Peyer's patches in the mucosa whose function is the immune surveillance system of the intestinal lumen (73).

3.4 Large intestine

The histology of the large intestine is similar to that of the small intestine. However, since the function of the large intestine is to absorb water there is no plicae circulares or villi. Therefore, compared with the small intestine, it is more uniform and flatter on the microscopic scale (38,73). The mean thickness of the large intestine wall is 1080 ± 239 μm in which the mean thickness of the mucosa is 499 ± 104 μm, the thickness of the muscularis mucosa is 62 ± 32 μm, and the submucosa is 519 ± 234 μm (74,76). The mucosa is composed by a thin layer of epithelial cells (epithelium), connective tissue (lamina propria), and muscle (muscularis mucosa). The submucosa surrounds the mucosa, and it is made up of mucous glands, blood vessels, lymph vessels, and nerves. The muscularis propria is a layer of muscle that surrounds the wall of the colon and rectum. The serosa is the outer layer of the colon that it is not found on most of the rectum (73).

3.5 Mucus

Mucus is an essential factor to consider in device development, having a direct impact on the navigation of a device inside the GI tract and its interaction with the tissue for diagnosis and treatment (e.g. drug delivery). Mucus is present on all surfaces of the GI tract and creates a physical barrier between the epithelium and the object in contact with it. For navigation, this can result in a slippage plane that facilitates the easy passage of the object through the GI tract, protecting the tissue from mechanical wear. Alternatively, it can be utilized for the opposite – leveraging muco-adhesion to gain traction for locomotion or anchoring. For diagnosis and treatment, this layer can be a source of information on gut health, or a physical barrier through which the tool, sensor or drug must penetrate.

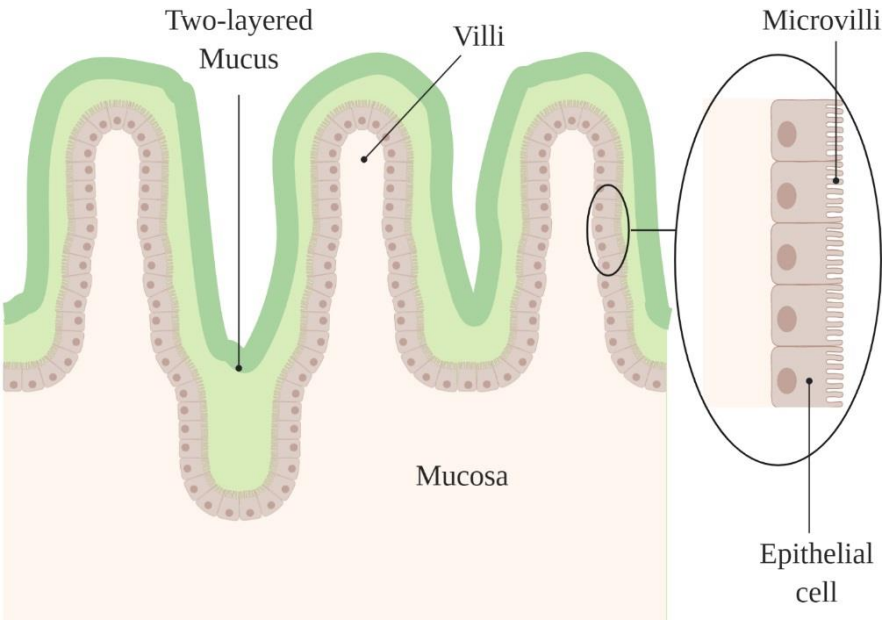

Figure 9: Mucus.

Mucus (Figure 9) is a complex biological material and its main functions are the lubrication of the tissue in order to transport the chyme from the esophagus to the colon (77), and the creation of a barrier to protect the surfaces of the GI tract and control the bacterial interaction with the immune system (77,78). The mucus is a semipermeable barrier that enables the exchange of nutrients, water, gases, and hormones, but at the same time, it is impermeable to most bacteria and pathogens (79). The mucus has an important role in drug delivery since it behaves as a barrier to some molecules and thus, drugs. Its viscoelasticity and pH properties can impact the delivery and absorption of drugs (80–82).

The composition of the mucus varies markedly along the GI tract. The mucus is normally composed of water, and so, it becomes a viscous structure when dehydrated (78). The mucus is composed of mucins, a protein that gives gel-like properties to the mucus. In the mouth, the salivary glands produce MUC5B and MUC7, which lubricate the food in order to pass through the esophagus. The stomach and colon have a two-layered system, and the major component of the

colon mucus is the MUC2 mucin while the MUC5AC mucin is the major component of the stomach mucus. Both are produced by the goblet cells (78). The small intestine has, in contrast to the stomach and colon, only one type of surface mucus, composed of MUC2 (83).

The two-layered structure of mucus in the colon is noteworthy (78): the outer layer is permeable, and therefore, is the typical habitat for bacteria; however, the bacteria in the colon do not have any direct contact with the epithelial cells since the inner mucus layer is impermeable. The inner mucus layer is continuously secreted from the goblet cells. The inner layer of both the colonic and stomach mucus is attached to the epithelial cells and is not easily removed, while the outer layer easily sloughs off. The outer layer of the colon is easier to remove compared to the outer layer of the stomach. The mucus of the small intestine does not normally adhere to the epithelial cells and it is easier to remove (78). The mucus in the small intestine covers the overall space between the villi, and since it is not anchored to the epithelial cells, it moves with the peristaltic waves. However, new mucus is constantly produced from the goblet cells. Here, the mucus is also formed by antibacterial proteins whose function is to limit the number of intact bacteria that can reach the epithelium (78).

In humans the thickness of the colonic inner layer is about 200 – 300 μm (78). The spontaneous mucus growth is 240 ± 60 μm/h and the final mucus thickness is 480 ± 70 μm in the colon (84). The mucus of the stomach has a mean value of 180 μm with a range of 50 – 450 μm. The thickness depends mainly on digestive activity in the small intestine (79).

The viscoelasticity of the mucus depends on the level of hydration and on mucin concentration (79). The slope of viscosity versus the shear rate for mucus is usually within the range of -1 to -0.5, with an average of -0.85. The viscosity of healthy gastric mucus is about 0.085 Pa s at a shear rate of 1.15 s^{-1}, but this value can increase significantly during duodenal ulceration (77).

4. Chemical makeup of the contents of each region

The chemical properties of the GI tract, such as the pH, the enzymatic composition and the metabolic activity, are crucial for determining appropriate materials for the design of the device, selecting sensors and for choosing a location inside the gut for targeted drug delivery.

4.1 pH

The pH has a crucial role in the digestive tract, helping to create a favorable environment for the breakdown of food and controlling bacteria metabolism. The pH along a healthy gut is presented in Table 8 (85–87). The saliva has a near neutral pH, but the oral cavity pH may be modified by food. Secretion of different enzymes and chemicals controls the overall pH profile of the gut. Regarding the esophagus, the normal value of pH is between 6.0 and 7.0 but it can drop down to 4.0 in the presence of gastroesophageal reflux (88,89).

Table 8: The pH values at different locations of the human gut.

Location	**pH (mean ± SD)**
Stomach (85)	2.9 ± 1.97
Duodenum (86)	6.6 ± 0.5
Jejunum (85)	7.1 ± 0.6
Ileum (fold) (86)	7.5 ± 0.4
Large intestine (86)	6.6 ± 0.7

560 **4.2 Chemicals and Enzymes**

561 Digestion is a complex process and consists of both mechanical and chemical mechanisms.
562 The former is relatively simple and involves physical breakdown of food through muscular
563 contractions. The latter is a more complex mechanism that reduces food into its chemical
564 components which are then absorbed. In healthy individuals a substantial amount of fluid and ions,
565 about 7 L, is secreted and reabsorbed daily by the GI tract.

566 Chemical digestion begins first in the mouth by means of the salivary enzyme amylase
567 which breaks down starches into glucose. The esophagus does not produce digestive enzymes but
568 does produce mucus for lubrication and protection as food travels to the stomach (90).

569 The cells in the lining of the stomach wall secrete hydrochloric acid (HCl), potassium
570 chloride (KCl), and sodium chloride (NaCl). Combined, these are known as gastric acid.
571 Bicarbonate, a base, is located to buffer the gastric fluid and mucus, a viscous fluid, protects the
572 stomach wall. The gastric chief cells in the stomach release pepsinogen and gastric lipase that help
573 to digest protein and lipid, respectively. Also, amylase, produced in the oral cavity and transferred
574 to the stomach with food, helps to continue the digestion of starch. A healthy adult human secretes
575 about 1.5 L of gastric fluids per day (90).

576 The intestinal gland, placed between the villi of the small intestine, secretes a solution
577 almost similar to interstitial fluid. The villi contain goblet cells that produce mucus. Intestinal
578 epithelium produces various enzymes (i.e., enterokinase, disaccharidases, and peptidases). Daily
579 volume of total intestinal secretion is about 1.8 L. These enzymes are mostly secluded within the
580 cells and do not contribute to luminal flow. The exocrine enzymes produced in the pancreas, along
581 with sodium bicarbonate, are propelled into the duodenum.

582 The pancreatic enzymes consist of amylase, lipase, colipase and phospholipase, cholesterol
583 esterase, trypsinogen, chymotrypsinogen, and carboxypolypeptidase. A total of 1.0 – 1.5 L of fluid
584 are secreted each day. Also, about 1.5 L of bile are secreted every day in the liver and the excess
585 is stored in the gall bladder. Bile flows to the small intestine in the presence of fats in the
586 duodenum. Bile contains water, bile salts, bile pigments, cholesterol, inorganic salts, fatty acids,
587 fat, and lecithin (90).

588 The large intestine secretes about 0.2 L of fluid per day, mostly in form of mucus, as the
589 primary function is the absorption. It can absorbs a large amount of water, electrolytes and minerals
590 secreted from other regions, but no chemical digestion is carried on in the large intestine (91).
591 A summary of the key enzymes and chemicals are presented in Table 9.
592 Table 9: Summary of enzymes and chemical composition at different locations of the human gut
593 (91).

Location	**Daily volume (cc)**	**Enzymes**	**Fluids and ions**
Stomach	1 500	Pepsinogen Gastric Lipase	Hydrochloric acid Potassium chloride Sodium chloride Mucus
Small Intestine	1 800	Enterokinase Disaccharidases Peptidases	Mucus Intestinal fluid
Large intestine	200	-	Mucus
Pancreas	1 500	Amylase	Sodium bicarbonate

		Lipase, Nucleases Cholesterol esterase Tripsinogen Chymotripsinogen Carboxypolypeptidase	
Liver	1 500	lactate dehydrogenase aspartate and alanine aminotransferases	Bile

4.3 Gut microbiota and metabolites

Gut microbiota play a major role in human physiology by producing vitamins, facilitating digestion, modulating the mucosal immune system and contributing to host defense against pathogens (92,93). A healthy human gut hosts trillions of microbes which are essential for maintaining immune and metabolic homeostasis and protecting against pathogens (94).

The esophagus is an environment that contains a consistent quantity of microbiota. The major component of the microbiota in a healthy esophagus is Streptococcus (95). The human stomach has acidic conditions and other antimicrobial factors and has been viewed as an inhospitable environment for microorganisms. However, a diverse community, as large as 128 phylotypes among eight bacterial phyla, have been detected in the human stomach, such as Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, and Fusobacteria phyla (96). The small intestine microbiota contains a facultative and strict anaerobes mainly consisting of Streptococcus sp., Escherichia coli, Clostridium sp., and high G+C organisms (97). These microbes have

608 developed different survival strategies to survive the harsh environment of the small intestine. A
609 total of 395 bacterial phylotypes are identified in large intestinal mucosal and fecal samples,
610 consisting mainly of Firmicutes and Bacteroidetes phyla (98,99). Only a few sequences associated
611 with the Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia phyla were found due
612 to the strict anaerobic mucosal regions (99).

613 The GI tract is not only a food digesting and absorbing system; it is also an endocrine organ
614 which secretes hormones in control of various metabolic processes and a lymphoid organ which
615 modulates the microbial control of host metabolism. Dietary substrates metabolized by the gut
616 microbiota comprise carbohydrates, amino acids, fatty acids, and phytochemicals. Some outputs
617 of the microbiota metabolism are acetate, propionate, butyrate derived from carbohydrates,
618 valerate, and caproate derived from amino acid (100).

619

620 **5. Passive mechanical properties**

621 The mechanical properties generally describe the ability of a tissue to resist deformation.
622 However, the stress-strain behavior is complex and understanding the hyperelastic nature of the
623 tissue is essential for the study of the locomotion of a device and the mechanical interaction with
624 the tissue. This can inform both the real-time control of the device and modelling during the early,
625 conceptualization stage. In this section, the passive mechanical properties of the hollow organs of
626 the GI tract are summarized.

627 **5.1 Stress–strain behavior**

628 The multi-layer structure of the GI tissue results in a complex stress-strain behavior that
629 not only varies with strain rate, but also depending on the region of the GI tract and direction of

stress applied. This is due largely to the fact that each layer of the GI tract has distinct mechanical properties which allow different tissue to bear different deformation and stress (101).

The mucosa is loosely adherent to the underlying structures in most areas and cannot withstand large stress. The submucosa has a mobile lattice of collagen fiber bundles with two layers of muscle lining: circular and longitudinal. This allows the submucosa to resist significant mechanical stress, but for a short duration. The serosa is typically the thinnest layer of the wall and hence contributes the least to the overall tissue wall strength (102). In summary, the mechanical strength of the bowel wall is determined largely by the submucosa and muscular layers while the serosa and mucosa have no significant strength (103). In Table 10, the values of maximal stress and destructive strain are provided for longitudinal and circumferential specimens of different locations of the gut. Herein, the values of longitudinal and circumferential testing of surgically removed stomach specimens are practically identical. On the other hand, stress and strain characteristics for small and large intestines, and the esophagus, vary significantly depending on direction of the load (i.e., are anisotropic) (101).

Table 10: Maximal stress and destructive strain for different locations of the gut.

Location	**Maximum ultimate stress (MPa)**	**Ultimate strain (%)**
Esophagus (cervical part) (104)	2.19 ± 0.06 (Longitudinal) 1.41 ± 0.05 (Circumferential)	70.0 ± 7 82.5 ± 9
Stomach (101)	0.67 ± 0.19 (Longitudinal) 0.5 ± 0.12 (Circumferential)	93.3 ± 18.57 103.12 ± 20.23
Small intestine (101)	0.548 ± 0.329 (Longitudinal) 0.92 ± 0.48 (Circumferential)	85.76 ± 18.6 84.02 ± 19.73

Large intestine (101)	1.188 ± 0.302 (Longitudinal) 0.645 ± 0.165 (Circumferential)	40.94 ± 12.5 87.85 ± 27.0

5.2 Viscoelasticity properties

A time- dependent mechanical test, performed on a excised porcine esophagus, showed that the esophagus has quasi-linear viscoelastic properties (105). Results showed that the stress relaxed by 20 – 30% of the peak within the first 10 s and stabilized at ~50% of the peak after 300 s. In a study of porcine stomach, it was shown that a higher stress relaxation rate appeared in the first 100 s, and it was about 70% of the total (106). An in-vitro porcine study found that small intestine tissue relaxes a lot faster than stomach or esophagus. With an increased shear strain from 50% to 200%, all stress curves decrease exponentially from their highest points to some steady states at ~20% within two seconds (107).

6. Motor behavior of the GI

The muscle contractions due to peristaltic movement are described in this section. These movements impact the navigation of the device inside the GI tract and must be taken into consideration during design. This includes the study of appropriate materials, device dimensions, device shape, and effective control strategies that ensure the device is able to cope with the movement of the organs while navigating the GI tract.

662 ### 6.1 Peristalsis and the migrating motor complex

663 Peristalsis in the GI tract comprises a series of propagating muscular contractions which
664 help with the digestion and transportation of food. Each part of the GI tract has a distinct type of
665 motility and these are described in the following.

666 The stomach can be divided into two functional regions: gastric reservoir and gastric pump.
667 The primary function of the gastric reservoir is to aid in digestion of the food (108). The reservoir
668 stores the food and then this is processed through a series of acids and enzymes secreted from the
669 gastric wall. The secretions act as a non-immunological defense against invading pathogens, and
670 food is processed for a complex diet. The primary function of the gastric pump, which is
671 anatomically provided by the antrum and the pylorus, is gastrointestinal motility, or rather the
672 transmission of the food through the intestine (108).

673 The food bolus is transferred to the distal part of the stomach with the help of tonic
674 contractions as shown in Figure 10. Tonic contractions are sustained contractions lasting from
675 several minutes to several hours. In the distal part of the stomach, peristaltic waves – muscular
676 contractions initiated by spontaneous electrical waves – are generated in order to move chime.
677 These are generated from a particular type of cell called interstitial cells of Cajal (ICC) (109,110).
678 These cells generate a potential within their membranes called the electrical pacesetter potential
679 (111). This potential drives the electrical events within the smooth muscle of the stomach and also
680 determines the frequency and velocity of the slow waves in the distal part of the stomach (112). In
681 Cheng's study (113), a laparoscopic device had been used to record these values and found that,
682 for humans, the frequency of the waves is 2.83 ± 0.35 min^{-1} and the propagation velocity is 3.0 –
683 8.0 mm s^{-1}.

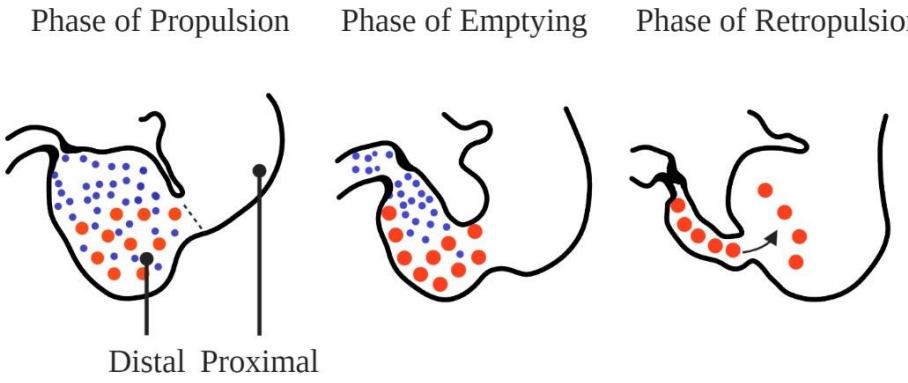

Figure 10: Different phases of gastric digestion.

Like the stomach, the intestines also have an ICC network between the tissue layers. The ICC produces electrical pacesetter potential which generates slow waves inside the intestine. Additionally, there are two types of motility in the intestines – segmentation and peristalsis. Segmentation is a mixing type of motility. The chyme moves back and forth through successive relaxation and contraction cycles of the stomach, as shown in Figure 11. In this type of movement, the inner muscle mass aids in the contraction and in the constricting of the food bolus. In the distal part of the duodenum, the frequency of segmentation is approximately 12 contractions min^{-1}, and for the ileum it is 3 – 4 contractions min^{-1} (114), (115).

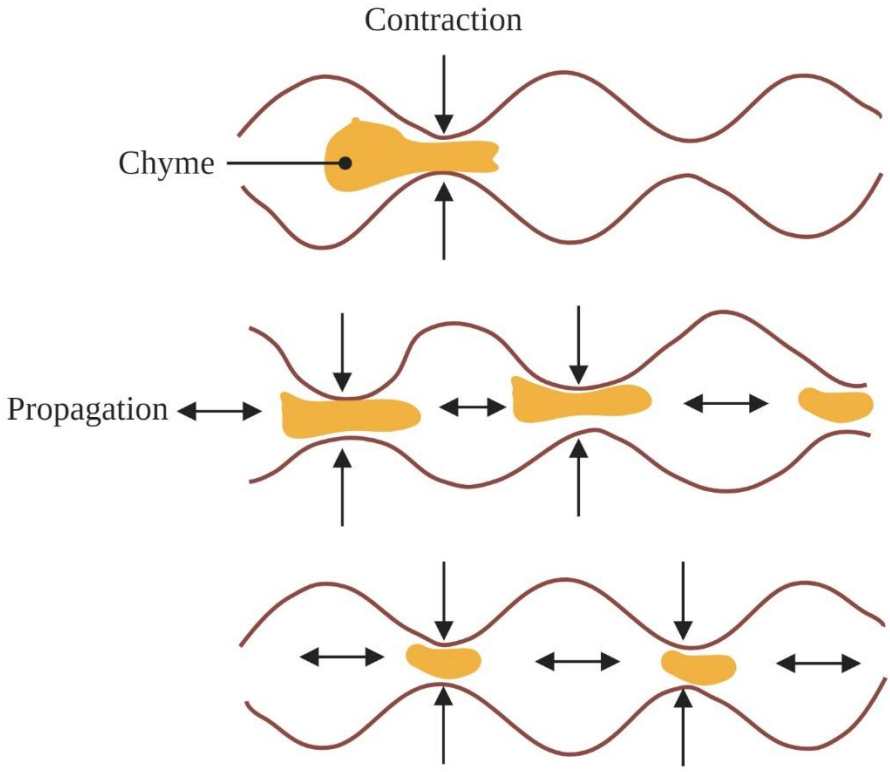

Figure 11: Segmentation motility inside small intestine.

Peristalsis moves the chyme from one segment of the lumen to the forward segment, as shown in Figure 12; it is called progressive movement. In order to generate this type of movement there is a sequential contraction and relaxation just like the segmentation motility; however, here the outer muscle layer contracts and shortens, while the inner layer relaxes and widens. The motion waves are generated along the entire length of the GI – from the mouth to the anus. There are two types of peristaltic waves: the basic peristalsis that moves only 10 cm along the small intestine at each contraction of the intestine and the "peristaltic rushes" that occur occasionally and move along the entire bowel with a high amplitude. The average velocity of basic peristalsis is around 1 – 2 cm min^{-1} (20) and the peristaltic rushes are around 2 cm sec^{-1} (116).

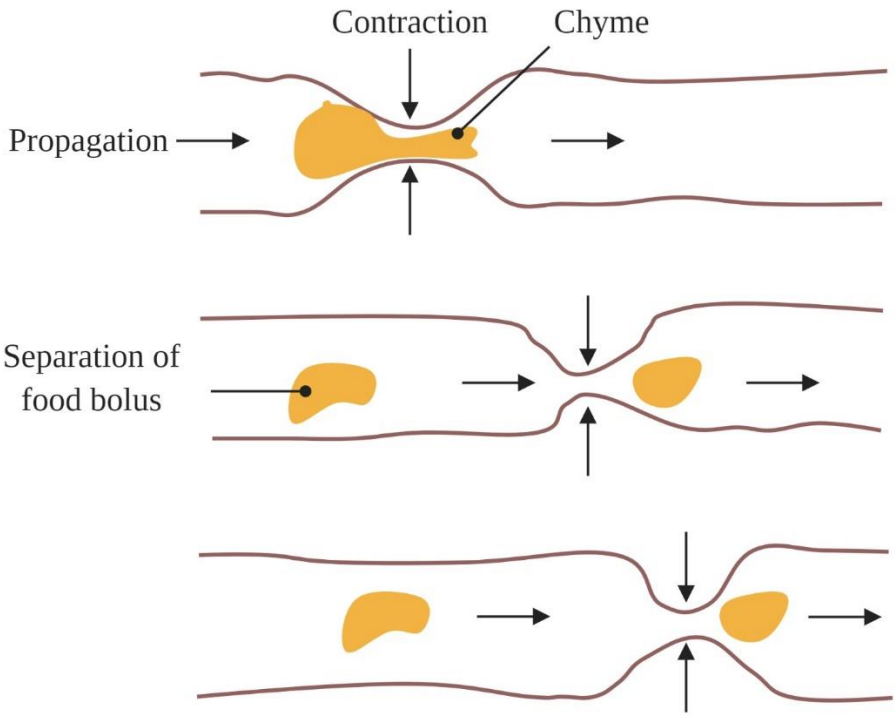

Figure 12: Peristalsis movement along the lumen.

The chyme, after passing the ileocecal valve, reaches the large intestine. Here the motility action is not as active as the stomach or small intestine. Colonic motility consists of three types of contractions: the rhythmic phasic contractions (RPCs), the giant migrating contractions (GMCs) and the tonic contractions. The first causes slow net distal propulsion, the second occurs infrequently but produces mass movements, and the third aids RPCs in their motor function (117). According to Sarna et.al. (117), the average frequency of giant migrating contractions is around 6 – 10 per day and each contraction lasts, on average, for 20 seconds. The propagation velocity at the distal part of the colon is about 1 cm sec^{-1}.

In a study by Rao et al. (118) the number of peristaltic contractions occurring in healthy humans during 24 hours was considered. The frequency of contractions increased after waking and a meal, while it decreased in the colon during sleep, when motor activity is reduced (118).

718 The frequency and the velocity of propagation in different sections of the GI tract are
719 summarized in Table 11.

720 Table 11 : Frequency and propagation velocity of different motilities in the human GI tract.

Region	**Motility Pattern**	**Frequency**	**Velocity**
Stomach (113,119)	Tonic Contraction	2.83 ± 0.35 min^{-1}	3.0 – 8.0 mm s^{-1}
Small intestine	Segmentation in Duodenum (115)	12 min^{-1}	12 cm min^{-1}
	Segmentation in Ileum (115)	8 min^{-1}	-
	Segmentation in Jejenum (116)	-	6 cm min^{-1}
	Peristalsis (20)	-	1 – 2 cm min^{-1}
	Rush peristalsis (116)		1.4 – 2.8 cm sec^{-1}
Colon (117,118,120)	Strong peristaltic movement	6 – 10 day^{-1}	1 cm s^{-1}

721

722 **6.2 Transit time through the various regions**

723 Transit time is the time that it takes food to travel from the mouth through the digestive
724 system to the anus. This can vary greatly between individuals and depends also on the composition
725 of the meal.

726 Fryne et al. (121) measured the transit time through various regions of the GI using a
727 magnetic tracking system. The observed gastric time was 35.5 min (range 4 – 73 min) and the
728 transit time for the small intestine was 261 min (range 241 – 402 min). They also measured the

motility data of the small intestine due to peristalsis. The propagation velocity was reported as 2.2 cm min^{-1} during post-prandial state and 2.3 cm min^{-1} during fasting phase. In addition, they measured the contraction frequency of the stomach and intestine. The measured value for the stomach was 2.85 ± 0.29 min^{-1} and for the intestine was 9.90 ± 0.14 min^{-1} post-prandial and 10.53 ± 0.29 min^{-1} during fasting. In a study by Degen and Phillips (122) it was demonstrated that there is not a substantial difference between the transit time in men and women. The gastrointestinal emptying time, measured with different techniques, is shown in Table 12.

Table 12 : The gastric and intestinal emptying time

Author	**Device**	**Gastric (min)**	**Intestinal (min)**
Fryne et. Al. (121)	Pillcam	57.5	275
	MTS -1	56	255
	Magnetic Pill	35.5	260.5
Maurer et. Al. (123)	Radiolabeled meal	-	231
Miller et. Al. (124)	Lactulose Breath test	-	234
Camilleri et. Al. (125)	Resin pellets	164	168

Most of the devices that have recorded data for transit time have been used in fasting states. In real-life scenarios, the diet has to be taken into consideration. Krevsky et al. (126) used a different approach to measure the transit times through different sections of the GI tract. Human volunteers ingested food containing indium pellets and the transit times through various sections of small bowel were determined by measuring the radioactive signal. The data showed that the

743 transit time to fully empty the stomach was 120 – 180 minutes and for emptying 50% of the small
744 intestine was 150 – 180 minutes. The transit time through the colon was about 300 – 360 minutes.
745 Cummings et al. (127) performed a study in which 12 human subjects were fed, after each meal,
746 with radio-opaque pellets for several weeks of controlled diet and measured the transit time. There
747 were three different types of diet: Ad libitum diet (i.e., free-feeding or feeding on demand),
748 standard diet, and high fiber diet. The mean transit time for each diet of the 12 individuals is shown
749 in Table 13.

750 Table 13 : Mean transit time (days) calculated from marker size *(127)*.

Ad libitum diet (studies 1-6)		**Standard diet (studies 7-12)**		**High fiber diet (studies 7-11)**	
Mean	Range	Mean	Range	Mean	Range
2.1	0.7 – 3.1	2.8	1.9 – 3.6	2.3	2.0 – 2.7
3.1	2.3 – 4.0	2.1	1.3 – 2.6	1.8	1.5 – 2.3
2.1	1.4 – 2.7	2.1	1.2 – 2.6	1.6	1.3 – 2.0
2.1	1.2 – 2.6	2.9	2.1 – 3.7	1.7	1.3 – 2.1
2.2	1.3 – 3.5	2.5	1.9 – 3.3	1.0	0.7 – 1.6
2.4	1.7 – 3.2	3.5	2.5 – 4.8		

751

752 **6.3 Post-prandial and fasting states and their effect on motor behavior**

753 The peristaltic motion still pertains during fasting, but it is different in action and timing
754 than during the post-prandial state. The movement is propulsive – originating from the pylorus up
755 to the ileum – and is called the migratory motor complex (MMC) (128). It is a kind of

"housekeeping" movement in which the MMC sweeps away any leftover food inside the lumen. This is a critical activity as a stagnant bolus can cause bacterial growth inside the lumen. The MMC is generated by a hormone called "motilin" which is secreted during the fasting state. This state lasts over a period of 90 – 120 min (128). During fasting, the MMC occurs in repeated cycles. This cyclic pattern, as shown in Figure 13, is divided into three phases. Phase I is the motor quiescent period lasting 40-60% of the cycle length and when slow waves are rarely associated with spikes. Phase II presents irregular contractions in the small intestine and lasts 20-30% of the cycle length. Phase III is the MMC characterized by spikes and contractions and lasts for 5 – 10 min (129).

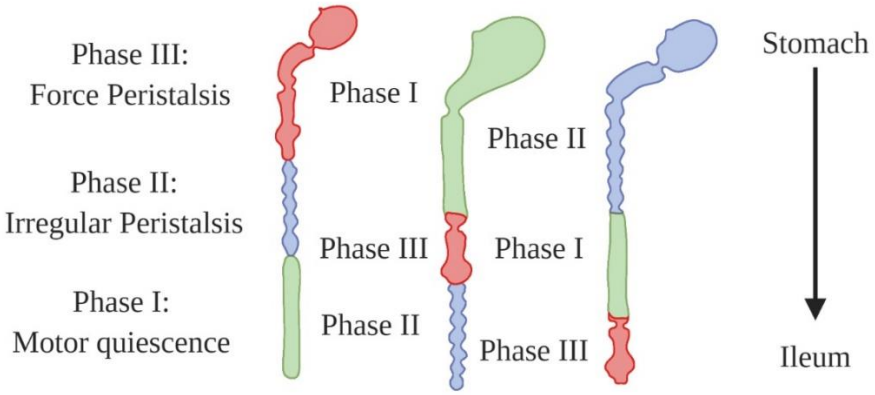

Figure 13: The three phases of interdigestive motility pattern.

During the fasting and post-prandial states, the proximal and distal colon experience two different motor activities, namely: 'tonic' and 'phasic'. The former consists of long contractions lasting for several minutes up to hours; the latter comprises brief periods of relaxation and contraction. During fasting, the motility is similar between the proximal and distal colon. On the contrary, during the post–prandial, the distal colon experiences an increase in the phasic motor activity. In addition, the tonic activity, due to the meal, causes immediate tonic contraction in the proximal and distal colon (130).

7. Forces on objects moving through the GI

The motion of a device through the GI tract is strictly related to all the forces acting on it in the environment, of which there are many. The forces are highly variable and often too complex to predict. Although they are derived from a variety of sources, they can be interdependent. These are separated here into *passive* forces – those that are not generated as a result of the movement of the object (e.g., muscular contractions in the bowel wall) and *active* forces – those that are (e.g., friction). These are summarized in Figure 14.

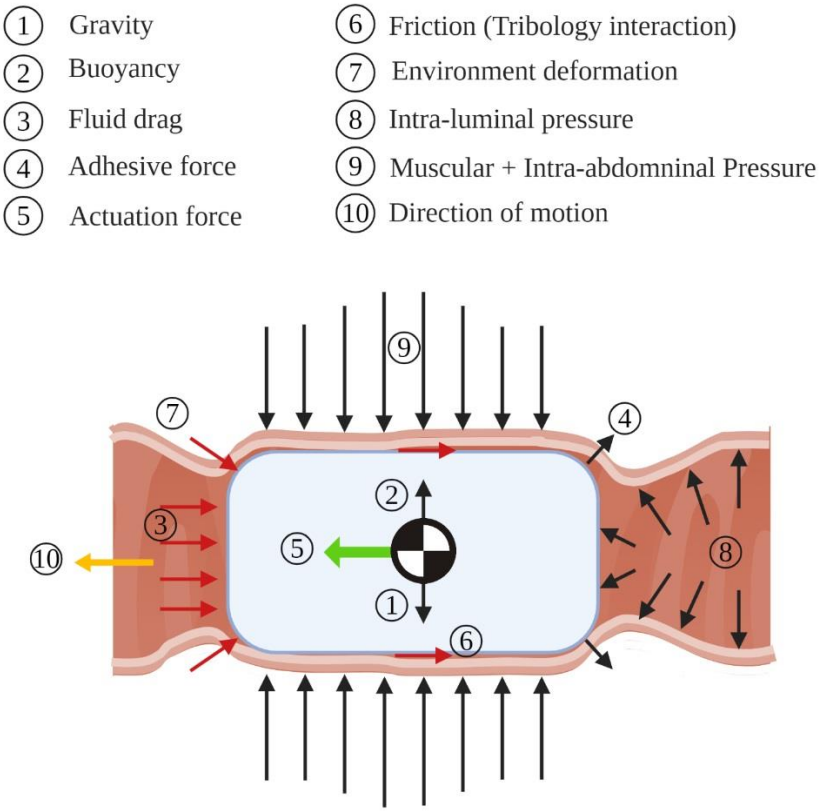

Figure 14: The forces acting on an object moving through the GI tract.

The aim of this chapter is to summarize all these forces applied to the object and provide the key factors affecting their magnitude. While it is challenging to predict them all accurately, it

786 is useful to have a broad understanding of them during the mechatronic design of a device for this
787 environment.

788 **7.1 Passive forces**

789 The passive forces acting on an object are shown with black arrows in Figure 14. They
790 include gravity, buoyancy, muscular contractions generated by the GI, abdominal pressure,
791 intraluminal pressure, and mucosal adhesion.

792 7.1.1 Gravity and buoyancy

793 The most constant and simple forces to define are gravitational force and buoyancy. The
794 magnitude of gravitational force is proportional to the mass of the object, and the direction is
795 always downward in the world frame. Buoyancy opposes gravity and is calculated as
796 $F_b = \rho V g$, where V is the volume of the object and ρ is the density of the fluid surrounding it,
797 which varies slightly along the GI region. In general, the fluid can be assumed to be a Newtonian
798 fluid with a density of 1Kg L^{-1} (131).

799 Since the directions of gravity and buoyancy are always along the vertical axis, how they
800 impact the object's dynamics depends on the orientation of the object and the surrounding
801 environment. For example, if the lumen and object are horizontal, they can align with and impact
802 object-tissue contact forces; if the lumen and object are vertical, they align with and can impact
803 propulsive force for locomotion.

804 7.1.2 Abdominal pressure

805 The GI tract runs through the core of the body and as such, passes by other organs and soft
806 tissues, all having mass and some of which are moving. The abdominal pressure exerted on an
807 object is the summation of the mass of tissue above the object (assuming bones are self-supporting)
808 and the forces generated by muscular contractions in the environment. The former could be

approximated by knowing the volume and density of the tissue above the object. Densities of soft tissues range from 0.95 g cm^{-3} to 1.05 g cm^{-3} (132), and volumes can be approximated by medical imaging and device localization. The latter include sources such as the beating heart, contracting diaphragm and skeletal muscle movements. This component is challenging to quantify, as it is dependent on the individual's physiology, level of activity during the procedure, the orientation of the body, and the pose of the object within the body.

A simpler approximation can be made by considering the abdomen as a whole and measuring the intra-abdominal pressure (IAP) – a clinical parameter that is typically measured by monitoring the pressure in the bladder. In a healthy adult, the pressure ranges from 5 – 7 mmHg but can vary considerably, particularly in ill and obese patients, where values can be > 25 mm Hg. Body posture can also have a significant impact on IAP, especially if the individual is lying prone or if the individual is inclined (or standing) (133–135). Muscular contractions can greatly alter IAP, with one study showing that during coughing and forced expiring, values of 46 mm Hg and 36 mm Hg respectively can be seen (136).

7.1.3 GI muscular contractions

GI muscular contractions are described in Chapter 6 and are mostly prominent in the small intestine. They are primarily generated by the myenteron (muscular layer of the intestine), which creates pendular movements, segmental contractions, peristalsis, and gradual reflexes (137,138). To estimate their effects on the object dynamics, it is necessary to understand the magnitude, shape, and frequency of the contact force (139). A general theoretical model of a solid bolus transported by peristalsis was formulated by Bertuzzi (139). Miftahof et al. described bolus transport models specific to the GI tract to predict contact forces (137,140,141).

831 7.1.4 Intraluminal pressure

832 Gases and liquids in the GI tract can become pressurized and exert forces on the
833 surrounding tissue and object. These can be artificially generated (e.g., insufflation from an
834 endoscope) or naturally generated (e.g., as a result of chemical processes in the gut). The primary
835 impact of intraluminal pressure is a reduction in contact pressure on the object as it counteracts the
836 other surrounding contact pressures, including those mentioned above. This is an important factor
837 to consider as the net contact pressure greatly impacts the degree of object-tissue contact, tissue
838 deformation, and therefore, both adhesion and the active forces on the object.

839 7.1.5 Summary - Net contact pressure

840 This subsection gives an indication of the expected contact pressures experienced by a
841 capsule in the small intestine - the region with the highest expected contact pressure due to its
842 muscular contractions and small lumen diameter. In other words, this gives a practical example of
843 the summation of pressures described in previous section. A device called the migrating motor
844 complex force sensor (MFS) was used to measure the force per centimeter of length exerted by the
845 small bowel on a capsule-like object (142–145). The contact force depends on the position of the
846 body, and the distal small bowel exerts 92% more contact force against the capsule than the
847 proximal small bowel, with the primary reason being that the distal small bowel has a smaller
848 diameter than the proximal small bowel (143). In Table 14 the mean values of the contact force
849 measured with different techniques in different works are summarized.

850 Table 14 : The contact force on capsule.

Author	**Length of capsule**	**Contact force**
Calio et al. (146)	33 mm	0.25 N cm^{-1}

Terry et al. (143)	35 mm	0.9-2.9 N cm^{-1}
Miftahof et al. (140)	35 mm	0.15-1.9 N cm^{-1}

851

852 7.1.6 Adhesion

853 Mucus, described in Section 3.5, lines the inner surface of the GI and is continually secreted
854 by goblet cells (78). The glycoprotein molecules in the mucus have an ability to adhere to solids
855 because of their hydrophilic and viscoelastic properties. Mucosal adhesivity is the interfacial
856 ability to bond with a solid surface. It is measured by the energy required to separate the two
857 adhered surfaces and can be affected by several factors, such as hydration, mucus surface tension,
858 wettability, temperature, and dwell time (the amount of time the mucosa is in contact with the solid
859 surface prior to separation) (147). Mucosa adhesivity can be useful in device design; for example,
860 it can be a solution to increase static friction to avoid migration of the capsule inside the GI tract.

861 The inherent adhesivity between a capsule and mucosa was investigated by changing the
862 factors of adhesive modality (peel and tack), material (polycarbonate, micropatterned
863 polydimethylsiloxane, stainless steel, and mucosa), and bowel region (proximal, middle, and
864 distal). The results show the mean tack strength of the mucosa to engineering materials was 0.198
865 ± 0.070 mJ cm^{-2}. The mean peel strength was 0.055 ± 0.016 mJ cm^{-2} (148). As the results suggest,
866 the adhesive tack strength between the mucosa and other material is larger than the peel strength.

867 Mucus thickness has some influence on mucoadhesion performance which is an important
868 factor to consider given the varying thickness throughout the GI tract. Varum at al. (149)
869 performed experiments on pigs, which is the closest model to human mucosa, in order to evaluate
870 the mucoadhesion. The experimental results showed the mean detachment forces are dependent

on mucus thickness: 0.084 ± 0.025 N for the stomach, 0.0575 ± 0.0125 N for the small intestine and 0.066 ± 0.009 N for the colon (149).

Other tests were conducted by Kern et al. (150) to find a nonlinear empirical model to describe the adhesion that includes the load (F_{load}), dwell time (T_{dwell}), and separation rate (v_{sep}). The main important parameters taken into consideration are the maximum stress (σ_{max}), defined as the ratio of the maximum measured force and the total capsule contact area achieved during the adhesion response, the total vertical probe displacement (δ_{total}) during the adhesion response, and total effective adhesion energy (E_{eff}), defined as the total area under the force displacement curve. The empirical equations are reported in Table 15. As the table shows, F_{load} is a significant factor only for σ_{max} and E_{eff} while T_{dwell} has no observed effect. Moreover, it has been noticed that as F_{load} increases σ_{max} and E_{eff} decrease.

Table 15 : Adhesion model (150).

Critical design parameter	**Model equation**
Maximum stress	$\sigma_{max} = 972.491 v_{sep}^{0.31} - 7.711 F_{load}^2 - 9.577 F_{load} v_{sep}$
Total displacement	$\delta_{total} = 0.791 v_{sep}^{0.3}$
Effective adhesion energy	$E_{eff} = (0.155 v_{sep} - 0.010 F_{load} v_{sep})^{0.583}$

Numerous studies have exploited mucoadhesion further by developing mucoadhesives to chemically bond to the mucosa to improve traction and/or adhesion. This can result in significantly higher adhesive forces while, in some cases, maintaining the ability to repeatedly reattach to the mucosa (151–154).

7.2 Active forces

The active forces on an object as it moves through the GI are shown with red arrows in Figure 14 and encompass the tribology of the contact, the drag of the object moving through a fluid, and tissue deformation during object motion. They depend largely on the properties of the GI tract and the object, as well as the properties of the surrounding tissue and fluid. These forces are applicable to all devices, including those with contact-based actuation, where the device must maximize traction against the tissue; passive locomotion, where the device must minimize frictional resistance to facilitate smooth passage through the lumen; and anchoring requirements, where the device must secure itself, through high friction or adhesion, to the lumen.

7.2.1 Tribology

Figure 15 aims to summarize the primary factors affecting the tribology of an object moving through the GI tract, including the size and shape of the object, its velocity, the properties of the mucus, the properties of the tissue, the contact force, the texture of the object, and the texture of the tissue. This is a complex interaction, with the mucosa and underlying tissue being viscoelastic, inhomogeneous, and nonlinearly deformable (Chapter 5). Additionally, the contact pressures – described in the previous section - vary considerably, as does the macro- and micro-scale morphology of the tissue. The tissue also continually excretes a non–Newtonian mucus (Section 3.5) which, depending on the velocity and scale of the device, can either increase or decrease total frictional resistance.

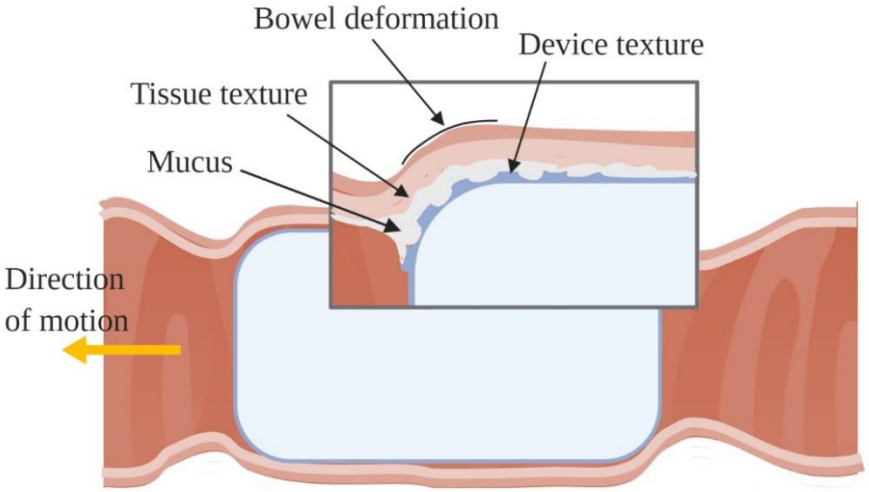

Figure 15: Factors affecting the tribology of an object moving through the GI tract.

Understandably, it is complicated to create an all-encompassing and accurate model that considers all the factors mentioned above. However, an understanding of the tribological properties is useful to design functional surfaces and appropriate control techniques for this unique environment. Sliker et al. developed a model to predict the resistance force on a capsule which was validated by performing drag force experiments (155). Kim et al. developed an analytical model based on a hoop stress analysis, and compared it to finite element model (FEM) results (156). A similar model was developed by Woo et al. (157), using a hoop stress analysis and tensile properties reported by Baek et al. (158), but including an empirical model for a propulsion force due to electrical stimulus of the bowel.

Perhaps the most intuitive is a study by Zhang et al., where a velocity-dependent model is presented (159). In this scenario, the total friction acting on a capsule can be written as a summation of the environmental resistance, Coulomb friction, and viscous resistance (or drag) (158,159)

$$F = F_e + F_v + F_c \quad (1)$$

where F_e is the environmental resistance, F_v is the viscous resistance and F_c is the Coulomb friction. The environmental resistance F_e is the amount of force required to deform the tissue in contact with the object and is related to an elastic restoring force as

$$F_e = P \cdot S \cdot sin\,(\theta) \qquad (2)$$

where θ is the slant angle of the object-tissue contact patch, P is contact pressure and S is the contact area. Tissue is viscoelastic, and so P increases with an increasing shear rate. This is shown to be the dominant component of resistance during an object's interaction with the GI tissue and has other names, including "edge effects" (160). The viscous friction or drag is related to the rheological properties of the fluid in the contact patch and can be expressed as

$$F_v = \delta v \qquad (3)$$

where the apparent viscosity coefficient, $\delta = 11.24\left(\frac{v}{d}\right)^{-0.7552} + 0.1148$, d is the mean value of intestinal mucus thickness and v is relative velocity (159). In other words, this is the resistance of the mucus during shear and is velocity dependent. While static, resistance comes from the adhesive bonds and, during shear, from the viscosity of the fluid (161,162). The Coulomb friction is decided by

$$F_c = \mu \cdot P \cdot S \cdot cos\,(\theta) \qquad (4)$$

where μ is the coulomb friction coefficient and the normal force has been replaced by $P \cdot S \cdot \cos(\theta)$ to account for the hoop stress. The friction coefficient is influenced by the texture of the capsule and intestinal surface.

Equations (1) – (3) are all velocity dependent, and other literature supports this, while also showing a total resistance dependency with object diameter, length (156,157,163,164), and normal force (165,166). The key factors affecting the friction are the capsule dimensions, surface geometry and the speed, while the effect of the weight is trivial. Ignoring the factor of weight, the

diameter affects the friction more than the length (167). Wang et al. (167) describe how resistance changes with capsule size and velocity as

$$f(v) = Kv^{1/n} + C \quad (5)$$

where K and $C > 0$ are related to the R and L, radius and length of the capsule, respectively.

7.2.2 Fluid drag

While there may not always be high volumes of fluid in the GI tract, it is important to consider any impact of drag as an object moves through a fluid-filled environment. In these cases, the drag opposes motion and is equal to

$$F_D = \frac{1}{2}\rho v^2 C_D A \quad (6)$$

where ρ is the density of the fluid, v is the velocity of the object, C_D is the drag coefficient, and A is the contact area of the front face of the object.

8. The impact of disease on GI physiology

Throughout this work we have described all the properties and characteristics of the GI tract in its healthy state, which can be considered as the generic and most common condition. However, having some knowledge of the possible GI alterations in the presence of digestive diseases is useful, and in–depth investigation can be done as required for the application. Therefore, here, we discuss the most common changes that can be seen from cancers and other diseases, including IBS, IBD and celiac disease. IBD includes Ulcerative colitis (UC) and Crohn's disease (CD), both characterized by chronic inflammation of the gut (168). Although UC and CD are grouped under IBD, they have different characteristics. UC is an inflammation condition of the mucosa of the large intestine and is related to the presence of bacteria in the colon, which produce colitis. However, CD usually occurs in the ileocaecal region (169). Both present an irregular

970 mucosal surface and transmucosal inflammation (169,170). Here we consider how these diseases
971 impact GI transit time, pH, microbiota and wall thickness (168).
972 Regarding the GI transit time, Bai et al. (168) report that there is no significant difference
973 in gastric emptying time and small intestine transit time between healthy subjects and IBS patients.
974 However, they report that the IBS patients have a longer colonic transit time. Regarding UC and
975 CD patients, Bai et al. report a slightly longer orocecal (mouth – cecum) transit time (168,171).
976 On–the–other–hand, celiac patients show a longer orocecal transit time but no alteration in small
977 intestine transit time (171).
978 Gastric and small intestine pH profiles in patients with IBD are similar to those in healthy
979 samples, while the pH of the CD colon is much lower (5.3 ± 0.3 in the right colon and 5.3 ± 0.7 in
980 the left colon) (172). Regarding celiac disease, a higher pH in the small bowel and unaltered pH
981 value in the stomach have been reported by Effinger et al. (171). Digestive diseases could also
982 mutate and reduce the intestinal concentration of bile salts, which affect the luminal pH and, thus,
983 the digestion of food (i.e. transit time) (168).
984 There is a strong correlation between gut microbiota, IBD, IBS and digestive diseases in
985 general. IBD has been shown to lead to a decrease of bacteria with anti–inflammatory capacities
986 (Proteobacteria) and an increase of bacteria with inflammatory capacities (Faecalibacterium,
987 Helicobacter species) (93,171). Regarding celiac patients, the microbiota was found to be rich in
988 potentially pathogenic bacteria and poor in species such as Lactobacilli and Bifidobacteria (171).
989 Regarding colorectal cancer, a study by Tojo et al. (173) shows that the alteration of composition
990 and function of the microbiota is correlated to the presence of colorectal cancer as well as IBD or
991 IBS. Sample of colorectal tumor have shown many bacterial such as Bacteroides vulgatus, E. coli
992 and Enterococcus faecalis (173). Other microbial systems have been reported in association with

gastroesophageal reflux (Veillonella, Prevotella, Haemophilus, Neisseria, Campylobacter, and Fusobacterium) and adenocarcinoma in the esophagus (Campylobacter) (95). Moreover, gut microbiota alterations may contribute to pancreatic diseases including pancreatitis, chronic pancreatitis, and pancreatic cancer (92).

Wall thickness is a common indication of disease as it is proportional to the resulting inflammation. With UC the small intestine is characteristically thickened and presents with ulceration of the mucosa (169), while the colon wall can thicken up to 8 mm in the presence of CD (170). With regard to GI cancers, it has been proven that wall thickness is a good approach to evaluate and target the presence of a tumor. For example, in the esophagus a thickness above 5 mm is considered abnormal (174). Similarly, Suk et al. (52) classify gastric diseases with respect to wall thickness. In particular, diseases have been classified as normal or benign disease (BD), early gastric cancer (EGC), and advanced gastric cancer (AGC). BD presents a thickness of the gastric wall of 4.9 ± 1.6 mm, the EGC shows a thickness of 5.6 ± 2.4 mm while a thickness of 10.3 ± 4.7 mm is an indication of AGC.

9. Conclusion and future developments

Considering that digestive disease can significantly impact the normal function of the GI tract and that GI cancer is one of the leading causes of death in the 21st century, the early diagnosis and subsequent treatment of GI disease is essential to reduce patient morbidity and mortality. Despite numerous technological advances in diagnosing and treating these diseases, the need for innovation still exists. This is partly due to the harsh, difficult–to–access environment that presents significant engineering challenges, but also to the increasing demand on health services by a growing population that has increasing disease prevalence. Therefore, there remains significant

motivation for engineers in the biomedical field to find innovative, more sophisticated, and minimally invasive technologies to access the GI tract. In order to develop effective devices, engineers need a broad spectrum of knowledge on the GI system, and so in this review, the fundamental properties of the GI system – focusing on the esophagus, stomach, small and large intestines – were described with the goal of presenting key information.

Developing disruptive medical devices for this region still has a number of major and open challenges. Firstly, the mechatronic design needs to be considered from the shape, dimensions, and materials of the device, to the research of innovative navigation strategies. The shape and dimensions must ensure safe and efficient passage through the tortuous and unstructured environment, while the material should be tailored to meet the friction, chemical resistance, and biocompatibility requirements (i.e. pH and microbiota of the environment). An innovative strategy for the device navigation is essential to ensure effective and real-time control and reduce the mean completion time of the procedure, which should at least be comparable with the existing procedure. This must be robust in an environment with numerous disturbances (i.e. respiration of the patient, peristaltic movements) and high variability between patients. To achieve this, localization, registration, and an effective locomotion mechanism (i.e. internal anchoring locomotion, external magnetic coupling locomotion or a novel hybrid combinations of internal and external locomotion) should be carefully considered depending on the context. Lastly, to bring added benefit, the device should provide effective diagnosis and or treatment. This should be accurately controlled with the device navigation and may be facilitated by context specific sensing, for example, combined time and pH measurements. In this context, the possibility of performing therapeutic functions, such as biopsy tissues, polyp ablation or drug delivery, is necessary. Therefore, enhanced and innovative

devices have the potential to improve all these features, and thus, advance in the next decade, the medical and endoscopic field.

List of Abbreviations:

GI: gastrointestinal

NIH: National Institutes of Health

IBS: irritable bowel syndrome

IBD: inflammable bowel disease

CD: Crohn's disease

UC: ulcerative colitis

IR: incidence rate

MR: mortality rate

CT: computed tomography

MRI: magnetic resonance imaging

CE: endoscopic capsule

VAS: visual analogue scale

ICC: interstitial cells of Cajal

RPC: rhythmic phasic contraction

GMC: giant migrating contraction

MMC: migratory motor complex

IAP: intra-abdominal pressure

MFS: migrating motor complex force sensor

FEM: finite element model

References

1. Caffrey CM, Chevalerias O, O'Mathuna C, Twomey K. Swallowable-Capsule Technology. IEEE Pervasive Computing. 2008 Jan;7(1):23–9.

2. Health Information [Internet]. National Institutes of Health (NIH). [cited 2019 Mar 13]. Available from: https://www.nih.gov/health-information

3. Tsai S, Wendt J, Cardarelli K, Fraser A. A mortality and morbidity study of refinery and petrochemical employees in Louisiana. Occup Environ Med. 2003 Sep;60(9):627–33.

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018 Nov;68(6):394–424.

5. Valdastri P, Ciuti G, Verbeni A, Menciassi A, Dario P, Arezzo A, et al. Magnetic air capsule robotic system: Proof of concept of a novel approach for painless colonoscopy. Surgical Endoscopy and Other Interventional Techniques. 2012;26(5):1238–1246.

6. CDC. CDC VitalSigns - Colorectal Cancer [Internet]. Centers for Disease Control and Prevention. 2011 [cited 2019 Mar 13]. Available from: https://www.cdc.gov/vitalsigns/cancerscreening/colorectalcancer/index.html

7. Joseph DA, Degroff AS, Hayes NS, Wong FL, Plescia M. The Colorectal Cancer Control Program: Partnering to increase population level screening. Gastrointestinal Endoscopy. 2011;73(3):429–434.

8. Bujanda L, Sarasqueta C, Zubiaurre L, Cosme A, Muñoz C, Sánchez A, et al. Low adherence to colonoscopy in the screening of first-degree relatives of patients with colorectal cancer. Gut. 2007;56(12):1714–1718.

9. Obstein KL. Advanced endoscopic technologies for colorectal cancer screening. World Journal of Gastroenterology. 2013;19(4):431.

10. Valdastri P, Simi M, Webster RJ. Advanced Technologies for Gastrointestinal Endoscopy. Annual Review of Biomedical Engineering. 2012;14(1):397–429.

11. Li B, Meng MQH, Lau JYW. Computer-aided small bowel tumor detection for capsule endoscopy. Artificial Intelligence in Medicine. 2011;52(1):11–16.

12. Brambs H-J, Juchems MS. Virtual endoscopy using CT scan. Minimally Invasive Therapy & Allied Technologies. 2003 Jan;12(5):207–16.

13. Kumar RR, Joseph J, Vidya PV, Pournami C, John NJ. Virtual colonoscopy: A plausible alternative to conventional colonoscopy. In: 2017 IEEE Region 10 Symposium (TENSYMP) [Internet]. Cochin, India: IEEE; 2017 [cited 2020 Jun 12]. p. 1–5. Available from: http://ieeexplore.ieee.org/document/8070107/

14. Slawinski PR, Obstein KL, Valdastri P. Emerging issues and future developments in capsule endoscopy. Techniques in Gastrointestinal Endoscopy. 2015 Jan 1;17(1):40–6.

15. Liao Z, Hou X, Lin-Hu E-Q, Sheng J-Q, Ge Z-Z, Jiang B, et al. Accuracy of Magnetically Controlled Capsule Endoscopy, Compared With Conventional Gastroscopy, in Detection of Gastric Diseases. Clinical Gastroenterology and Hepatology. 2016 Sep;14(9):1266-1273.e1.

16. Nam S-J, Lee HS, Lim YJ. Evaluation of Gastric Disease with Capsule Endoscopy. Clinical Endoscopy. 2018 Jul 31;51(4):323–8.

17. Riccioni ME. Colon capsule endoscopy: Advantages, limitations and expectations. Which novelties? World Journal of Gastrointestinal Endoscopy. 2012;4(4):99.

18. Slawinski PR. Capsule endoscopy of the future: What's on the horizon? World Journal of Gastroenterology. 2015;21(37):10528.

19. Ciuti G, Menciassi A, Dario P. Capsule Endoscopy: From Current Achievements to Open Challenges. IEEE Rev Biomed Eng. 2011;4:59–72.

20. Liu L, Towfighian S, Hila A. A Review of Locomotion Systems for Capsule Endoscopy. IEEE Reviews in Biomedical Engineering. 2015;8:138–51.

21. Pittiglio G, Barducci L, Martin JW, Norton J, Avizzano CA, Obstein K, et al. Magnetic Levitation for Soft-Tethered Capsule Colonoscopy Actuated with a Single Permanent Magnet: a Dynamic Control Approach. IEEE Robotics and Automation Letters. 2019;1–1.

22. Zhang P, Li J, Hao Y, Ciuti G, Arai T, Huang Q, et al. A compensation strategy for accurate orientation of a tethered robotic capsule endoscope. In: 2017 IEEE International Conference on Cyborg and Bionic Systems (CBS) [Internet]. Beijing: IEEE; 2017 [cited 2020 Jun 12]. p. 257–61. Available from: http://ieeexplore.ieee.org/document/8266111/

23. Paul Glass, Metin Sitti, Arjun Pennathur, Ragunath Appasamy. A Swallowable Tethered Capsule Endoscope for Diagnosing Barrett's Esophagus. GIE [Internet]. 2009 Apr 1;69(5). Available from: https://www.giejournal.org/article/S0016-5107(09)00561-6/fulltext

24. Gora MJ, Sauk JS, Carruth RW, Gallagher KA, Suter MJ, Nishioka NS, et al. Tethered capsule endomicroscopy enables less invasive imaging of gastrointestinal tract microstructure. Nature Medicine. 2013;19(2):238–240.

25. Caprara R, Obstein KL, Scozzarro G, Natali CD, Beccani M, Morgan DR, et al. A Platform for Gastric Cancer Screening in Low- and Middle-Income Countries. IEEE Trans Biomed Eng. 2015 May;62(5):1324–32.

26. Dehghani H, Welch CR, Pourghodrat A, Nelson CA, Oleynikov D, Dasgupta P, et al. Design and preliminary evaluation of a self-steering, pneumatically driven colonoscopy robot. Journal of Medical Engineering and Technology. 2017;41(3):223–236.

27. Mapara SS, Patravale VB. Medical capsule robots: A renaissance for diagnostics, drug delivery and surgical treatment. Journal of Controlled Release. 2017 Sep;261:337–51.

28. Toennies JL, Tortora G, Simi M, Valdastri P, Webster RJ. Swallowable medical devices for diagnosis and surgery: The state of the art. Proceedings of the Institution of Mechanical Engineers, Part C: Journal of Mechanical Engineering Science. 2010 Jul;224(7):1397–414.

29. Valdastri P, Quaglia C, Susilo E, Menciassi A, Dario P, Ho C, et al. Wireless therapeutic endoscopic capsule: in vivo experiment. Endoscopy. 2008 Dicembre;40(12):979–982.

30. Beccani M, Di Natali C, Aiello G, Benjamin C, Susilo E, Valdastri P. A Magnetic Drug Delivery Capsule Based on a Coil Actuation Mechanism. Procedia Engineering. 2015;120:53–6.

31. Kong KC, Cha J, Jeon D, Cho DID. A rotational micro biopsy device for the capsule endoscope. 2005 IEEE/RSJ International Conference on Intelligent Robots and Systems, IROS. 2005;3057–3061.

32. Norton JC, Slawinski PR, Lay HS, Martin JW, Cox BF, Cummins G, et al. Intelligent magnetic manipulation for gastrointestinal ultrasound. Sci Robot. 2019 Jun 19;4(31):eaav7725.

33. Hounnou G, Destrieux C, Desmé J, Bertrand P, Velut S. Anatomical study of the length of the human intestine. Surgical and Radiologic Anatomy. 2002;24(5):290–294.

34. McKay DM, Bienenstock J. The interaction between mast cells and nerves in the gastrointestinal tract. Immunology Today. 1994 Nov 1;15(11):533–8.

35. Soybel DI. Anatomy and Physiology of the Stomach. Surgical Clinics. 2005 Oct 1;85(5):875–94.

36. Gelberg HB. Comparative Anatomy, Physiology, and Mechanisms of Disease Production of the Esophagus, Stomach, and Small Intestine. Toxicologic Pathology. 2014 Jan;42(1):54–66.

37. Helander HF, Fändriks L. Surface area of the digestive tract – revisited. Scandinavian Journal of Gastroenterology. 2014 Jun;49(6):681–9.

38. Ødegaard S, Nesje LB, Lærum OD, Kimmey MB. High-frequency ultrasonographic imaging of the gastrointestinal wall. Expert Review of Medical Devices. 2012 May;9(3):263–73.

39. Daniela Urma BK. Esophagus - anatomy and development. GI Motility online (2006) [Internet]. 2006 May 16; Available from: https://www.nature.com/gimo/contents/pt1/full/gimo6.html

40. Wolfram T Knoefel PA. Swallowed Foreign Bodies in Adults. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3536040/

41. Ikenberry SO, Jue TL, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, et al. Management of ingested foreign bodies and food impactions. Gastrointestinal Endoscopy. 2011 Jun;73(6):1085–91.

42. Bekkerman M, Sachdev AH, Andrade J, Twersky Y, Iqbal S. Endoscopic Management of Foreign Bodies in the Gastrointestinal Tract: A Review of the Literature. Gastroenterology Research and Practice. 2016;2016:1–6.

43. Xia F, Mao J, Ding J, Yang H. Observation of normal appearance and wall thickness of esophagus on CT images. European Journal of Radiology. 2009 Dec;72(3):406–11.

44. Moss A, Schnyder P, Thoeni R, Margulis A. Esophageal carcinoma: pretherapy staging by computed tomography. American Journal of Roentgenology. 1981 Jun;136(6):1051–6.

45. Diana C. Peterson SRC. Anatomy, Abdomen and Pelvis, Stomach. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482334/

46. ramkumar d., schulze k. s. The pylorus. Neurogastroenterology and Motility. 2005 Jun;17(s1):22–30.

47. Doran S, Jones KL, Andrews JM, Horowitz M. Effects of meal volume and posture on gastric emptying of solids and appetite. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 1998;275(5):R1712–R1718.

48. Moore JG, Datz FL, Christian PE, Greenberg E, Alazraki N. Effect of body posture on radionuclide measurements of gastric emptying. Digestive Diseases and Sciences. 1988;33(12):1592–1595.

49. Sanaka M, Anjiki H, Tsutsumi H, Abe K, Kawakami T, Saitoh M, et al. Effect of cigarette smoking on gastric emptying of solids in Japanese smokers: a crossover study using the 13C-octanoic acid breath test. Journal of Gastroenterology. 2005 Jul 8;40(6):578–82.

50. Bennink R, Peeters M, Van den Maegdenbergh V, Geypens B, Rutgeerts P, De Roo M, et al. Comparison of total and compartmental gastric emptying and antral motility between healthy men and women. European journal of nuclear medicine. 1998;25(9):1293–1299.

51. Vasavid P, Chaiwatanarat T, Pusuwan P, Sritara C, Roysri K, Namwongprom S, et al. Normal Solid Gastric Emptying Values Measured by Scintigraphy Using Asian-style Meal:A Multicenter Study in Healthy Volunteers. J Neurogastroenterol Motil. 2014 Jul;20(3):371–8.

52. Suk KT, Lim DW, Kim MY, Park DH, Kim KH, Kim JM, et al. Thickening of the gastric wall on transabdominal sonography: A sign of gastric cancer. Journal of Clinical Ultrasound. 2008 Oct;36(8):462–6.

53. Huh CH, Bhutani MS, Farfán EB, Bolch WE. Individual variations in mucosa and total wall thickness in the stomach and rectum assessed via endoscopic ultrasound. Physiol Meas. 2003 Nov;24(4):N15-22.

54. Kararli TT. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Biopharmaceutics & Drug Disposition. 1995 Jul 1;16(5):351–80.

55. Madhu Badireddy JTC. Anatomy, Abdomen and Pelvis, Small Intestine. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459366/

56. Meyers MA. Treitz redux: the ligament of Treitz revisited. Abdom Imaging. 1995 Sep 1;20(5):421–4.

57. Ellis H. Anatomy of the small intestine (jejunum and ileum). Surgery (Oxford). 2011 Aug;29(8):355–7.

58. Weaver LT, Austin S, Cole TJ. Small intestinal length: a factor essential for gut adaptation. Gut. 1991 Nov 1;32(11):1321–3.

59. Hosseinpour M, Behdad A. Evaluation of small bowel measurement in alive patients. Surgical and Radiologic Anatomy. 2008 Nov;30(8):653–5.

60. Uro DD. Overview of short bowel syndrome and intestinal transplantation. Colombia Médica. 2007;38:5.

61. Cronin CG, Delappe E, Lohan DG, Roche C, Murphy JM. Normal small bowel wall characteristics on MR enterography. European Journal of Radiology. 2010 Aug 1;75(2):207–11.

62. stany lobo PK. Anatomy, Abdomen and Pelvis, Large Intestine. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470577/

63. Eickhoff A, Pickhardt PJ, Hartmann D, Riemann JF. Colon anatomy based on CT colonography and fluoroscopy: Impact on looping, straightening and ancillary manoeuvres in colonoscopy. Digestive and Liver Disease. 2010 Apr;42(4):291–6.

64. Alazmani A, Hood A, Jayne D, Neville A, Culmer P. Quantitative assessment of colorectal morphology: Implications for robotic colonoscopy. Medical Engineering and Physics. 2016;38(2):148–154.

65. Sadahiro S, Ohmura T, Yamada Y, Saito T, Taki Y. Analysis of length and surface area of each segment of the large intestine according to age, sex and physique. Surgical and Radiologic Anatomy. 1992 Sep;14(3):251–7.

66. Wiesner W, Mortelé KJ, Ji H, Ros PR. Normal Colonic Wall Thickness at CT and Its Relation to Colonic Distension: Journal of Computer Assisted Tomography. 2002 Jan;26(1):102–6.

67. Trefts E, Gannon M, Wasserman DH. The liver. Current Biology. 2017 Nov;27(21):R1147–51.

68. Turumin JL, Shanturov VA, Turumina HE. The role of the gallbladder in humans. Revista de Gastroenterología de México. 2013 Jul;78(3):177–87.

69. Anatomy and Histology of the Pancreas [Internet]. The University of Michigan Library; [cited 2020 Jan 7]. Available from: http://pancreapedia.org/?q=node/8098

70. Coffey JC. Surgical anatomy and anatomic surgery–clinical and scientific mutualism. The Surgeon. 2013;11(4):177–182.

71. Byrnes KG, Walsh D, Dockery P, McDermott K, Coffey JC. Anatomy of the mesentery: Current understanding and mechanisms of attachment. Seminars in Cell & Developmental Biology [Internet]. 2018 Oct 15 [cited 2018 Dec 17]; Available from: http://www.sciencedirect.com/science/article/pii/S1084952118302052

72. White EJ, Cunnane EM, McMahon M, Walsh MT, Coffey JC, O'Sullivan L. Mechanical characterisation of porcine non-intestinal colorectal tissues for innovation in surgical instrument design. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine. 2018 Aug;232(8):796–806.

73. Canadian Cancer Society [Internet]. Available from: www.cancer.ca

74. Kimmey MB, Martin RW, Haggitt RC, Wang KY, Franklin DW, Silverstein FE. Histologic Correlates of Gastrointestinal Ultrasound Images. Gastroenterology. 1989 Feb;96(2):433–41.

75. Nylund K, Hausken T, Ødegaard S, Eide G, Gilja O. Gastrointestinal Wall Thickness Measured with Transabdominal Ultrasonography and Its Relationship to Demographic Factors in Healthy Subjects. Ultraschall in der Medizin - European Journal of Ultrasound. 2012 Apr 13;33(07):E225–32.

76. Marchesini R, Pignoli E, Tomatis S, Fumagalli S, Sichirollo AE, Palma SD, et al. Ex vivo optical properties of human colon tissue. Lasers in Surgery and Medicine. 1994;15(4):351–7.

77. Lai SK, Wang Y-Y, Wirtz D, Hanes J. Micro- and macrorheology of mucus. Advanced Drug Delivery Reviews. 2009 Feb;61(2):86–100.

78. Pelaseyed T, Bergström JH, Gustafsson JK, Ermund A, Birchenough GMH, Schütte A, et al. The mucus and mucins of the goblet cells and enterocytes provide the first defense line

of the gastrointestinal tract and interact with the immune system. Immunological Reviews. 2014 Jul;260(1):8–20.

79. Cone RA. Barrier properties of mucus. Advanced Drug Delivery Reviews. 2009 Feb;61(2):75–85.

80. Leal J, Smyth HDC, Ghosh D. Physicochemical properties of mucus and their impact on transmucosal drug delivery. International Journal of Pharmaceutics. 2017 Oct;532(1):555–72.

81. Lock JY, Carlson TL, Carrier RL. Mucus models to evaluate the diffusion of drugs and particles. Advanced Drug Delivery Reviews. 2018 Jan;124:34–49.

82. Boegh M, Nielsen HM. Mucus as a Barrier to Drug Delivery - Understanding and Mimicking the Barrier Properties. Basic & Clinical Pharmacology & Toxicology. 2015 Mar;116(3):179–86.

83. Johansson MEV, Sjövall H, Hansson GC. The gastrointestinal mucus system in health and disease. Nature Reviews Gastroenterology & Hepatology. 2013 Jun;10(6):352–61.

84. Gustafsson JK, Ermund A, Johansson MEV, Schütte A, Hansson GC, Sjövall H. An ex vivo method for studying mucus formation, properties, and thickness in human colonic biopsies and mouse small and large intestinal explants. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2012 Feb;302(4):G430–8.

85. Lindahl A, Ungell A-L, Knutson L, Lennernäs H. Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women. Pharm Res. 1997 Apr 1;14(4):497–502.

86. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut. 1988 Aug 1;29(8):1035–41.

87. McDougall CJ, Wong R, Scudera P, Lesser M, DeCosse JJ. Colonic mucosal pH in humans. Digest Dis Sci. 1993 Mar 1;38(3):542–5.

88. Donald O. Castell RT. Gastroesophageal reflux monitoring: pH and impedance. GI Motility online (2006) [Internet]. 2006 May 16; Available from: https://www.nature.com/gimo/contents/pt1/full/gimo31.html

89. Singh H, Ye A, Horne D. Structuring food emulsions in the gastrointestinal tract to modify lipid digestion. Progress in Lipid Research. 2009 Mar;48(2):92–100.

90. Boland M. Human digestion - a processing perspective. Journal of the Science of Food and Agriculture. 2016 May;96(7):2275–83.

91. C. E. Stevenson RLW. Chemical Digestion and Absorption: A Closer Look. In. Available from: https://opentextbc.ca/anatomyandphysiology/chapter/23-7-chemical-digestion-and-absorption-a-closer-look/

92. Akshintala VS, Talukdar R, Singh VK, Goggins M. The Gut Microbiome in Pancreatic Disease. Clinical Gastroenterology and Hepatology. 2019 Jan;17(2):290–5.

93. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin J Gastroenterol. 2018 Feb;11(1):1–10.

94. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell. 2006;124(4):837–848.

95. Di Pilato V, Freschi G, Ringressi MN, Pallecchi L, Rossolini GM, Bechi P. The esophageal microbiota in health and disease: Esophageal microbiota and disease. Annals of the New York Academy of Sciences. 2016 Oct;1381(1):21–33.

96. Bik EM, Eckburg PB, Gill SR, Nelson KE, Purdom EA, Francois F, et al. Molecular analysis of the bacterial microbiota in the human stomach. Proceedings of the National Academy of Sciences. 2006 Jan 17;103(3):732–7.

97. Zoetendal EG, Raes J, van den Bogert B, Arumugam M, Booijink CC, Troost FJ, et al. The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates. ISME J. 2012 Jul;6(7):1415–26.

98. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Microbiology: Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635–1638.

99. Jandhyala SM. Role of the normal gut microbiota. World Journal of Gastroenterology. 2015;21(29):8787.

100. Krishnan S, Alden N, Lee K. Pathways and functions of gut microbiota metabolism impacting host physiology. Current Opinion in Biotechnology. 2015 Dec;36:137–45.

101. Egorov VI, Schastlivtsev IV, Prut EV, Baranov AO, Turusov RA. Mechanical properties of the human gastrointestinal tract. Journal of Biomechanics. 2002 Oct 1;35(10):1417–25.

102. Lim Y-J, Deo D, Singh TP, Jones DB, De S. In situ measurement and modeling of biomechanical response of human cadaveric soft tissues for physics-based surgical simulation. Surgical endoscopy. 2009;23(6):1298.

103. Egorov VI, Schastlivtsev V, Turusov RA, Baranov AO. Participation of the intestinal layers in supplying of the mechanical strength of the intact and sutured gut. Eur Surg Res. 2002 Dec;34(6):425–31.

104. Vanags I, Petersons A, Ose V, Ozolanta I, Kasyanov V, Laizans J, et al. Biomechanical properties of oesophagus wall under loading. Journal of Biomechanics. 2003 Sep 1;36(9):1387–90.

105. Yang W, Fung TC, Chian KS, Chong CK. Viscoelasticity of Esophageal Tissue and Application of a QLV Model. J Biomech Eng. 2006 May 11;128(6):909–16.

106. Jia ZG, Li W, Zhou ZR. Mechanical characterization of stomach tissue under uniaxial tensile action. Journal of Biomechanics. 2015 Feb 26;48(4):651–8.

107. Tan R, Liu H, Su G, Zhang C, Li H, Wang Y. Experimental investigation of the small intestine's viscoelasticity for the motion of capsule robot. In: 2011 IEEE International Conference on Mechatronics and Automation [Internet]. Beijing, China: IEEE; 2011 [cited 2020 Mar 4]. p. 249–53. Available from: http://ieeexplore.ieee.org/document/5985665/

108. O'Connor A, O'Moráin C. Digestive Function of the Stomach. DDI. 2014;32(3):186–91.

109. Sanders KM, Koh SD, Ro S, Ward SM. Regulation of gastrointestinal motility-insights from smooth muscle biology. Nature Reviews Gastroenterology and Hepatology. 2012;9(11):633–645.

110. Takaki M. Gut Pacemaker Cells: the Interstitial Cells of Cajal (ICC). Journal of Smooth Muscle Research. 2003;39(5):137–161.

111. Hinder RA, Kelly KA. Human gastric pacesetter potential. The American Journal of Surgery. 1977 Jan;133(1):29–33.

112. O'Grady G, Du P, Egbuji JU, Lammers WJEP, Wahab A, Pullan AJ, et al. A novel laparoscopic device for the measurement of gastrointestinal slow wave activity. Surg Endosc [Internet]. 2009 Dec [cited 2018 Aug 25];23(12):2842–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4106912/

113. Cheng LK. Slow wave conduction patterns in the stomach: from Waller's Foundations to Current Challenges. Acta Physiologica. 2015 Feb;213(2):384–93.

114. Vilarino F, Spyridonos P, DeIorio F, Vitria J, Azpiroz F, Radeva P. Intestinal Motility Assessment With Video Capsule Endoscopy: Automatic Annotation of Phasic Intestinal Contractions. IEEE Transactions on Medical Imaging. 2010 Feb;29(2):246–59.

115. Vu H, Echigo T, Sagawa R, Yagi K, Shiba M, Higuchi K, et al. Detection of contractions in adaptive transit time of the small bowel from wireless capsule endoscopy videos. Computers in Biology and Medicine [Internet]. 2009 Jan [cited 2018 Aug 25];39(1):16–26. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0010482508001522

116. Fleckenstein P. Migrating electrical spike activity in the fasting human small intestine. The American Journal of Digestive Diseases. 1978 Sep;23(9):769–75.

117. Sarna SK. Colonic Motility in Health [Internet]. Morgan & Claypool Life Sciences; 2010 [cited 2019 Mar 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53471/

118. Rao SSC, Sadeghi P, Beaty J, Kavlock R, Ackerson K. Ambulatory 24-h colonic manometry in healthy humans. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2001 Apr;280(4):G629–39.

119. O'Grady G, Du P, Cheng LK, Egbuji JU, Lammers WJEP, Windsor JA, et al. Origin and propagation of human gastric slow-wave activity defined by high-resolution mapping. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2010 Sep;299(3):G585–92.

120. Bassotti G, Gaburri M. Manometric investigation of high-amplitude propagated contractile activity of the human colon. American Journal of Physiology-Gastrointestinal and Liver Physiology. 1988 Nov 1;255(5):G660–4.

121. Worsøe J, Fynne L, Gregersen T, Schlageter V, Christensen LA, Dahlerup JF, et al. Gastric transit and small intestinal transit time and motility assessed by a magnet tracking system. BMC Gastroenterology [Internet]. 2011 Dec [cited 2018 Aug 22];11(1). Available from: http://bmcgastroenterol.biomedcentral.com/articles/10.1186/1471-230X-11-145

122. Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. Gut. 1996 Aug 1;39(2):299–305.

123. Maurer AH. Gastrointestinal Motility, Part 2: Small-Bowel and Colon Transit. J Nucl Med [Internet]. 2015 Sep 1 [cited 2018 Sep 30];56(9):1395–400. Available from: http://jnm.snmjournals.org/content/56/9/1395

124. Miller MA, Parkman HP, Urbain JL, Brown KL, Donahue DJ, Knight LC, et al. Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. Dig Dis Sci. 1997 Jan;42(1):10–8.

125. Camilleri M, Colemont LJ, Phillips SF, Brown ML, Thomforde GM, Chapman N, et al. Human gastric emptying and colonic filling of solids characterized by a new method. American Journal of Physiology-Gastrointestinal and Liver Physiology. 1989;257(2):G284–G290.

126. Krevsky B, Maurer AH, Niewiarowski T, Cohen S. Effect of verapamil on human intestinal transit. Digestive Diseases and Sciences. 1992 Jun;37(6):919–24.

127. Cummings JH, Jenkins DJ, Wiggins HS. Measurement of the mean transit time of dietary residue through the human gut. Gut [Internet]. 1976 Mar [cited 2019 Mar 24];17(3):210–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1411154/

128. Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. Nature Reviews Gastroenterology &

Hepatology [Internet]. 2012 May [cited 2018 Aug 27];9(5):271–85. Available from: https://www.nature.com/articles/nrgastro.2012.57

129. Takahashi T. Interdigestive migrating motor complex -its mechanism and clinical importance. Journal of Smooth Muscle Research. 2013;49(0):99–111.

130. Jouet P, Coffin B, Lémann M, Gorbatchef C, Franchisseur C, Jian R, et al. Tonic and phasic motor activity in the proximal and distal colon of healthy humans. American Journal of Physiology-Gastrointestinal and Liver Physiology. 1998 Mar;274(3):G459–64.

131. Ferrua M, Singh R. Modeling the Fluid Dynamics in a Human Stomach to Gain Insight of Food Digestion. J Food Sci. 2010 Sep;75(7):R151–62.

132. Milo R, Jorgensen P, Moran U, Weber G, Springer M. BioNumbers—the database of key numbers in molecular and cell biology. Nucleic Acids Research. 2010 Jan;38(suppl_1):D750–3.

133. Malbrain MLNG, De laet IE, De Waele JJ, Kirkpatrick AW. Intra-abdominal hypertension: Definitions, monitoring, interpretation and management. Best Practice & Research Clinical Anaesthesiology. 2013 Jun;27(2):249–70.

134. Balogh Z, Jones F, D'Amours S, Parr M, Sugrue M. Continuous intra-abdominal pressure measurement technique. The American Journal of Surgery. 2004 Dec;188(6):679–84.

135. De Keulenaer BL, De Waele JJ, Powell B, Malbrain MLNG. What is normal intra-abdominal pressure and how is it affected by positioning, body mass and positive end-expiratory pressure? Intensive Care Medicine. 2009 Jun;35(6):969–76.

136. Neumann P, Gill V. Pelvic Floor and Abdominal Muscle Interaction: EMG Activity and Intra-abdominal Pressure. International Urogynecology Journal. 2002 Apr;13(2):125–32.

137. Miftahof R, Akhmadeev N. Dynamics of intestinal propulsion. Journal of theoretical biology. 2007;246(2):377–393.

138. Arshak A, Arshak K, Waldron D, Morris D, Korostynska O, Jafer E, et al. Review of the potential of a wireless MEMS and TFT microsystems for the measurement of pressure in the GI tract. Medical engineering & physics. 2005;27(5):347–356.

139. Bertuzzi A, Salinari S, Mancinelli R, Pescatori M. Peristaltic transport of a solid bolus. Journal of biomechanics. 1983;16(7):459–464.

140. Miftahof R, Fedotov E. Intestinal propulsion of a solid non-deformable bolus. Journal of Theoretical Biology. 2005;235(1):57–70.

141. Miftahof RN. The wave phenomena in smooth muscle syncytia. In silico biology. 2005;5(5, 6):479–498.

142. Terry BS, Schoen JA, Rentschler ME. Characterization and experimental results of a novel sensor for measuring the contact force from myenteric contractions. IEEE Transactions on Biomedical Engineering. 2012;59(7):1971–1977.

143. Terry BS, Schoen JA, Rentschler ME. Measurements of the contact force from myenteric contractions on a solid bolus. Journal of robotic surgery. 2013;7(1):53–57.

144. Terry BS, Francisco MM, Schoen JA, Rentschler ME. Sensor for Measuring the Contact Force From Human Myenteric Contractions for In Vivo Robotic Capsule Endoscope Mobility. J Med Devices. 2013 Sep 1;7(3):030911.

145. Terry BS, Lyle AB, Schoen JA, Rentschler ME. Preliminary Mechanical Characterization of the Small Bowel for In Vivo Robotic Mobility. Journal of Biomechanical Engineering. 2011;133(9):091010.

146. Calio R, Camboni D, Alcaide JO, Oddo CM, Carrozza MC, Menciassi A, et al. Robotic endoscopic capsule for closed-loop force-based control and safety strategies. In: 2017 IEEE International Conference on Cyborg and Bionic Systems (CBS) [Internet]. Beijing: IEEE; 2017 [cited 2018 Oct 4]. p. 253–6. Available from: http://ieeexplore.ieee.org/document/8266110/

147. King M. Experimental models for studying mucociliary clearance. European Respiratory Journal. 1998;11(1):222–228.

148. Terry BS, Passernig AC, Hill ML, Schoen JA, Rentschler ME. Small intestine mucosal adhesivity to in vivo capsule robot materials. Journal of the mechanical behavior of biomedical materials. 2012;15:24–32.

149. Varum FJO, Veiga F, Sousa JS, Basit AW. An investigation into the role of mucus thickness on mucoadhesion in the gastrointestinal tract of pig. European Journal of Pharmaceutical Sciences. 2010 Jul;40(4):335–41.

150. Kern MD, Ortega Alcaide J, Rentschler ME. Soft material adhesion characterization for in vivo locomotion of robotic capsule endoscopes: Experimental and modeling results. Journal of the Mechanical Behavior of Biomedical Materials. 2014 Nov;39:257–69.

151. Dodou D, van den Berg M, van Gennip J, Breedveld P, Wieringa PA. Mucoadhesive films inside the colonic tube: performance in a three-dimensional world. Journal of The Royal Society Interface. 2008 Nov 6;5(28):1353–62.

152. Dodou D, Girard D, Breedveld P, Wieringa PA. Intestinal locomotion by means of mucoadhesive films. In: ICAR '05 Proceedings, 12th International Conference on Advanced Robotics, 2005 [Internet]. Seatle, WA, USA: IEEE; 2005 [cited 2019 Oct 4]. p. 352–9. Available from: http://ieeexplore.ieee.org/document/1507435/

153. Pensabene V, Valdastri P, Tognarelli S, Menciassi A, Arezzo A, Dario P. Mucoadhesive film for anchoring assistive surgical instruments in endoscopic surgery: in vivo assessment of deployment and attachment. Surgical Endoscopy. 2011 Sep;25(9):3071–9.

154. Dodou D, Breedveld P, Wieringa PA. Stick, unstick, restick sticky films in the colon. Minimally Invasive Therapy & Allied Technologies. 2006 Jan;15(5):286–95.

155. Sliker L, Ciuti G, E. Rentschler M, Menciassi A. Frictional resistance model for tissue-capsule endoscope Sliding contact in the gastrointestinal tract. Tribology International. 2016 Jun 1;102.

156. Kim JS, Sung IH, Kim YT, Kim DE, Jang YH. Analytical model development for the prediction of the frictional resistance of a capsule endoscope inside an intestine. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine. 2007;221(8):837–845.

157. Woo SH, Kim TW, Mohy-Ud-Din Z, Park IY, Cho J-H. Small intestinal model for electrically propelled capsule endoscopy. Biomedical engineering online. 2011;10(1):108.

158. Baek NK, Sung IH, Kim DE. Frictional resistance characteristics of a capsule inside the intestine for microendoscope design. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine. 2004;218(3):193–201.

159. Zhang C, Liu H, Tan R, Li H. Modeling of velocity-dependent frictional resistance of a capsule robot inside an intestine. Tribology Letters. 2012;47(2):295–301.

160. Lyle AB, Luftig JT, Rentschler ME. A tribological investigation of the small bowel lumen surface. Tribology International. 2013 Jun;62:171–6.

161. Lyle AB, Terry BS, Schoen JA, Rentschler ME. Preliminary Friction Force Measurements on Small Bowel Lumen When Eliminating Sled Edge Effects. Tribology Letters. 2013 Sep;51(3):377–83.

162. Kim J-S, Sung I-H, Kim Y-T, Kwon E-Y, Kim D-E, Jang YH. Experimental investigation of frictional and viscoelastic properties of intestine for microendoscope application. Tribology Letters. 2006 May;22(2):143–9.

163. Wang KD, Yan GZ. Research on measurement and modeling of the gastro intestine's frictional characteristics. Measurement Science and Technology. 2008;20(1):015803.

164. Jiwoon Kwon, Sukho Park, Byungkyu Kim, Jong-Oh Park. Bio-Material Property Measurement System for Locomotive Mechanism in Gastro-Intestinal Tract. In: Proceedings of the 2005 IEEE International Conference on Robotics and Automation [Internet]. Barcelona, Spain: IEEE; 2005 [cited 2018 Nov 6]. p. 1303–8. Available from: http://ieeexplore.ieee.org/document/1570295/

165. Wang X, Meng MQ. An experimental study of resistant properties of the small intestine for an active capsule endoscope. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine. 2010;224(1):107–118.

166. Kwon J, Cheung E, Park S, Sitti M. Friction enhancement via micro-patterned wet elastomer adhesives on small intestinal surfaces. Biomed Mater. 2006;1(4):216.

167. Xiaona Wang, Meng MQ-H. Study of Frictional Properties of the Small Intestine for Design of Active Capsule Endoscope. In: The First IEEE/RAS-EMBS International Conference on Biomedical Robotics and Biomechatronics, 2006 BioRob 2006 [Internet]. Pisa, Italy: IEEE; 2006 [cited 2018 Nov 1]. p. 124–9. Available from: http://ieeexplore.ieee.org/document/1639071/

168. Bai JPF, Burckart GJ, Mulberg AE. Literature Review of Gastrointestinal Physiology in the Elderly, in Pediatric Patients, and in Patients with Gastrointestinal Diseases. Journal of Pharmaceutical Sciences. 2016 Feb;105(2):476–83.

169. Salminen S, Bouley C, Boutron M-C, Cummings JH, Franck A, Gibson GR, et al. Functional food science and gastrointestinal physiology and function. Br J Nutr. 1998 Aug;80(S1):S147–71.

170. Gajendran M, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, et al. A comprehensive review and update on ulcerative colitis. Disease-a-Month. 2019 Dec;65(12):100851.

171. Effinger A, O'Driscoll CM, McAllister M, Fotaki N. Impact of gastrointestinal disease states on oral drug absorption - implications for formulation design - a PEARRL review. J Pharm Pharmacol. 2019 Apr;71(4):674–98.

172. Sasaki Y, Hada R, Nakajima H, Fukuda S, Munakata A. Improved localizing method of radiopill in measurement of entire gastrointestinal pH profiles: colonic luminal pH in normal subjects and patients with Crohn's disease. Am J Gastroenterol. 1997 Jan;92(1):114–8.

173. Tojo R. Intestinal microbiota in health and disease: Role of bifidobacteria in gut homeostasis. WJG. 2014;20(41):15163.

174. Liao Z, Liu H, Komaki R. Target Delineation for Esophageal Cancer. Journal of Women's Imaging. 2003 Nov;5(4):177–86.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests: Not applicable

Funding: Not applicable

Authors' contributions:

Lavinia Barducci, substantial contributions to the design of the work, to the writing and to the design of the figures

Joseph C. Norton, contributions to the design and to the writing of the work

Sunandita Sarker, substantial contribution to the writing of the work

Sayeed Mohammed, contribution to the writing and to the design of the figures

Ryan Jones, substantial contributions to the conception of the work and to the revision of the manuscript

Pietro Valdastri, substantively revised the manuscript

Benjamin Terry, substantial contributions to the conception of the work and to the revision of the manuscript.

Acknowledgements: Not applicable