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Mechanical Characterization of the Small Intestine for In vivo Robotic Capsule Endoscope Mobility

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MECHANICAL CHARACTERIZATION OF THE SMALL INTESTINE FOR
IN VIVO ROBOTIC CAPSULE ENOSCOPE MOBILITY

by

Benjamin Spencer Terry

B.S. Brigham Young University, 1997
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This thesis entitled:
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Capsule Endoscope Mobility
written by Benjamin Spencer Terry
has been approved for the Department of Mechanical Engineering

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Mark E. Rentschler

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Date____________

The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.
Terry, Benjamin Spencer (Ph.D., Department of Mechanical Engineering)

Mechanical Characterization of the Small Intestine for *In vivo* Robotic Capsule Endoscope Mobility

Thesis directed by Assistant Professor Mark E. Rentschler

The state-of-the-art in enteroscopic surgery and therapeutic care continues to minimize invasiveness, cost, surgery time, and patient trauma. To this end, a new class of medical device, called the robotic capsule endoscope, is being pursued by multiple research groups. These potentially swallowable devices will radically expand the capabilities of natural orifice surgery by performing non-invasive tasks within the gastrointestinal tract that are now only possible with enteroscopic, laparoscopic, or open surgery. It is necessary for a robotic capsule endoscope to possess active, controlled mobility, which involves interactions between gastrointestinal tissue and engineering materials. Design challenges stem from the nonlinear and variable mechanical and physiological response of tissue and organs to the robot and from poor understanding of interfacial properties. In this work we initiate a study of the mechanical properties of the small intestine with the goal of accelerating the development of *in vivo* robotic capsule endoscopes for the gastrointestinal tract. To this end, four investigative devices and testing methods are presented: 1) A novel tribometer that measures the *in vivo* coefficient of friction between the mucosa and the robot surface; 2) An *in vitro* biaxial test apparatus and method for characterizing in-plane biomechanical
properties of the bowel wall; 3) An in vitro test protocol to characterize the adhesive properties of mucosa; and 4) A novel manometer and force sensor array that measure the in vivo myenteric contact force against a solid bolus. Using these devices and test methods, the tribometry, passive biomechanics, mucosal adhesivity, and contractile response of the small intestinal tissue from multiple porcine models are measured. The results of this study offer crucial yet previously unknown biomechanical properties of the small intestine and have provided a foundation for the development of a unified and comprehensive model of the interactions between a robotic capsule endoscope and the intraluminal environment.
DEDICATION

This work is dedicated to my wife and children: Rachel, Rebecca, Spencer, and Evangeline. They have sacrificed much so that I could pursue my personal goal of returning to academia to do two things I love: research and teach. Hopefully, my children have gained something valuable from this experience such as an acute awareness of the importance of exploring the world and learning as much as possible about it during our short tenure here.
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Chapter 1: Introduction

Multiple research groups are investigating the feasibility of miniature, swallowable, in vivo, untethered robots that are capable of traversing the gastrointestinal tract for the purpose of diagnosing pathologies, acquiring biometrics, and performing next-generation minimally invasive surgical procedures [1], [2]. The gastrointestinal (GI) tract, however, is a challenging environment for an in vivo robotic capsule endoscope (RCE). A robot must navigate a tortuous path, ascend and descend mucus coated surfaces, and travel against peristaltic forces generated by the migrating motor complex (MMC). In addition, the intestine wall is soft, delicate, and narrow, which constrains the size of a robot and provides minimal mechanical support [3]. This design effort of RCEs has also been hindered, in part, by the lack of knowledge concerning the biomechanical properties of the intraluminal environment. A unified model of this environment will speed the development of RCEs, and to this end, we have established a comprehensive program for characterizing both the active and passive forces exerted by the small
intestine on an RCE-shaped solid bolus [4]. If proficient mobility within the lumen can be achieved, RCEs could perform tasks in a minimal or even non-invasive manner, which are currently only possible with open or laparoscopic surgery. Candidate procedures for RCEs are numerous. For example, gallstone and polyp removal, biopsy acquisition, identification and repair of ulcers, and radiopaque marking may all be possible with the RCE platform [5], [6].

Current research in this area is growing, with various groups developing RCEs using a variety of methods for locomotion [7–13]. Limited research, however, has been done to characterize the intraluminal forces experienced by an RCE. Some numerical modeling has been developed [14]; however, with the exception of a few groups [5], [15–20], there is little work regarding the magnitude and spatiotemporal nature of the forces experienced by a solid bolus within the small bowel. Calculating these forces requires detailed knowledge of the interfacial and biomechanical response of the gastrointestinal (GI) tissue to an RCE. In this work, our primary goal is to accelerate the development of in vivo robotic capsule endoscopes for the GI tract by characterizing four important biomechanical properties of the small intestine: the coefficient of friction between the inner surface (the mucosa) of the bowel and the surface of the RCE, the adhesivity of the mucosa to the RCE, the passive biomechanical response of the small intestinal tissue to stress, and the physiological response of the tissue to a solid bolus.
1.1 *In vivo* Forces

In general, five phenomena contribute to the forces experienced by a solid bolus such as an RCE: active forces, biomechanical response of tissue, tribology, adhesion, and gravity (Figure 1). Active forces are generated by muscle layers of the GI, which generally propel a bolus aborally. Intra-abdominal pressure gradients are created by respiration, cardiovascular activity, and skeletal muscle tone and movement. The stomach acts like a pump and generates hydrostatic pressure against the oral side of the bolus. The GI tract is an incompressible, viscoelastic, and multilayered organ system that, in its relaxed state, readily deforms under stress. The biomechanical response of the tissue to stress contributes to the forces experienced by a bolus. Tribological factors contribute forces that affect the movement of an RCE. For example, dry friction and fluid shear stress (or lubricated friction) between the robot’s surface and the mucosal lining of the intestine oppose travel. Adhesion of the mucus to itself and the robot also impede movement. If the RCE is administered orally, gravity will generally propel it aborally, with buoyancy having the opposite effect. All of these forces are stochastic due to variability inherent in biological systems.
1. Forces experienced by an RCE traveling in the aboral direction are from myenteric contractions, “pump” pressure generated by the stomach and duodenum, abdominal pressure, hydrostatic pressure, biomechanical response of the tissue, mucoadhesion, dry friction, fluid shear, and gravity (mg).

1.2 Scope of Research

The aim of this work is to create a suite of devices and test methods to characterize or measure the active forces, passive biomechanical response, tribology, and mucosal adhesivity associated with the mobility of an RCE within the GI tract. The effects of gravity and buoyancy were not investigated in this work. Also, the research was limited to the small intestine of the GI tract because the esophagus, stomach, and colon are more readily accessible using traditional endoscopy. Because of the small intestine’s remote location,
therapeutics, diagnostics, and treatment of the small intestine would be enhanced by RCE technology more than any other region of the GI tract.

Specifically, the following four devices or test methods were developed:
1) An \textit{in vivo} tribometer consisting of a linear actuator, sliding platen, and force sensor to characterize friction forces between the mucosa of the intestine and the robot’s surface; 2) An \textit{in vitro} method to measure the adhesivity of mucosa; 3) An \textit{in vitro} biaxial test method and device to characterize the passive in-plane strain response of the small intestinal tissue to stress; 4) An \textit{in vivo} device, called the migrating motor complex force sensor (MFS), consisting of a monometer and linear array of force sensors to characterize active myenteric response to a solid bolus. Multiple live porcine models were used for \textit{in vivo} testing, after which the tissue is harvested for further testing \textit{in vitro}.

1.3 Definition of Terms

The following table lists definitions of the acronyms and terms.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboral</td>
<td>In the direction opposite the oral cavity</td>
</tr>
<tr>
<td>COF</td>
<td>Coefficient of friction</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>LRS</td>
<td>Lactated ringer’s solution</td>
</tr>
<tr>
<td>MMC</td>
<td>Migrating motor complex</td>
</tr>
<tr>
<td>Myenteron</td>
<td>Smooth muscle layers of the small intestine</td>
</tr>
<tr>
<td>NOTES</td>
<td>Natural orifice translumenal surgery</td>
</tr>
<tr>
<td>PDMS</td>
<td>Polydimethylsiloxane</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate buffered saline</td>
</tr>
<tr>
<td>RCE</td>
<td>Robotic capsule endoscope</td>
</tr>
</tbody>
</table>
Chapter 2: Background and Literature Review

Following is a discussion of the anatomy and physiology of the small intestine and research performed to date regarding the characterization of the tribology and adhesivity between engineering materials and the mucosa, the passive biomechanical response of the intestinal tissue to stress, and the active myenteric response of the tissue to a solid bolus. These topics are discussed in the context of in vivo robotic capsule endoscope mobility within the small intestine.

2.1 Anatomy and Histology of the Small Intestine

The human gastrointestinal (GI) tract (Figure 2) is a septic, multilayered tube that begins at the oral cavity and ends at the anus, two natural orifices that are the focus of NOTES [6], [21], [22]. To reach the small intestine in a minimally invasive fashion, an RCE must either traverse the esophagus, stomach, and pyloric valve (the sphincter between the stomach and the small intestine), or it must traverse the anus, rectum, and large intestine.
2.1.1 Gross Anatomy

The small intestine itself is divided into three anatomical regions, the duodenum, jejunum, and ileum (from oral to aboral). Its length for the average male is 7 m (range of 5 m to 10 m) [23]. The duodenum is about 0.4 m long and is the region of small intestine with the largest diameter at about 4.5 cm [24]. The jejunum is about 2.7 m long, 4 cm wide, vascular, and distinguished by large circular folds in the mucus membrane that can be felt by grasping the tissue between the finger and thumb. The circular folds contain microscopic villi and microvilli, which dramatically increase the surface area of the small intestine for absorption. The villi and microvilli are actuated by the muscularis mucosae so that they undulate, thus further increasing absorption due to the microscale currents generated by their movement [25], [26]. The folds themselves tend to slow transit of intestinal contents. The ileum is about 4 m long and gradually diminishes in diameter to about 3.5 cm. It is less vascular than the jejunum and possesses few circular folds. The folds disappear altogether at the aboral end of the ileum [27]. The wall thickness of the small intestine measures between 1 and 2 mm and thins slightly along its length [24].

The small intestine maintains a slight curvature and is attached to the mesentery along the inner radius. The mesentery anchors the organ to the posterior peritoneal wall and its vasculature provides nutrition to the organ and receives absorbed nutrients [28].
2.1.2 Histology

The small intestine is an incompressible, viscoelastic, and multilayered organ. Examining the cross section of the small intestine reveals (from the outermost layer to the innermost) the serosa, which is a thin layer of loose connective tissue, mesothelium, and oriented elastin and collagen fibers (Figure 3). Beneath the serosa is the muscularis externa, which consists of the longitudinally and circularly oriented, mutually orthogonal smooth muscle layers (the myenteron). The myenteron is innervated and vascularized by the myenteric plexus. Next is the submucosa, a fibrous, loose connective tissue layer, which provides an attachment point to the myenteron for the remaining layers. The submucosal plexus innervates and vascularizes the mucosa. The muscularis mucosa is a thin layer of randomly oriented
smooth muscles cells that keep the mucosa in a constant state of agitation to facilitate the dispersal of the mucus from the glandular epithelial cells in the mucosa, and as mentioned, facilitate absorption [29]. The mucus layer consists of phospholipids, sloughed cells, electrolytes, glycoproteins, various cellular and serum macromolecules, and water [30]. The function of the mucus is to protect the mucosa from “autodigestion” and mechanical abrasion of the intestinal contents.

The morphology of the small bowel, and presumably the biomechanics, vary throughout its length. As discussed, the duodenum and proximal end of the jejunum are generally wider, more vascular, and have greater wall thickness than the ileum. The myenteron provides most of the mechanical support while the mucus and serous layers provide little [5]. The cross-section of the lumen is somewhat asymmetrical due to its natural curvature and the attachment of the mesentery to the inner radius. The attachment point is highly vascular, whereas the outside radius of the lumen contains fewer blood vessels.
2.1.3 Validity of Porcine Models

Porcine models are used throughout this study because the gastrointestinal tract of pigs is anatomically similar to that of humans [31].

2.2 Tribology

Characterizing friction between the robot and the inner surface of the small intestine (the mucosa) is important for RCE mobility in terms of energy losses as well as mechanical advantage for movement. Characterization of friction, however, is complicated by several factors. For one, the mucosa and its underlying tissue are viscoelastic, inhomogeneous, composite, nonlinear deformable materials. In addition, there are random bends throughout the length of the GI tract, some very tortuous. The surface of the mucosa contains numerous folds and small valleys on multiple length scales, and continually excretes mucus—a non-Newtonian fluid [32].

Creating a comprehensive friction model of the small bowel involves characterizing the tribological components, which are dry or coulomb friction...
and viscoelasticity of the mucosa, fluid shear and other rheological properties of the mucus, the biomechanical properties of the tissue (discussed in Section 2.4), and robot surface geometry and materials. Presently, there is no comprehensive tribological model in the literature that considers the friction force between the mucosa and an \textit{in vivo} RCE. Current intestinal tribological research focuses on a particular robot or geometry of interest, and thus the literature reports only data for the specific device being tested [33–38].

2.2.1 Dry Friction and Tissue Viscoelasticity

An RCE experiences dry or coulomb friction when the robot’s surface comes into contact with the mucosa. The degree of contact between these two surfaces is a function of the mucus layer thickness, the geometry of the RCE tread or other mechanism used for mechanical advantage, speed, and pressure. Friction between viscoelastic and relatively stiff surfaces has been investigated by several groups; for example, Ludema and Tabor study the friction coefficient between rubber and a glass hemisphere. They investigate speeds from $10^{-5}$ to 1 cm s$^{-1}$, a range that corresponds well to robotic endoscopes. They report that there is a close relation between friction force and viscoelasticity [39]. Significant research has been conducted to measure the friction coefficient of human skin to a multitude of engineering materials and there are sufficient anatomical and physiological differences between skin and mucosa that these studies are probably not applicable to \textit{in vivo} RCE
applications. No known studies measure the dry friction coefficient of engineering materials on mucosa.

2.2.2 Mucus Rheology

An RCE will have significant interactions with the mucosal excretions of the small intestine. Understanding the rheology of mucus is critical for the optimization of RCE. Lai et al. report that the rheological behavior of mucus depends on the scale. At the nano scale it behaves as a low-viscosity fluid, but at the macro scale it behaves as a non-Newtonian gel and responds to shear rate and stress [32]. Scale will need to be considered in order to create an effective model for in vivo mobility due to the likelihood of multiple scales interacting with the mucus, such as an RCE with a micro- or nano-scale tread features. This characteristic of mucus is confirmed by Zhou et al. who studied the viscous properties of GI mucus from 50 healthy individuals. They also discovered that the mucus behaves as a non-Newtonian fluid: its viscosity decreases with increased shear rate up to a point and then becomes constant [40]. Multiple apparatuses have been developed to characterize mucus rheology, such as the cone and plate rheometer, capillary viscometer, magnetic microrheometer, filancemeter (which measures spinnability and is particularly useful for measuring elasticity), and particle tracking microrheology [32]. These tools have been used to quantify some of the rheological properties of GI mucus. Using the cone and plate rheometer, Bell et al. found the elastic modulus is greater than the viscous modulus in the
range of $10^{-2}$ to $10^2$ rad s$^{-1}$ [41]. The viscosity has been reported to be about 0.085 Pa-s at a shear rate of 1.15 s$^{-1}$ [42].

2.2.3 Geometry Specific Testing

Various research groups have conducted experiments by sliding rectangular and capsule-shaped sleds along a flattened specimen [34] and sliding capsules of varying geometries and weights through a closed intestinal specimen [43], [44]. Most of the current work is \textit{in vitro} testing with the colon. For example, Wang and Yan investigate the effects of four surface geometry profiles on friction force (including the edge effects). Each profile progressively becomes smoother, thus testing a combination of dry friction (with the triangular shaped profile) and fluid shear (the flat profile). The sled is dragged at a constant speed across the colon’s surface. Weights of 10, 20, 30, 50, 60, 70, and 100 grams are placed on the sled to increase the normal force. The test is repeated for each weight. Regardless of weight and speed, the coefficient of friction decreased from one profile to the next as shown in Figure 4. Coefficients of friction ranged from about 0.1 to 0.9 depending on the weight and sled geometry profile. They conclude that the dry frictional force is related to the viscoelastic properties of the tissue and the contact angle of the sled surface against the tissue, and fluid shear force is determined by contact area and contact angle [38].
Figure 4. Four sled surface geometry profiles investigated by Wang et al. on the mucosa of the colon.

Dodou et al. investigate the impact of plane geometry on friction of mucoadhesive films for robotic endoscope applications. They develop a theoretical model that predicts static friction of a mucoadhesive against the mucosa of the colon. The model considers the material properties of the colon and the planar geometrical characteristics of the adhesive. The optimal pattern is circular with concentric rings of mucoadhesive. Other patterns were investigated such as rectangles, squares, triangles, and permutations of those shapes with varying aspect ratios or altered shearing directions [45].

2.3 Mucosal Adhesivity

The mucosa of the small bowel is comprised of an epithelial layer of simple columnar goblet cells that continually excrete a protective mucus coating that affects the mobility of an RCE navigating in this environment. Mucus consists of two layers: a gel-like substance that is firmly adhered to the mucosa, and a loosely adhered layer that is readily removed by
mechanical shear or suction [46]. The glycoprotein molecules in the mucus have hydrophilic and viscoelastic properties and an ability to adhere to particulate matter, e.g. an RCE, thus facilitating the removal of intestinal contents from the GI tract without damaging the mucosa. The mucus layer flows like a fluid under low shear forces yet is also able to elastically recover from deformation [47]. To gain passage while traveling in vivo, the RCE will expend energy to overcome adhesivity of the mucosa collapsed on itself as well as energy to overcome peel forces between the RCE tread (in the case of a wheeled robot) and the mucosa (these regions of energy expenditure due to peel are shown in Figure 5). Manipulation of the bowel tissue by the RCE may also involve coplanar contact between the RCE or its instruments and the mucosa. Coplanar contact and separation between the RCE and the mucosa is called tack, and together with peel, are the two primary adhesive modalities. Following is a discussion of mucus properties that are relevant to adhesivity.

![Image of RCE traveling in vivo through the collapsed small intestine](image.png)

**Figure 5.** Schematic of RCE traveling in vivo through the collapsed small intestine. Regions of mucosal peeling are indicated by dotted lines.
2.3.1 Mucus Thickness

As mentioned, the mucosa continually excretes mucus. At the time of writing, there is no experimental data regarding the thickness of the mucus layer in the human small intestine; however, the thickness of the mucus layer assessed in a single porcine model is 25.9 ± 11.8 μm at the proximal end of the duodenum, and gradually thickens to 31.0 ± 15.7 μm at the distal end of the ileum [48]. The thickness is a function of the secretion rate of the goblet cells, erosion by mechanical shear, and bacterial digestion [49]. Thus, the mechanical actions of an RCE will alter the thickness of this layer and could expose the delicate mucosa to mechanical abrasion or autodigestion. Effects from mechanically disrupting the mucus layer should be temporary, however, because the mucus layer completely regenerates in 24 and 48 hours [50].

2.3.2 Mucosal Bioadhesives

Mucosal bioadhesives, or mucoadhesives are polymers that form bonds with mucus and have been developed primarily for the enhancement of drug delivery. There are benefits of developing such devices for RCE applications. For example, tread material made from mucoadhesives could be a means of increasing static friction for enhanced traction of an in vivo mobile device [51], [52]. To date, however, literature regarding the adhesive and cohesive properties of mucus in the human gastrointestinal tract is limited to the application of drug delivery enhancement through the use of new bioadhesives. For example, Varum et al. determine the effectiveness of a
mucosal bioadhesive by mounting a sample of the small intestine in the lower test grip of a pull test apparatus heated to 37° C (Figure 6). The bioadhesive is adhered to the upper grip using double sided tape then lowered into contact with the tissue sample at a speed of 10 mm min\(^{-1}\). The upper grip is stopped when the compressive force reaches 0.5 N. The upper grip is raised at 20 mm min\(^{-1}\) and displacement and force on the grip are recorded [48]. Work of adhesion is calculated by:

\[
W = \int_{0}^{\delta_f} F \cdot \delta_s
\]  

(2.1)

Where \(F\) is the force to separate the mucosa from the bioadhesive, \(\delta_f\) is the final displacement of the upper grip (starting at zero displacement when the bioadhesive is pressed against the mucosa).

Figure 6. Setup used by Varum et al. for testing work of adhesion of bioadhesives. The bioadhesive is first lowered until it contacts the small intestine (A) and then retracted (B).
One shortcoming of this approach is that the work calculated in (2.1) includes not only the adhesion, which is the energy dissipated in the material, but it also includes the energy related to the deformation of the bulk material. In other words, this is combined interfacial and bulk dissipation energy. Some recent work has been performed to create a test method for determining the interfacial and bulk deformation energy separately; however the method requires a transparent adhesive, which the mucus is not [53].

2.3.3 Adhesivity and In vivo Robotic Mobility

Mucosal adhesivity is how well mucosa bonds to a solid surface, which is also measured by the energy required to separate the solid surface from the mucosa. Several factors affect adhesivity, such as hydration, mucosa surface tension, wettability, and dwell time, which is the amount of time the mucosa is in contact with the solid surface prior to separation [54]. At present, there is no literature regarding adhesivity of small intestinal mucosa to an RCE or mucosa adhered to mucosa. One of the primary objectives of this work is to determine the adhesive properties of the mucosa and estimate the effect of adhesion on an RCE.

2.4 Passive Biomechanics

Prior to the past 10 years, gastroenterological research was based primarily on experimental methods. The recent success of mathematical and numerical modeling of the cardiovascular and respiratory systems has
recently prompted their application to the GI tract. Dong-Hua et al. broadly categorize recent mathematical and numeric modeling of the GI tract into three areas: In vivo medical image-based models, anatomy-based GI modeling, and theoretical analysis-based modeling [55]; however, most of this new modeling is focused on the esophagus and colon. The primary purpose of these modeling studies is for early disease prediction and diagnosis, whereas the purpose of this work is to characterize the soft tissue of the small intestine for in vivo robotic applications.

2.4.1 Modeling Soft Tissue Mechanics

Development of the constitutive equations that describe the passive biomechanics of the small intestine is a necessary component for the efficient development of RCEs. In order to develop these constitutive equations, accurate, multi-dimensional data describing the stretch response of the tissue to stress is needed. One of the four primary objectives of this research is to obtain the experimental data needed for the derivation of the constitutive equations, which should be addressed by future research. To corroborate the need for this data, and subsequent equations, Gregersen states:

It is clear that what is most needed are the constitutive equations of the gastrointestinal tract. Once the constitutive equation is known, the distribution of physical stresses and strains in the duodenum in vivo, and the function of bolus transport and fluid movement in the gastrointestinal tract can be analyzed by methods of continuum mechanics. The analytical
results will relate the stress and function with the geometric parameters (e.g., the circumferential length, wall thickness, tangent rotation angle, etc.). The task of determining the constitutive equations is not as daunting as it seems, because the mathematical form of most soft tissues is known [56].

The mathematical form of soft tissue spoken of here is based on work commenced by Fung and further refined by many others [56–60]. Examples of analytical and numerical modeling of the small intestine for in vivo robotics applications are limited; therefore, as stated, one objective of this work is to experimentally generate data that describes the biomechanical response of the tissue to stress.

2.4.2 Experimental Data

Little experimental data exists regarding the biomechanical response of the small intestine. A very simple, uniaxial experiment is performed by Viacheslav et al. who test the circumferential and longitudinal tensile properties of the small intestine of 46 cadavers (mean age at death 55±9 years, tested within 24 hours of death). Each sample is uniaxially stretched (without preconditioning) past tissue failure. Their data show that the small intestine supports a maximum stress of $0.83 \pm 0.28$ MPa at $87.93 \pm 22.97\%$ strain in the circular direction and a maximum stress of $1.472 \pm 0.499$ MPa at $36.76 \pm 10.77\%$ strain in the longitudinal direction. This result suggests the tissue is more distensible in the circular direction [19].
Frokjaer et al. insert a fluid filled bag into the duodenum containing an ultrasonic probe and pressure transducer. As they inflate the bag they obtain ultrasonic images of the duodenal cross-section from which they calculate the outside diameter and wall thickness. They are then able correlate intraluminal pressure with cross-sectional geometry and formulate the tension-strain relationships of the tissue [61]. One shortcoming of this approach is that the tension-strain relationship does not consider the structured and layered histological attributes of the tissue, but bases the analysis on the three-dimensional surface geometry.

Høeg et al. perform mechanical characterization the small intestine for their specific in vivo robotic application: an inchworm-type robot that generates radial pressure against the mucosa by inflating balloon segments [16]. They create an in vivo biomechanical modeling test apparatus (Figure 7) where an intestinal segment is clamped onto the apparatus with the mesentery intact, pressurized, and axial and longitudinal measurements are recorded. Mesentery is kept intact to maintain blood supply to the tissue. In particular, their study focuses on pressure thresholds that may cause ischemia in the bowel tissue and subsequent damage. The small bowel of a single live pig is tested with the ischemia observed at an average internal bowel pressure of 4.6 kPa (standard deviation of 0.6 kPa). They also investigate the stress-strain relationship of the tissue using their device and conclude that the circumferential direction is stiffer than the longitudinal
direction. Interestingly, this is the opposite result obtained by Viacheslav et al [19].

Figure 7. In vivo biomechanical modeling test apparatus created by Høeg et al.

Recent work by Bellini et al describes the measurement of the in-plane biaxial stress-stretch response of small intestinal tissue [62]. They measure tissue samples from the duodenum, jejunum, and ileum and develop parameters for numerical and analytical phenomenological constitutive models. Due to the high variability in the tissue mechanical properties, they fit data to so-called “averaged isotropic” models, which resulted in very poor fitting: “R² for the nonlinear regressions were 0.17, 0.44, and 0.93 for the average Neo-Hookean, Mooney-Rivlin, and Fung models, respectively.” [62] Although it appears the data fit the Fung model well (R² of 0.93), in actuality this is only the case for specific samples—general fitting was unacceptably low.
2.4.3 Analytical Modeling

At the time of writing there are no analytical models that successfully and generally describe the stress-stretch response of the small intestine. Therefore following is a discussion of modeling work and methods that could be directly applied or adapted to stress-strain data from the small intestine. Mechanical modeling of the colon is more common and various groups have modeled that tissue based on porcine samples. Dario et al. create a model of the porcine colon wall that captures its composite nature by modeling it as an anisotropic continuum with mutually orthogonal muscle fibers and cross-ply submucosal collagen arrangement using a strain energy density function of the following form [5]:

$$
\psi = \psi_{\text{ISO}}(C) + \psi_{\text{LM}}(C, A) + \psi_{\text{CM}}(C, B) + \psi_{\text{Coll}}(C, D, D')
\quad - \frac{p}{2} [\det(C) - 1]
$$

(2.2)

Where $\psi_{\text{ISO}}$ is the isotropic contribution of the extracellular matrix, $\psi_{\text{LM}}$ is the strain energy function for the longitudinal muscle layer contribution, $\psi_{\text{CM}}$ is the circular muscle layer contribution, $\psi_{\text{Coll}}$ is the anisotropic reinforcement behavior of the collagen network in the submucosa, $p$ is the Lagrange multiplier to restore incompressibility, $C$ is the right Cauchy strain tensor, and $A, B, D,$ and $D'$ are structural tensors. The model was fit well to uniaxial data based on the rationale that the fiber reinforcement planes were symmetrical; therefore, two uniaxial tests and the two shear tests were
performed along the two mutually orthogonal principal directions and were sufficient for estimating the material parameters.

In addition to studying the effects of internal bowel pressure on ischemia, Høeg et al. model the small bowel as an idealized, axisymmetric, anisotropic, homogenous, nonlinear, viscoelastic pressure vessel undergoing large deformations. They develop constitutive equations for the model based on these assumptions [16].

Sacks et al. has pioneered work creating constitutive models of soft tissue (primarily aortic valve cusps) using a biaxial tester (Figure 8). The device independently applies stress to two orthogonal axes of the tissue, records measurements of force on each axis, tracks the deformation gradient of the tissue, and allows the specimen to shear freely. In a study of the mechanical properties of bovine pericardium, they fit the biaxial data to the following strain energy function:

\[
\psi = \frac{C}{2} \left[ \exp\left( A_1 E_{11}'^2 + A_2 E_{22}'^2 + 2A_3 E_{11}' E_{22}' + A_4 E_{12}'^2 + 2A_5 E_{11}' E_{12}' + 2A_6 E_{22}' E_{12}' \right) - 1 \right]
\] (2.3)

Where \( E_{ij}' \) is the Green's strain tensor in the material axes coordinate system and \( C \) and \( A_1 \) are material constants [63]. The authors suggest that their model is general enough to be applied to any tissue that has an identifiable material axis, is anisotropic and planar. The small intestine, with its mutually orthogonal smooth muscle layers, may have these attributes.
The model’s developed by Dario and Sacks are phenomenological in nature. Indeed, Sacks mentions that the presence of the material constants $A_5$ and $A_6$ do not improve the fit of data to the model and are probably not needed. Recent work by Kao et al. present a crimped fiber model for proximal pulmonary artery tissue in which every parameter is correlated with a physiologic structure, geometry, or mechanically measured material property of the composite tissue [64]. The proposed strain energy of their model is:

$$\Psi = f_{el}\Psi_{el} + \Psi_{CF}$$  \hspace{1cm} (2.4)

Where $f_{el}$ is the volume fraction of the elastin network in the tissue, $\Psi_{el}$ and $\Psi_{CF}$ are the strain energy contributions of the elastin and collagen, respectively. Solving this equation for the second Piola-Kirchhoff stress tensors, the stress contributions of the elastin and collagen are, respectively:
\[ S^{\text{el}} = \mu I + (\mu_a - \mu) \left( 1 - l_i^{\frac{3}{2}} \right) a_0 \otimes a_0 + (\mu_g - \mu) \left( 1 - l_6^{\frac{3}{2}} \right) g_0 \otimes g_0 \tag{2.5} \]
\[ - pC^{-1} \]

\[ S^{CF} = K \frac{F_F(\lambda_F)}{\lambda_F} \left[ \left( \frac{\kappa + \gamma - 1}{3} \right) I + (1 - \kappa) a_0 \otimes a_0 + (1 - \gamma) g_0 \otimes g_0 \right] \tag{2.6} \]
\[ - pC^{-1} \]

Where \( \mu \) is the shear modulus of the tissue, \( \mu_a \) is the effective fiber modulus, \( \mu_g \) is the shear modulus in axial direction, \( l_i \) are invariants of the structure tensors, \( K \) is the fiber density, \( \kappa \) and \( \gamma \) are shape factors for the ellipsoidal tensor, \( \lambda_F \) is the apparent fiber stretch, \( F_F \) is the force from the apparent fiber stretch, \( C \) is the Cauchy-Green deformation tensor, and \( a_0 \) and \( g_0 \) are the circumferential and longitudinal directions of the ellipsoidal structure tensor.

Kao et al. fit biaxial stretch-stress data the above model.

Considering the above previous work, there is no clear precedent or well-established method for characterizing and modeling the passive biomechanics of the small intestinal tissue. The in-plane biaxial test method appears to have certain advantages, however, including the ability to test multiple stretch ratios between the circumferential and longitudinal axes of the tissue. In addition, unlike the uniaxial test apparatus presented by Dario, the biaxial tester also allows in-plane shearing and real-time measurements of the shear angle. Fitting biaxial stress-stretch data from small bowel tissue
to a model with meaningful physiological parameters could yield insights, comparisons, and contrasts even (or especially) if the model does not fit well.

2.5 Active Forces

Much of the motor activity of the human body causes pressure gradients that could affect the *in vivo* mobility of an RCE. Respiration and cardiovascular activity cause periodic pressure waves. Abdominal muscle tone and skeletal muscle contractions generate pressure within the abdominal cavity. The distal stomach and duodenum behave like a pump, generating pressure at the oral end of the small intestine [65]. The circular and longitudinal muscles of the myenteron work together to create complicated rhythmic contractions within the bowel known as the migrating motor complex (MMC) [66]. The circular muscles are primarily responsible for segmentation waves, which increase peripheral resistance and slow transit of intraluminal contents. Longitudinal muscle contractions, on the other hand, facilitate transit [67].

2.5.1 Intraluminal Pressure

The intraabdominal and intraluminal pressures and traction forces associated with the active forces are well understood. Very early work used balloon kymography to measure intraluminal pressures [68]. This method was replaced with open-tipped catheters, which proved to be more accurate and reliable. For example, Texter et al. use an open-tipped catheter to measure the intraluminal pressure to be approximately 5 kPa in the
The current state-of-the-art uses water perfused catheters or microtip transducer catheters for manometry. Samsom et al. developed a portable perfused manometer to measure small intestine motility in seven males (21-32 years). Their study shows pressure within the small bowel fluctuates with a mean amplitude of 3.5 kPa (range 2.5 kPa to 5.8 kPa) over a 30 minute period for a fasting male in the supine position [66]. Other manometric studies show similar results [69], [70].

2.5.2 Contraction Propagation Speed

Maximum pressures within the small intestine are associated with myenteric contractions, which propagate throughout the bowel. In a study of 15 males and 4 females (22-50 years) adults, Husebye et al. report a mean propagation speed in the jejunum of 1.8 mm s\(^{-1}\) with standard deviations of 0.62 mm s\(^{-1}\) and 0.68 mm s\(^{-1}\) between individuals and within individuals, respectively [70]. Contraction amplitude becomes more vigorous postprandially; however, propagation speed is constant regardless of the fasting state of the subject [71].

2.5.3 Axial Force

Traction (or axial) force in the small intestine has been measured by Ahluwalia et al. using the traction force detector pictured in Figure 9 [71]. The device is inserted into the jejunum, and the balloon is inflated to contact and apply pressure to the mucosa. Proximal and distal perfusion ports measure intraluminal pressure on either side of the balloon blockage.
Traction force is defined as the amount of force exerted by the Kevlar thread on the electronic strain gauge (Figure 9). This is primarily the axial force generated by the small bowel on the balloon. In Ahluwalia’s study of 19 humans (10 women, mean age 27 years, range 21-39), preprandial traction forces measured 91 mN (standard error of 24 mN). Mean postprandial traction forces were the same but had a slightly higher standard error (27 mN).

Figure 9. Traction force detector developed by Williams et al. for measuring traction forces in the esophagus [72]. Ahluwalia et al. adapted the device to measure traction force in the jejunum [71].

2.5.4 Contact Force

The contact forces exerted by the bowel wall on a solid bolus have not been experimentally determined. Work by Bertuzzi et al. formulated a general theoretical model of a solid bolus transported by peristalsis [73]. Miftahof et al. have followed with the creation of bolus transport models specific to the gastrointestinal tract that predict radial forces exerted by the bowel on a solid bolus [14], [74], [75]. Their theoretical models predict the total force exerted by the bowel on a solid bolus per unit of axial length to be in the range 0.15 to 1.9 N cm⁻¹. A complete and accurate understanding of the
magnitude, shape, and frequency of the contact forces is highly desirable in order to estimate the dynamics and power requirements of the *in vivo* robot. To date, designers of RCEs use unsubstantiated theoretical values to optimize their designs to function against the active forces of the small bowel [9]. Therefore, one component of this work is to develop a novel sensor for measuring contact force.
Chapter 3: Experimental Approach and Results

A broad experimental program was initiated that will add to the body of work needed to characterize the active and passive forces acting on an *in vivo* RCE. Specifically, the following experimental methods were designed to answer the questions:

1) **Tribometry experiment:** What is the coefficient of friction between the live mucosa and the surface of an RCE and how does it compare to COF measured on excised tissue?

2) **Mucosal adhesivity experiment:** What is the adhesivity of the small intestine mucosa to RCE engineering materials?

3) **Biaxial experiment:** What is the in-plane biomechanical response of excised small bowel tissue?

4) **MFS experiment:** What is the magnitude and the spatiotemporal nature of the myenteric contact force experienced by an RCE?

These experiments were performed on multiple porcine models. Shown in Table 2 is a summary of the porcine studies indicating which protocols were tested on which pig. Note that the pre-anesthetic Atropine was not
administered in pig studies 3, 4, and 5. Atropine prevents the bradycardial effects of the anesthetic, but is also an anticholinergic, which may hinder contraction of the small bowel myenteron. This was discovered after the first two porcine studies and was therefore eliminated from the remaining three.

Table 2. Porcine studies.

<table>
<thead>
<tr>
<th>Pig ID</th>
<th>Euthanization Date</th>
<th>Mass (Kg)</th>
<th>Pre-anesthetic</th>
<th>Tribometry</th>
<th>Mucosal Adhesion</th>
<th>Biaxial</th>
<th>MFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>03/30/2010</td>
<td>56</td>
<td>Atropine</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>05/25/2010</td>
<td>54</td>
<td>Atropine</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>09/07/2010</td>
<td>53.3</td>
<td>None</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>02/09/2011</td>
<td>62.3</td>
<td>None</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>07/26/2011</td>
<td>57</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

All pigs were female with a mean weight of 56.5±4.6 Kg. A test protocol was approved by the Institutional Animal Care and Use Committee (IACUC protocol 87909(05)1D).

In addition to the pigs listed in Table 2, four more pigs were used for a follow-on study of mucosal adhesion to engineering materials (described in Section 3.2.5). The tissues from the pigs used for the follow-on study were acquired in an ad-hoc manner, therefore the gender, weight, and other details regarding those animals is not known.

3.1 Tribology

As discussed in the literature review (Section 2.2), current tribological research of RCEs does not investigate the in vivo friction forces but focuses narrowly on geometry, pressure, speed, and material. Mucus rheology has been investigated, but not in the context of RCE applications.
The purpose of this experimental method is, therefore, to create a hardware platform that is capable of measuring \textit{in vivo} tribological characteristics of the small bowel. The novel tribometer presented in this work is a portable device that facilitates taking measurements in a large animal operating room at a remote location. A single geometry, material, speed, and pressure are tested both \textit{in vivo} and \textit{in vitro} to compare the COF between living and excised tissue. The tribometer is used to derive a lumped COF that includes resistive forces from coulomb friction and fluid shear.

3.1.1 System Description

The tribometer is comprised of a linear actuator (Haydon-Kerk, 25844-05-001ENG) that propels a load cell (Loadcell Central, ESP4-1KG) along a linear slide, with the load cell pulling a curved polycarbonate sled along the intestinal specimen (Figure 10). A motor driver (Sparkfun, A3967), data acquisition system, and bridge strain measurement module (National Instruments, USB-6218, USB-9237) control the motion of the sled and record position, time, and force. The tribometer system is designed to be portable such that it can be positioned adjacent to the animal’s abdomen for \textit{in vivo} testing (Figure 11).
The radius of curvature of the tray is 1.5 cm, which corresponds to the nominal diameter of the porcine small bowel and allows the position of the villi to face radially inward to maintain their natural in vivo orientation. The radius of the leading edge of the sled is 1.2 mm.

3.1.2 Test Protocol
To test, a live section of the porcine small bowel was pulled through an incision in the abdominal wall. With the mesentery intact, the bowel was cut along the longitudinal axis and placed on the tribometer specimen tray. The
A weighted polycarbonate sled was placed on the exposed mucosa and pulled at a rate of 1 mm/s. The sled weighed 0.53 N and had a contact surface area of 6.97 cm², which created contact pressure on the mucosa by the sled of 0.76 kPa. Total sample length and travel distance of the sled was approximately 90 mm. Two samples each from the proximal, middle, and distal small bowel were tested. The experiments were repeated in vitro with porcine specimens excised from the same animal and preserved in phosphate buffered saline (PBS) at 3°C and tested at room temperature. The COF is calculated by:

\[
\text{COF} = \frac{F_t}{F_n}
\]

where \(F_t\) is the force required to pull the sled at 1 mm/s, and \(F_n\) is the weight of the sled (0.53 N). Throughout the tests, the mucosa was kept hydrated with PBS at room temperature.

### 3.1.3 Tribometry Results

Four live tissue samples (2 proximal and 2 distal) and five excised samples (2 proximal, 1 middle, and 2 distal) were tested. The mean COFs are 0.0164±0.0002 and 0.020±0.003 for the in vivo and in vitro tests, respectively. Therefore, previous work that is based solely on in vitro measurements is possibly slightly overestimating the COF. Insufficient samples were taken to determine if there is a significant difference in the COF for proximal, middle, and distal regions of the small bowel.

Shown in Figure 13 is the COF versus sled position for three runs on a single sample taken from the distal small bowel. The COF varies over the
length of the test segment, which is a similar result to Baek et al, who suggest that the heterogeneity in the COF is “related to the local change in the viscoelastic property of the intestine” [43]. Another explanation is that the local changes in topography from the many wrinkles and folds in the muscularis mucosae affect the COF. The inset in Figure 13 shows the relative size of these wrinkles and folds, which are the same scale as the local variations in the graph of the COF. Also note that the first time the sled is pulled over the mucosa it produces a higher COF than subsequent runs, which all yield similarly smaller COFs.

![Graph showing COF comparison between in vivo and in vitro tissues](image)

**Figure 12.** The COF of the sled on *in vivo* and *in vitro* tissue. Note only one tissue sample from the middle bowel was tested (*in vitro*).
Figure 13. COF versus sled position for three runs on a single sample (*in vitro* test, distal small bowel). Inset: portion of an intestine sample illustrating relative size of mucosa topographical features.

The tribological results presented here can also be found in the author’s published work [4].

### 3.2 Mucosal Adhesivity

Presently, there is no standard for measuring the adhesivity of biological tissue to engineering materials. Mucosa, however, can be thought of as a pressure-sensitive adhesive (PSA). Similar to the mucosa, PSAs, such as self-stick tapes, form bonds between surfaces simply by pressure without the aid of activating agents such as water, solvents, or heat. Therefore, the rigorous, well-developed ASTM test protocol and apparatuses for...
characterizing PSAs were used in this work to measure mucosal adhesivity. Adhesion between the mucosa and the RCE primarily follows two modalities: tack and peel. Tack is when two adhered surfaces separate while maintaining parallel and flat orientation. Peel is the separation of two adhered surfaces by applying a force to the leading edge of one of the surfaces so that it is no longer flat relative to its mating surface. Both tack and peel were tested using an Insight II tensile testing machine (MTS systems), 2 or 5 N loadcell (MTS Systems, PN 569326-01), and custom fixtures.

The following describes the experimental approach for measuring the adhesivity of the mucosa. The approach is summarized as follows: 1) The test apparatuses are built and validated; 2) The tack adhesive modality is explored for only mucosa adhered to mucosa. This experiment was exploratory and preliminary, yet a large number of samples (74) were tested from three porcine models, so the results are presented here for completeness; 3) A full factorial adhesivity experiment was performed that investigates both peel and tack modalities, adhesivity of a particular engineering material to mucosa (stainless steel, micropatterned PDMS, and polycarbonate), and region of the small intestine (proximal, middle, or distal).

3.2.1 Validation of Test Apparatus

The purpose of the validation protocol is to measure the repeatability of the adhesive tack and peel strength test apparatuses and to provide an intuitive feel for the adhesive strength of a commercial tape for anecdotal
comparison with the biological adhesive strength of the mucosa. A commercial adhesive (3M, PN 9471LE) was the adhesive used for this validation due to its excellent geometric uniformity and its environmental stability. Cast polypropylene was used as the adherend due to its moderate surface energy characteristics. Since testing lasts one hour (a fraction of the tape’s two-year shelf life), it is assumed variation in tack and peel results are due only to the apparatuses and methods and not to deviation in tape material properties. The adhesivity of mucosa, on the other hand, is expected to be highly variable, similar to the other mechanical properties of biological tissue.

The test procedure used to measure the tack adhesivity of the mucosa was modeled after the ASTM standard test method for tack (designation: D2979) [76]. The standard specifies a protocol and apparatus (Figure 14, Left) to determine the pressure sensitive tack strength of a commercial adhesive to a test material. Tack is defined as the force required to separate an adhesive and the adherend shortly after they have touched. As mentioned, the tack test apparatus was validated using a commercial adhesive in place of the mucosa, and polypropylene as the test material (the adherend). To validate, the commercial adhesive was transferred to a substrate and mounted on the lower grip of the test apparatus. A 1 cm$^2$ square piece of cast polypropylene was brought into contact with the adhesive and held for 10 seconds with a mean pressure of 5 kPa. After the 10-second dwell time, the
polypropylene was pulled from the tape at 10 mm s\(^{-1}\). The pull force was recorded during pull-away for ten samples and the mean tack strength was calculated by

\[ W_{tack} = \int_0^{\delta_t} F \cdot ds \]  

(3.2)

where \( F \) is the force to separate the two surfaces and \( \delta_t \) is the displacement of the upper grip during the tack test. Note that zero displacement corresponds to the no-load position prior to separation. Tack strength per unit area is found by dividing (3.2) by the contact area in cm\(^2\).

The test protocol to measure the peel adhesivity of the mucosa was modeled after the ASTM standard test method for peel adhesion (designation: D3330/D3330M – 04) [77]. The standard specifies a protocol and apparatus (Figure 14, Right) to determine the peel strength of an adhesive. Peel strength is defined as the average force required to cleanly pull tape at 90° from a substrate. Similar to the tack test, the peel test is validated by peeling the commercial adhesive from a polypropylene substrate. A 5.1 mm \( \times \) 147 mm length of transfer tape was rolled onto polypropylene. Following 30\(\pm\)15 seconds of dwell time, one end of the tape was pulled 90° at 10 mm s\(^{-1}\) while the pull force was recorded. As described in the standard, the pull force is maintained at 90° by a linear slide that moves in the horizontal direction at the same rate as the vertical pull rate. The total force experienced by the loadcell during the peel is
where $F_a$ is the adhesive force, and $w$ is the weight of the adhesive suspended by the grip. During validation, the weight ($w$) is negligible due to the small mass of the tape and its relatively strong adhesivity (i.e. $F_a \gg w$). However, during biological testing, the weight of the tissue is significant because its mass is large relative to its adhesive force ($F_a < w$). Assuming uniform adhesive samples, $w$ is a function of instantaneous peel length $s$:

$$w(s) = s \frac{w_T}{\delta_p}$$

where $w_T$ and $\delta_p$ are the total weight and length of the peeled tissue sample, respectively. Total adhesive force is found by substituting (3.4) into (3.3) and solving for $F_a$:

$$F_a(s) = F_T - s \frac{w_T}{\delta_p}$$

Peel strength is calculated by integrating the adhesivity force, $F_a(s)$, over the peel length, $\delta_p$:

$$W_{\text{peel}} = \int_0^{\delta_p} \left( F_T - s \frac{w_T}{L} \right) \cdot ds.$$ 

Peel strength per unit area is found by dividing (3.6) by the contact area in cm$^2$. 

$$F_T = F_a + w$$ (3.3)
Figure 14. The tack test apparatus consists of a square piece of test material attached to a loadcell (Left, A), which is brought into contact with the test adhesive (Left, B). The peel test apparatus consists of a linear slide that translates horizontally and a grip attached to a loadcell that peels the adhesive from the test material at 90°. The vertical movement of the grip is matched by the horizontal movement of the linear slide to maintain the 90° peel angle (Right).

3.2.2 Validation of Test Apparatus Results

Figure 15 and Figure 16 show the raw tack and peel data, respectively, for ten test samples each. The mean tack strength of the 3M 9471LE commercial tape to polypropylene per unit area was $87\pm36$ mJ cm$^{-2}$. The mean peel strength of the tape to polypropylene per unit area was $45\pm2$ mJ cm$^{-2}$. Errors are one standard deviation of the mean. Notice the large standard deviation of the tack modality as compared to peel. This is due to the location of the abrupt separation of the adhesive from the adherend. Also note that the first ~1.5 mm of peel data is highly transient, which is due to tensioning of the tape prior to actual separation; therefore, peel adhesivity measurements do not include this region. Separation of the commercial adhesive from polypropylene via the tack modality requires approximately 190% more energy per unit area than by peel. The larger energy required for
separation via tack is probably explained by the contribution bulk deformation of the adhesive as explained previously in Section 2.3.2.

Figure 15. Raw tack test data from ten samples of commercial adhesive (3M 9471LE) adhered to polypropylene. Error bars are one standard deviation of the mean. Notice the high variability beginning around 1 mm of travel. This is due to the variable nature of the abrupt release of the adhesive from the adherend.
Figure 16. Raw tack peel data from ten samples of commercial adhesive (3M 9471LE) adhered to polypropylene. Error bars are one standard deviation of the mean. Notice the tension ramping as the slack is removed from the adhesive tape. Adhesion calculations due not include the ramping region.

3.2.3 Exploratory Mucosa-Mucosa Tack Test

An Insight II tensile testing machine (MTS Systems) was used to measure the adhesivity of two opposing sides of mucosa. A tubular intestine segment was adhered with cyanoacrylate to a custom mount, which was fastened to the Insight II grips (Figure 17). The Insight II machine used a 5 N load cell (MTS Systems, PN 100-090-674). The load cell’s nonlinearity and hysteresis are no greater than 0.05% and 0.03% of full scale, respectively.
Sections of the proximal, middle, and distal small bowel were excised from three porcine models and are stored in PBS at 3° C. Tissue was tested 18, 3, and 1 days after excision from pigs 1, 2, and 3, respectively. Tissue from pigs 2 and 3 appeared new; however, tissue from pig 1 showed some signs of aging including browning and leaching of fluid into the PBS. Discoloration of the vasculature was also observed in the 18-day-old tissue. Tubular sections of intestine (25 mm in length) were excised along the longitudinal axis, which corresponded to the length of the test mount (Figure 17). The width of each sample was dependent on the diameter of the intestine but was trimmed so that it did not exceed the 25 mm width of the test mount.

The test mount was secured to the lower grip of the MTS machine and the upper test mount was secured to the upper grip. Cyanoacrylate adhesive was applied to the outer serosa of the sample and the upper grip was lowered so that it contacted and adhered to the sample. With both test mounts adhered to opposite sides of the sample, the intestinal wall was severed on either side of the sample using surgical shears (Figure 17). The sample was then pulled apart at 2.5 mm per second to a separation distance of 20 mm.
The separation distance was chosen such that the mucus boundary layer was totally separated. The separation speed was chosen based on the anticipated speed and diameter of an *in vivo* robot.

In all, 74 tissue samples were tested from the three porcine models. Shown in Table 3 are the samples tested from each pig and small bowel region.

Table 3. Number of samples used for the mucus adhesivity test.

<table>
<thead>
<tr>
<th>Pig ID</th>
<th>Proximal Samples</th>
<th>Middle Samples</th>
<th>Distal Samples</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>6</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>22</td>
<td>23</td>
<td>74</td>
</tr>
</tbody>
</table>

Force and position during separation were recorded at 100 samples s⁻¹. Total work required for separation per unit area of intestine was calculated by:

\[ W_L = A^{-1} \int F(s) \cdot ds \]  

(3.7)

Where \( A \) is the mucosal surface area of the test sample, \( F(s) \) is the force registered by the load cell during separation, and \( s \) is the separation displacement.

3.2.4 Exploratory Mucosa-Mucosa Tack Test Results

The raw tack adhesivity data from a representative tissue sample are shown in Figure 18. Note that the data is corrected for the weight of the tissue sample, so that force values are only from adhesivity as the two pieces
of mucosa are pulled apart. Positive values indicate tension. Shown in Figure 19 are the adhesivity results from the three porcine models. The mean adhesivity per unit area of mucosa is $0.042\pm0.015$, $0.062\pm0.030$, and $0.060\pm0.026$ mJ cm$^{-2}$ for the tissue from pigs 1, 2, and 3, respectively. Note that the mucus adhesivity of pigs 2 and 3 is about 45% greater than that of pig 1, which may be due to the relatively old age of the tissue.

Figure 18. Representative data of raw adhesivity from pig 1 proximal tissue sample.
Figure 19. Mucosa-mucosa adhesivity per unit area (cm²) of intestine. Error bars are standard deviations of the mean.

3.2.5 Full Factorial Adhesivity Experiment

Similar to the exploratory experiment outlined in 3.2.3, small bowel tissue was acquired from the University of Colorado Hospital. The tissue was packaged in plastic Ziploc®-style bags filled with LRS and transported on ice to the testing facility. Note that the exploratory procedure discussed in Section 3.2.3 used PBS instead of LRS. LRS was chosen for the full factorial experiment because of its ability to better preserve the in vivo condition of the tissue. Care was taken to not freeze the tissue due to a study by Samuel et al [78] that finds cryogenically preserved and then thawed bowel tissue exhibits different adhesive characteristics than fresh tissue. Most samples
were tested within 12 hours of euthanization and all samples were tested within 43 hours. Every permutation of the factors and levels shown in Table 4 were tested, which resulted in 24 tests per pig intestine and 96 total tests for the four porcine models. The test order was randomized.

Table 4. Factors and levels that define the 96 adhesivity tests.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesivity test</td>
<td>Tack, peel</td>
</tr>
<tr>
<td>Region of bowel</td>
<td>Proximal, middle, distal</td>
</tr>
<tr>
<td>Pig</td>
<td>One, two, three, four</td>
</tr>
<tr>
<td>Material</td>
<td>Mucosa, stainless steel, polycarbonate, micropatterned polydimethylsiloxane</td>
</tr>
</tbody>
</table>

Stainless steel, polycarbonate, and micropatterned PDMS are candidate materials for use in present or future robotic capsule endoscope designs and are therefore of interest to the author. The micropatterned PDMS is manufactured by the author and is a drive component of a robotic capsule endoscope discussed in previous work [79]. The surface of the PDMS is covered with 70 μm tall, 140 μm diameter cylindrical pillars that are equally spaced at 245 μm center-to-center distance. In addition to testing the adhesivity of mucosa to these engineering materials, the adhesivity of mucosa to itself is also investigated similarly to the test in Section 3.2.3. Shown in Table 5 is the randomized adhesivity test matrix for Pig 1. Similar matrices exist for Pigs 2, 3, and 4.
Table 5. Randomized adhesivity test matrix for pig 1. “Proximal”, “Middle”, and “Distal” indicates the test was performed on tissue from that region of the small bowel. “SS”, “PC”, “MT”, or “Mucosa” indicates that stainless steel, polycarbonate, micropatterned tread, or mucosa were in contact with the mucosa during the test. “Tack” and “Peel” are the test protocols. Note that tests are shown randomized.

<table>
<thead>
<tr>
<th>Middle,PC,Peel</th>
<th>Distal,PC,Peel</th>
<th>Proximal,MT,Peel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle,SS,Tack</td>
<td>Middle,MT,Peel</td>
<td>Proximal,Mucosa,Tack</td>
</tr>
<tr>
<td>Distal,MT,Peel</td>
<td>Proximal,PC,Tack</td>
<td>Distal,SS,Tack</td>
</tr>
<tr>
<td>Distal,Mucosa,Peel</td>
<td>Distal,Mucosa,Tack</td>
<td>Proximal,SS,Peel</td>
</tr>
<tr>
<td>Proximal,PC,Peel</td>
<td>Middle,PC,Tack</td>
<td>Distal,PC,Tack</td>
</tr>
<tr>
<td>Proximal,SS,Tack</td>
<td>Distal,SS,Peel</td>
<td>Middle,SS,Peel</td>
</tr>
<tr>
<td>Middle,MT,Tack</td>
<td>Proximal,MT,Tack</td>
<td>Proximal,Mucosa,Peel</td>
</tr>
<tr>
<td>Middle,Mucosa,Tack</td>
<td>Distal,MT,Tack</td>
<td>Middle,Mucosa,Peel</td>
</tr>
</tbody>
</table>

Tack tests were performed on each permutation of bowel region, material of interest, and porcine model. For example, for the test permutation “Distal, PC, Tack” shown in Table 5, a 6.45 cm² piece of polycarbonate is gripped by the upper grip of the tensile tester. A segment of small bowel is adhered with cyanoacrylate to the lower platform with mesentery facing upward. The bowel is cut longitudinally along the mesentery and splayed open, exposing the mucosa. The polycarbonate is brought downward at 1 mm s⁻¹ until the material of interest is pressed against the tissue with a force of 0.2 N for 10 s of dwell time. The upper grip is then raised at 10 mm s⁻¹ until the polycarbonate is fully separated from the tissue. Force and displacement of the upper grip are measured at 500 samples s⁻¹. The test is repeated twice to yield a total of three contiguous measurements per tack test permutation.

Similarly, the peel tests are performed on each permutation of bowel region, material of interest, and porcine model. For example, for the test
"Proximal, MT, Peel", an 8 cm × 2 cm rectangular section of small bowel is excised and rolled on micropatterned PDMS tread with the mucosa facing downward so that it is in contact with the PDMS without entrapping air bubbles between the two surfaces. One end of the rectangular section of tissue is clamped in the upper grip. The upper grip is then raised at 10 mm s⁻¹, which peels the tissue from the PDMS at 90°. The section of adhered tissue travels horizontally at the same rate the upper grip travels vertically, thus maintaining the 90° peel angle. The force on the loadcell is recorded at 500 samples s⁻¹ throughout approximately 6 cm of peel.

Four-way analysis of variance (ANOVA) was performed to examine the effects of the factors listed in Table 4 on the mean adhesivity. P-values less than 0.05 were considered statistically significant. The validity of the ANOVA was verified by testing the data for normality using the Shapiro-Wilk test.

3.2.6 Full Factorial Adhesivity Experiment Results

The mean tack strength of the mucosa per unit area was 0.198±0.07 mJ cm⁻². The mean peel strength of the mucosa per unit area was 0.055±0.016 mJ cm⁻². Errors are one standard deviation of the mean. Separation of the mucosa from the tested materials via the tack modality requires approximately 360% more energy per unit area than by peel. Shown in Figure 20 and Figure 21 are the raw tack and peel adhesivity data, respectively.
Figure 20. Representative data for raw mucosal tack separation force versus separation position for polycarbonate. Adhesive force shown in this figure is normalized in terms of unit contact area.
Figure 21. Raw mucosal peel separation force versus separation position for polycarbonate. Adhesive force shown in this figure is normalized in terms of unit length of the peel edge. Note that the leading and trailing portions of the peel data are excluded from the adhesive strength calculations and not shown in this figure.

Shown in Figure 22 and Figure 23 are the summaries of the mucosal tack and peel strength, respectively. Each of these figures contain 11 box plots. The plots show the median, the 25th and 75th percentiles of the data (the box), and the extents of the data (the whiskers). Outliers are denoted by plusses. The bars are grouped first by pig, then bowel region, and finally material. For example, the four leftmost boxes indicated by the labels “Pig 1” through “Pig 4” compare the median adhesivity of all materials and bowel regions of each pig. The next three boxes labeled “Proximal”, “Middle”, and “Distal” compare the median adhesivity of all pigs and materials for each bowel region. The last four boxes labeled “SS”, “PC”, “MT”, and “Mucosa”
compare the median adhesivity of all pigs and bowel regions for each material. Note that Figure 22 and Figure 23 are both interpreted in this way.

Figure 22. Summary of the adhesivity tack strength. From left to right, boxes 1-4 show the strength per porcine model. Boxes 5-7 show strength per region of the small intestine. Boxes 8-11 show strength per material tested against the mucosa: SS is stainless steel, PC is polycarbonate, MT is micropatterned PDMS tread, and Mucosa (11th bar) indicates the tack strength of mucosa adhered to itself.
Figure 23. Summary of the adhesive peel strength. From left to right, boxes 1-4 show the strength per porcine model. Boxes 5-7 show strength per region of the small intestine. Boxes 8-11 show strength per material tested against the mucosa: SS is stainless steel, PC is polycarbonate, MT is micropatterned PDMS tread, and Mucosa (11th bar) indicates the peel strength of mucosa adhered to itself.

The Shapiro-Wilk test confirmed normal distributions within the tack and peel tests for both the commercial adhesive and mucosal testing but rejected the null hypothesis for lumped tack and peel means. Therefore, the two adhesive modalities were analyzed separately. For both tack and peel tests, ANOVA identified significant differences between porcine models ($p=0.05$, 0.00 for tack and peel, respectively). The differences in adhesivity between bowel regions were not significant, although there may be a weakening trend from proximal end to the distal end. The adhesive strength of the mucosa to itself is significantly stronger than that of mucosa to the
engineering materials ($p=0.02$, $0.01$ for tack and peel, respectively). Although not significant, the mean adhesive strength of the engineering materials to mucosa varied from least to greatest as follows: stainless steel, polycarbonate, and PDMS micropatterned tread. This trend is manifest in both the tack and peel tests.

3.3 Biaxial Biomechanical Characterization

Based on the advantages of in-plane biaxial biomechanical testing discussed in Section 2.4.3, it was decided to use that test apparatus to measure the passive biomechanics of the small intestine tissue. The stress-stretch data are then fit to an existing constitutive model suitable for hyperelastic, anisotropic tissue that exhibits the J-shaped behavior typical of soft tissues.

3.3.1 Biaxial Tester

The biaxial test apparatus (Figure 8) used for the biomechanical analysis is constructed based on plans and software developed by M. Sacks and J. Grashow, who present a detailed description of the equipment and its functionality [63], [80]. Briefly, the device uses four linear actuators (404XR, Parker Daedal, Irwin, PA), with one actuator per side of the square tissue sample. Stepper motors (OS22B, Parker Daedal, Irwin, PA) drive the linear actuators and are microstepped to 50,800 steps per revolution. The resolution of the drive system is approximately 0.394 µm per microstep and positioning is repeatable to less than 3.0 µm [80]. Two 1000 g load cells (Honeywell
Model 34) measure the force loaded on each axis. The load cells are accurate to 0.20% of full scale. The camera (Sony XCD-X710) and telephoto lens provide an undistorted image and have a resolution of 1024 × 768 pixels with a field of view about 1 cm x 0.8 cm, which yields a displacement resolution of about 10 μm.

3.3.2 Stress-Stretch Test Protocol

Square segments of porcine small bowel were taken from three pigs and excised within minutes of euthanization. Samples were cut from the proximal, middle, and distal regions of the small intestine opposite the mesentery (Figure 24) and stored in phosphate buffered saline at 3°C. The PBS was calcium free to help ensure the tissue did not experience muscle contractions which may mask the passive biomechanics of the tissue. Sample sizes were excised from the bowel using a 2 cm² template. Testing was performed at room temperature within 72 hours of excision. Four black marks were placed in the center of the serous surface of the sample, which is then secured to the biaxial test device via nylon string and four equally-spaced hooks per sample side (Figure 25).
Figure 24. Excised region of the small intestine used for biaxial testing.

Figure 25. Small intestine sample mounted for biaxial stress-stretch test.

The black markers form the corners of a ~2 mm square, whose positions are tracked in real-time and are treated as nodes of a four-sided finite element, which allows direct measurement of deformation from the material, rather than assuming deformation from the linear actuator displacements. The area encompassed by the markers is about 1% of the sample size, which makes the marker area essentially free from edge effects due to specimen tethering [81]. The longitudinal and circumferential
directions of each sample were aligned with the device axes 1 and 2, respectively (indicated by the indices in equations 3.8 through 3.12 below). Prior to each test, the sample was preconditioned with 13 contiguous cycles of equibiaxial tension. The maximum tension for the samples was determined by destructively stressing several samples equibiaxially until tearing was visually observed in the muscle layers at the hook-tissue interface (tearing of the serosa seemed to occur at higher tensions). The maximum tension levels for the tests were set to the values shown in Table 6, which are 90% of the failure level.

Table 6. Peak tension during biaxial stress-stretch tests.

<table>
<thead>
<tr>
<th>Pig Test</th>
<th>Peak Tension (N m⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
</tr>
</tbody>
</table>

Tension is defined as:

\[
\mathbf{N} = \begin{bmatrix}
  \frac{P_{11}}{L_{22}} & 0 & 0 \\
  0 & \frac{P_{22}}{L_{11}} & 0 \\
  0 & 0 & 0
\end{bmatrix}
\]  

\( (3.8) \)

Where \( P \) are the loads, and \( L \) are the length and width of the sample in its reference configuration acting along the device axes. Note that \( N_{i3} \) and \( N_{3j} \) are assumed to be zero due to the assumption of plane stress, and \( N_{12} \) and \( N_{21} \) are assumed to be zero because the loading regimen is normal to the edges. Piola stress is calculated from tension by:
where $h$ is the original thickness of the sample.

The test protocol consists of load-controlled biaxial testing where the ratio $N_{11}:N_{22}$ varies according to Table 7.

Table 7. The nine biaxial stress test protocols.

<table>
<thead>
<tr>
<th>Test number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longitudinal tension %</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td><strong>Circumferential tension %</strong></td>
<td>10</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

The protocols are designed to be exhaustive, i.e. to probe the biomechanical response of the tissue from near uniaxial loading in the longitudinal direction (test 1) to the near uniaxial loading in the circumferential direction (test 9). After 13 preconditioning cycles of equibiaxial tension, the sample underwent the nine stretch tests in random order. The tension along each axis was ramped from near-zero pre-stress to the peak tension, back down to near-zero pre-stress using a triangular waveform [57]. Tension was applied at 0.14 N m$^{-1}$ s$^{-1}$, which is physiological considering interaction between a typical robotic endoscope and the tissue. Based on existing studies of the viscoelastic response of soft tissue, we assume that the stress-stretch response is independent of this and similar tension rates [82]. Each test was cycled 13 times and all data reported in this study are taken from the loading curve of the 13th cycle. Data acquisition occurred at approximately 10 Hz and at each data point, the locations of the four markers were recorded and Piola stress and tension were calculated.
from (3.9) and (3.8), respectively. The biaxial deformation of the tissue sample was calculated as follows, similarly to work by Sacks and Sun [58]:

\[ x_1 = \lambda_1 X_1 + \kappa_1 X_2, \quad x_2 = \lambda_2 X_2 + \kappa_2 X_1, \quad x_3 = \lambda_3 X_3 \]  

(3.10)

where \( x_i \) and \( X_i \) are the vectors of a particle on the sample’s surface in the reference and deformed states, respectively, \( \lambda_i \) and \( \kappa_i \) are the stretch ratios and measures of in-plane shear, and indices 1 and 2 correspond to the longitudinal and circular directions of the smooth muscle layers. Solving for \( \lambda_i \) and \( \kappa_i \) at each time point yields, in real-time, the deformation gradient tensor:

\[
F = \begin{bmatrix}
\frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\
\frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\
\frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3}
\end{bmatrix} = \begin{bmatrix}
\lambda_1 & \kappa_1 & 0 \\
\kappa_2 & \lambda_2 & 0 \\
0 & 0 & \lambda_3
\end{bmatrix}
\]

(3.11)

The Piola stress from (3.9) and stretch ratios from (3.11) were plotted against each other to obtain the stress-stretch curves. The shear angle is computed by:

\[ \alpha = \sin^{-1} \frac{2E_{12}}{\sqrt{1 + 2E_{11}} \sqrt{1 + 2E_{22}}} \]  

(3.12)

where \( \mathbf{E} = 1/2(\mathbf{F}^T \mathbf{F} - \mathbf{I}) \), and \( \mathbf{I} \) is the identity tensor [83]. The maximum shear angle that occurred during the uniaxial tests is recorded for each sample, then averaged based on intestinal region (proximal, middle, and distal).
3.3.3 Stretch-Stress Results

Shown in Figure 26, Figure 27, and Figure 28 are the mean, post collagen engagement equibiaxial stretches of preconditioned tissue in the longitudinal and circumferential directions for the three pig tests. The stretch corresponds to a particular stress, which is indicated in the figures. The stress value indicated in each figure is the maximum post collagen stress that is experienced by ALL the samples in the test. The error bars indicate one standard deviation of the mean. The stretch means from Pig tests 1 and 2 appear to show no statistically significant difference in stress for the circumferential and longitudinal directions. Pig test 3 indicates that the circumferential direction is less stiff than the longitudinal direction. This is an interesting result as it is opposite from vascular tissue, which is stiffer in the circumferential direction [84].

A subset of the stretch-tension results from pig test 3 is shown in Figure 29. The results are for the proximal, middle, and distal regions of the small bowel. The three pairs of curves in each graph correspond to 100% longitudinal vs. 50% circumferential, equibiaxial, and near uniaxial stretch ratios. Note that the tissue exhibits behavior typical of collagenous material, i.e. the biomechanical response of the tissue is stable and repeatable after preconditioning and there are low and high modulus regions depending on the amount of stretch. As shown by the solid lines in Figure 29, the tissue behaves anisotropically, with the circumferential direction exhibiting more elasticity than then axial direction.
Figure 26. Pig test 1. Mean equibiaxial stretch of preconditioned tissue in the longitudinal and circumferential directions at 32.8 kPa. Number of proximal, middle, and distal samples (respectively): 2, 2, 2.

Figure 27. Pig test 2. Mean equibiaxial stretch of preconditioned tissue in the longitudinal and circumferential directions at 82.1 kPa. Number of proximal, middle, and distal samples (respectively): 9, 8, 8.
Figure 28. Pig test 3. Mean equibiaxial stretch of preconditioned tissue in the longitudinal and circumferential directions at 53.0 kPa. Number of proximal, middle, and distal samples (respectively): 5, 5, 6.

Figure 29. Pig test 3. Typical stress-stretch response of Pig 3 for three stretch ratios along the proximal, middle, and distal regions of the small bowel. Longitudinal and circumferential stretch directions are indicated by L and C; stretch ratios are indicated by the legend.
3.3.4 Material Modeling

The crimped fiber model described in Section 2.4.3 was fit to the stretch-stress data from pig 3’s proximal small bowel. The model was fit to data from test numbers 5, 7, and 9, which are the near uniaxial circumferential stretch, equibiaxial, and 50% to 100% longitudinal versus circumferential stretch regimens (see Table 7). The model is fit to the data using a nonlinear, least-squares approach implemented by the trust-region-reflective optimization algorithm [85]. Shown in Figure 30 are the raw data and associated model fits. As seen in the figure, the model and data correlate well in the equibiaxial case, but not with the circumferential direction in the other two other cases.

Figure 30. Stress-stretch data and corresponding fits of the crimped fiber model. Tissue is from the proximal small intestine of pig test 3.
3.4 MFS

The MFS is surgically implanted in the small intestine. It measures manometric pressure from a perfused manometer port, spatial and temporal contact pressure exerted by the mucosa, and intraluminal temperature. The sensing surface that measures contact pressure is segmented, with each 0.88 cm long segment independently measuring temperature and pressure. The device is modular, so up to eight segments can be used. For this study, four contiguous segments are used so that the length of the sensing surface is 3.5 cm (0.88 cm × 4). Propagation speed of myenteric contractions can also be measured due to the sensor’s segmented construction, although that analysis was not performed in this study. Following are the test results and a detailed description of the system components, their fabrication, MFS characterization methodology, and in vivo testing.

3.4.1 MFS System Description

The MFS consists of a custom perfused monometer and an array of torus-shaped balloon segments that expand to the nominal inner diameter of the small intestine (Figure 31, top). The manometer is a 25 mL syringe pump with distribution valve (XLP 6000, Tecan Systems, Inc.) that pumps 0.9 % phosphate buffered saline (PBS) at 0.3 mL min⁻¹ through a nylon 0.45 µm filter and 0.2 mm ID × 0.61 m long stainless steel flow restrictor. The distal end of the flow restrictor transitions to 0.81 mm ID × 1.5 m PTFE tubing that terminates in vivo at the MFS. A pressure transducer (4426-05G, Measurement Specialties) located on the proximal end of the flow restrictor
measures total pressure loss over the length of the tubing as well as intraluminal pressure at the MFS. Pressure loss contributed by the tubing is characterized beforehand and subtracted from the readings taken while in vivo. Several balloon segments are attached to the distal end of the manometer pressure port. Each 0.88 cm wide segment is a self-contained module, so up to eight total segments can be used, as the application requires. A balloon segment consists of a torus-shaped custom latex balloon attached to a 0.8 cm diameter stainless steel hub. The internal pressure of each balloon segment is transmitted to ex vivo transducers via 0.81 mm ID × 1.5 m PTFE tubing. When inflated with air to their nominal pressure of 14 kPa, the torus-shaped balloons are 2.2 cm in diameter and 0.7 cm wide under ambient air conditions. The pneumatic line and thermocouple wire enter the balloon from the center radius of the torus by passing through the hub and a Viton® rubber gasket. The balloons are made by dipping custom aluminum forms into H1438 natural rubber latex (Textile Rubber and Chemical Co. Inc.) and curing according to manufacturer’s instructions for 0.6 mm thickness catheters. The balloon segments independently measure the spatial and temporal changes in contact force from the myenteron.

The pressure and temperature of the balloon segments are independently monitored by a pressure transducer (Measurement Specialties, 4426-05G) and thermocouple (J-Kem Scientific, TEF-30-T). Pressure transducer and thermocouple outputs are recorded to a computer via data
acquisition systems (National Instruments, USB-6218, USB-9213). Shown in Figure 31 (bottom) is an image of the complete MFS system.

3.4.2 MFS System Characterization and Testing

Prior to surgical implantation, the MFS is inflated with air to its nominal pressure of 14 kPa, and then calibrated based on room temperature and atmospheric pressure. Therefore subsequent in vivo pressure measurements are relative to the calibrated state. Characterization of changes in sensor pressure due to the in vivo environment is performed empirically.

Shown in Figure 32 is a Section view schematic of the MFS within the contracted small bowel. Factors that affect the internal sensor pressure \( P_z \) are labeled in this image. For example, the contact pressure \( P_z \) occurs where the mucosa contacts the balloon surface and will slightly deform the balloon, thus changing its internal pressure. Changes in intraluminal pressure \( P_l \), abdominal pressure \( P_a \), sensor temperature \( T_s \), and contact area \( A_c \) directly or indirectly affect the internal sensor pressure. The in vivo sensor pressure is also a function of the nominal ex vivo inflation pressure \( P_{s,i} \), as well as stress relaxation \( \frac{\partial \sigma_r}{\partial t} \) of the balloon.
Figure 31. Schematic of the MFS *in vivo*. This illustration shows six segments, while four segments were used in this study. (Top) MFS complete system (Bottom).
Figure 32. Section view schematic of the MFS in vivo within the contracted small bowel. Factors that influence MFS internal sensor pressure ($P_s$) are the contact area ($A_c$) between the bowel wall and the balloon’s surface, sensor temperature ($T_s$), contact pressure ($P_c$) of the mucosa acting on the balloon surface, intraluminal pressure ($P_l$), abdominal pressure ($P_a$), initial ex vivo inflation pressure ($P_{s,i}$) and the stress relaxation ($\frac{\partial \sigma}{\partial t}$) of the balloon (not shown).

The relationship between these variables is established experimentally by simulating the in vivo environment through the use of a characterization test chamber and also a test fixture that applies a radial contact load. In addition to simulating the in vivo environment, the stress softening and relaxation characteristics of the latex balloons are also experimentally determined.

3.4.2.1 Stress Softening and Relaxation Characterization

The sensing surface of the MFS is made from natural latex rubber, which does not have a fixed equilibrium state, but may be characterized by so called “equilibrium hysteresis” [86]. Latex rubber also undergoes stress softening [87], in which the material modulus decreases because of the strain
history. To reduce the effects of stress softening, following fabrication, each balloon segment is inflated to its maximum expected pressure of 17.5 kPa for 5 minutes. If the balloon does not experience future pressure above this threshold, minimal stress softening will occur, and the contact load characterization (discussed hereafter) remains valid.

Stress relaxation, however, occurs throughout the experiment and therefore must be accounted for. To compensate for stress relaxation, the linear pressure decay rate is characterized by inflating the MFS balloon segments to their nominal operating pressure of 14 kPa and holding ambient pressure and temperature constant by submerging them in a 500 mL, room temperature water bath for 16 minutes, which is the duration of the in vivo portion of the experiment. The balloons are then removed from the bath, and the experiment is performed. Following the experiment, the MFS balloon segments are returned to the water bath for 16 minutes. Pressure and temperature data are acquired before, during, and after the experiment. The decay coefficient \( c_d \) for each balloon segment is determined by linear regression over the intervals of constant pressure and temperature:

\[
c_d = \frac{\partial p_s}{\partial t'}
\]

\[ t = \{[0,16], [32,48]\} \]
\[ P_d(t) = P_s(t) - c_d t \] (3.14)

\[ t = [16,32] \]

where \( t \) is the time in minutes, \( P_d \) is the decay compensated sensor pressure, \( P_s \) is the raw sensor pressure, and \( c_d \) is the decay coefficient. Note that the notation \([0,16],[32,48]\) means time on the interval from 0 to 16 minutes and from 32 to 48 minutes, excluding time from 16 to 32 minutes. The notation \([16,32]\) means time on the interval from 16 to 32 minutes.

### 3.4.2.2 Sensor Pressure versus Force Distribution

*In vivo*, the mucosa exerts contact force distributed along the circumference and acting radially inward on the sensor. During bench-top testing it was observed that the pressure change of the sensor is proportional to the total force exerted on the sensor, regardless of the location and distribution of the force. To test this observation, two techniques were used to impart a radially oriented contact load that was distributed along the circumference of the balloon. First, the MFS was radially loaded using custom sized and characterized rubber bands that imparted a radially-oriented force similarly to what would be experienced *in vivo*. Secondly, a jig was created (Figure 35) that radially loads a single MFS balloon segment at discrete points along the circumference and uses load cells to measure the force at each point. Note that two different balloons were used for these experiments, so the results from radial loading using the rubber bands should not be compared to the results from radial loading using the test jig.
**Distributed Loading With Rubber Bands:** To test this observation, 15 custom natural latex rubber bands (Figure 33) of varying diameters and widths were manufactured. Table 8 shows the diameter and width of each band. Note that the largest diameter (band S5) was still smaller than the inflated diameter of the MFS so that when the band is placed on the circumference of the sensor balloon, the band is stretched.

![Figure 33. Calibration bands.](image)

Table 8. Diameters and widths of calibration bands used for contact load characterization validation.

<table>
<thead>
<tr>
<th>Band</th>
<th>Diameter (mm)</th>
<th>Width (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>13.9</td>
<td>2.4</td>
</tr>
<tr>
<td>S2</td>
<td>15.8</td>
<td>2.6</td>
</tr>
<tr>
<td>S3</td>
<td>17.6</td>
<td>2.5</td>
</tr>
<tr>
<td>S4</td>
<td>18.7</td>
<td>2.6</td>
</tr>
<tr>
<td>S5</td>
<td>21.9</td>
<td>2.6</td>
</tr>
<tr>
<td>M1</td>
<td>13.9</td>
<td>3.1</td>
</tr>
<tr>
<td>M2</td>
<td>15.5</td>
<td>3.2</td>
</tr>
<tr>
<td>M3</td>
<td>17.0</td>
<td>3.3</td>
</tr>
<tr>
<td>M4</td>
<td>18.6</td>
<td>3.4</td>
</tr>
<tr>
<td>M5</td>
<td>20.1</td>
<td>3.5</td>
</tr>
<tr>
<td>L1</td>
<td>13.7</td>
<td>5.3</td>
</tr>
<tr>
<td>L2</td>
<td>15.1</td>
<td>5.4</td>
</tr>
<tr>
<td>L3</td>
<td>16.4</td>
<td>5.3</td>
</tr>
<tr>
<td>L4</td>
<td>18.4</td>
<td>5.0</td>
</tr>
<tr>
<td>L5</td>
<td>20.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>
The bands are used to establish a relationship between the total force acting on the perimeter of an MFS balloon segment and its internal pressure. This is done by inflating the balloon segment to 14 kPa and then placing a calibration band of known elasticity, diameter, and width on the perimeter of the inflated balloon (Figure 34). The radius \((r)\) and width \((w)\) of the stretched rubber band are measured, and the tension \((T)\) in the rubber band is determined based on its stretch. Average pressure \((P_b)\) exerted by the rubber band on the balloon is calculated from the hoop stress equation:

\[
P_b = \frac{T}{rw}
\]  
(3.15)

The total force of the band acting on the MFS segment is:

\[
F_b = P_b 2\pi w r
\]  
(3.16)

Substituting (3.16) into (3.15) and solving for total force \((F_b)\) yields:

\[
F_b = 2\pi T
\]  
(3.17)

We can now compare the total force exerted by the calibration bands on the sensor to the total force exerted by contact loading.
Figure 34. Cross section of a single MFS balloon segment showing the radial contact load characterization test using calibrated rubber bands.

*Distributed Loading With Test Jig:* The jig has three independent pairs of contact plates, equally spaced at 60°. These are labeled 1, 2, and 3 in Figure 35. Turning the lead screws translates the contact plates so that they impart a distributed, radial, contact load, compressing the balloon approximately 4 mm (about 2 mm from each plate in the pair). The sensor balloon is contacted with plate pairs so that there is no reaction force at the hub where the sensor is mounted to the jig. Each contact plate pair is equipped with a button-style force sensor (Honeywell, FSS1500NSB) attached to a 24-bit bridge module (National Instruments 9237). Data is gathered from the force sensors at 100 samples s⁻¹ and then resampled at equally spaced force intervals. The lead screws are turned by hand, so the samples are irregularly spaced spatially. After resampling, the minimum number of force-pressure measurements is 32. The total error from the sensor at the maximum expected force is ±0.26 N. Through the use of this jig, the sensor is contacted simultaneously by the three plate pairs such that the
contact force is distributed uniformly and radially around the circumference of the sensor, similarly to what would be experienced *in vivo* by the sensor balloon. Pressure and total force are recorded during the test. Next, the force-pressure response is measured using simple plane contact (see Figure 36). A single contact plate is pressed against the sensor balloon. The contact plate is retracted, the balloon is rotated to the 120° position and is again contacted by the plate. The process is repeated a final time after rotating the balloon sensor to the 240° position. Total force from planar contact is calculated by multiplying the loadcell values by two to account for the reaction force at the hub where the sensor is held. Both experiments (uniformly distributed radial loading and single plane contact loading) are conducted at room temperature and ambient pressure. The force-pressure responses of the two experiments are compared using analysis of covariance. Verifying that the force-pressure response of the single contact location experiment yields the same result as the radial loading configuration allows for simpler device characterization (discussed hereafter).
Figure 35. Test jig for verifying the observation that pressure change is proportional to the total force exerted on the sensor (Left). The MFS balloon segment is mounted in the center of the jig. Turning lead screws moves the contact plates radially toward the center of the sensor. Schematic of test jig showing the contact plate pairs compressing the balloon segment (Right). The white arrows indicate the direction of movement of the contact plate pairs.

3.4.2.3 Sensor Pressure Versus In vivo Environment

In addition to empirically characterizing the total force acting on a balloon segment as a function of contact load location and distribution, a characterization chamber (Figure 36) was used to experimentally determine the relationship between an externally applied load \( F \), the sensor pressure \( P_d \), intraluminal (or ambient) pressure \( P_t \), and sensor temperature \( T_s \). Note that in the following discussion \( P_d \) indicates the MFS sensor segment pressure after it has been compensated for decay due to creep of the elastomer. The uncompensated sensor pressure is \( P_s \).
Figure 36. Characterization chamber. Each segment is independently tested at three locations under various temperatures, pressures, and contact loading.

The sensor pressure is empirically described as a function of these factors as

\[ P_d = P_{d,i} + \Delta P_{d,l} + \Delta P_{d,T} + \Delta P_{d,F} \]  \hspace{1cm} (3.18)

where \( P_{d,i}, \Delta P_{d,l}, \Delta P_{d,T}, \Delta P_{d,F} \) are the sensor pressure under initial conditions prior to implantation, the changes in sensor pressure due to intraluminal pressure, temperature, and mucosal contact force, respectively.

Note that there is no term in (3.18) to compensate for the abdominal pressure. This is because changes in the abdominal pressure are nearly wholly represented by like changes intraluminal pressure, which are measured by the manometer and represented by \( \Delta P_{d,l} \).
The chamber provides a controlled environment for characterization of the MFS, in which the sensor stimuli are simultaneously varied to match the range of conditions the MFS will experience in vivo. The characterization procedure is as follows: 1) A single MFS balloon segment is inflated to the nominal pressure of 14 kPa and placed in a room temperature water bath for 16 minutes. 2) The segment is removed from the bath and placed in the mounting fixture inside the chamber. 3) Temperature is varied at four discrete intervals between room temperature and 38°C and gauge pressure is varied at four discrete intervals between 0 and 2 kPa. 4) A flat aluminum plate attached to a 5 N loadcell (PN 100-090-674, MTS Systems Corporation) is brought into contact with the MFS balloon segment at a rate of 1 mm s⁻¹. The contact plate is brought within 2 mm of the central rigid hub and then is retracted at the same rate. After the plate has fully retracted and is no longer in contact with the balloon, the balloon segment is rotated 120° and then 240° with the contact load applied at each location. Applying contact pressure to three regions along the circumference enables characterization of slight non-uniformities in the hand-made latex balloons. 5) Steps 3 and 4 are repeated until all permutations of pressure, temperature, load, and contact location are experienced by the balloon segment. 6) The balloon segment is removed from the characterization chamber and placed back in the room temperature water bath for 16 minutes. Pressures, temperature, force, and location are
recorded throughout the characterization at 50 samples s\(^{-1}\) channel\(^{-1}\). 7) The characterization protocol is repeated for each MFS balloon segment. Experimentation yields the following empirical relationships:

\[
\Delta P_{d,l} = \beta_1 P_I \quad (3.19)
\]

\[
\Delta P_{d,T} = \beta_2 \Delta T_s \quad (3.20)
\]

\[
\Delta P_{d,F} = \beta_3 F \quad (3.21)
\]

where \(P_I\), \(\Delta T_s\), and \(F\) are the ambient (intraluminal) pressure measured by the manometer, change in sensor temperature from room temperature, and total contact force. Unknown constant coefficients are \(\beta_{1-3}\). Substituting (3.19), (3.20), and (3.21) into (3.18), solving for \(F\), and renaming coefficients yields

\[
F = c_1 \Delta P_d + c_2 P_I + c_3 \Delta T_s \quad (3.22)
\]

The constants \(c_{1-3}\) are discovered through linear regression fit of the data collected with the characterization chamber. Note that the characterization contact force, \(F\), is \(2F_{lc}\), where \(F_{lc}\) is the force reported by the load cell. \(F\) is the total force acting on the MFS balloon segment, i.e. the force from contact with the MFS sensor and the reaction force at the hub at the center of the balloon segment, where it is fixed. In \textit{vivo}, contact force is applied radially along the entire circumference; therefore, there is no reaction force at the hub as there is during characterization.
3.4.2.4 Perfused Manometer Validation

The pressure drop across the manometer flow restrictor is a function of the viscosity of the PBS, which varies with temperature. The flow restrictor and PBS reservoir are *ex vivo*, therefore the ambient room temperature dictates pressure drop. To mitigate the effects of varying room temperatures, the manometer is zeroed immediately prior to each use. To zero, the distal end of the manometer is placed at the elevation at which it will be used *in vivo* and PBS is pumped through the tubing for 16 minutes at 0.3 mL min\(^{-1}\). The manometer pressure is recorded, averaged, and then subtracted from subsequent *in vivo* manometer readings.

The characterization chamber is used to validate manometer performance. To validate, the manometer is zeroed as described above, then the distal end of the manometer is placed in the mounting fixture inside the chamber. The temperature is varied at four discrete intervals between room temperature and 38° C and gauge pressure is varied at four discrete intervals between 0 and 2 kPa. This process is repeated until all permutations of pressure and temperature are experienced by the manometer. Pressures and temperature are recorded at 50 samples s\(^{-1}\) channel\(^{-1}\). The manometer response to the ambient pressure change is evaluated by absolute error:

\[
E_{\text{absolute}} = |P_l - P_m|
\]

(3.23)

where \(P_l\) and \(P_m\) are the ambient and manometer pressure arrays, respectively.
3.4.3 MFS System Characterization Results

Following are the results from the system characterization and testing protocols.

3.4.3.1 Stress Softening and Relaxation Characterization

The effects from stress softening were mitigated by over-pressurizing each balloon segment as described in the methods section.

To compensate for the relaxation of the elastomer during the characterization tests, decay coefficients for each MFS balloon segment were determined using (1) from pressure data prior to, and immediately after the characterization tests, yielding a mean decay rate of $-0.034\pm0.001\ \text{kPa min}^{-1}$. The decay coefficients were used to calculate the decay compensated sensor pressure ($P_d$).

3.4.3.2 Sensor Pressure versus Force Distribution

_Distributed Loading With Rubber Bands:_ In Figure 37, total force ($F_p$) is plotted against the corresponding change in sensor pressure for the 15 calibration bands. As shown in this figure, there is general agreement between total force due to radial loading from the calibration bands and total force on the sensor due to contact loading. The calibration bands exert a total force in the range of about 0.5 N to almost 6 N, whereas the contact loading exerts a maximum of about 1.5 N. Due to this disparity, the degree of fit is not calculated between the radially distributed load and the contact load.
Figure 37. Total force from radial and contact loads.

*Distributed Loading With Test Jig:* Shown in Figure 38 is the comparison of the force-pressure relationship between the radially loaded balloon (loading configuration shown in Figure 35) and loading from the single plate contact test (loading configuration shown in Figure 36).
Figure 38. Comparison of the force-pressure relationship between the radially loaded MFS sensor balloon (as shown in Figure 35, and listed here as radial load) and loading from the single plate contact test (as shown in Figure 36, and listed here as contact load). Note that the single plate contact test was repeated three times at three different locations along the balloon’s circumference equally spaced at 120° (represented by the thin, solid lines in the figure). A line was fit to radially loaded force-pressure data (dotted dark line) and the single plate contact data (solid dark line). Analysis of covariance indicates no statistical difference between the slopes of the two fitted lines (99% confidence level).

The slope of the best fit line to the single plate contact load data is similar to the slope of the best fit line to the radial load data. Analysis of covariance confirms no significant difference between the slopes given a 99% confidence level. Note that the maximum force value (approximately 3 N) was physically limited by the single plate contact test. In the test, the contact plate compressed the balloon to within 2 mm of the central hub. The
significance of this result is that minimal, acceptable error is incurred using the simpler characterization method of single plate contact.

3.4.3.3 Sensor Pressure versus \textit{In vivo} Environment

Shown in Table I are the contact load characterization coefficients of each sensor balloon segment. Half the data from the characterization procedure were used for fitting coefficients, and the other half for coefficient validation. The mean R$^2$ values from fitting and validation of the four sensor segments are 0.86±0.04 and 0.85±0.05, respectively.

Table 9. Characterization coefficients for the four MFS balloon segments.

<table>
<thead>
<tr>
<th>Balloon segment</th>
<th>c1</th>
<th>c2</th>
<th>c3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.44</td>
<td>-0.21</td>
<td>-0.15</td>
</tr>
<tr>
<td>2</td>
<td>1.48</td>
<td>-0.27</td>
<td>-0.19</td>
</tr>
<tr>
<td>3</td>
<td>1.59</td>
<td>-0.18</td>
<td>-0.20</td>
</tr>
<tr>
<td>4</td>
<td>1.53</td>
<td>-0.23</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

3.4.3.4 Perfused Manometer Validation

The perfused manometer validation test yields a mean absolute error of 0.15±0.09 kPa. The accuracy of the contact force measurement depends on the accuracy of the intraluminal pressure measurement of the manometer. Therefore, the impact of this error on the myenteric force measurement is determined by multiplying the error by the mean absolute value of $c_2$ from Table I, which is the coefficient of the intraluminal pressure variable in (7). The mean absolute value of $c_2$ is 0.22; therefore in terms of myenteric force, the mean total error contributed by the manometer is approximately 0.03 N, which is about 5% of the mean contact force per cm length measured in the porcine study (discussed hereafter).
The MFS system characterization methods and results presented here can also be found in the author’s published work [88].

### 3.4.4 *In vivo* MFS Porcine Study

The MFS is used to measure the myenteric contact force exerted on a solid bolus in the proximal, middle, and distal regions of five live porcine models. Up to three MFS sensors were simultaneously placed in the small bowel during each surgery. All pigs were female with a mean weight of 56.5±4.6 Kg. A test protocol was approved by the Institutional Animal Care and Use Committee (IACUC protocol 87909(05)1D). The animals were fed nothing but water and Jell-O® 48 hours prior to surgery and then only water the last 24 hours to ensure that the entire length of small bowel was clear of solids. The pig was generally anesthetized with Ketamine and Xylazine (anesthetic and sedative, respectively). The identification number, animal age range, weight, pre-anesthetic, region tested, and vendor are shown in

Table 10. Identification, age, weight, pre-anesthetic, and region of the small intestine tested of the five female pigs used in the study.

<table>
<thead>
<tr>
<th>Pig ID</th>
<th>Age (months)</th>
<th>Weight (Kg)</th>
<th>Pre-anesthetic</th>
<th>Bowel Region tested</th>
<th>Vendor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8-24</td>
<td>56</td>
<td>Atropine</td>
<td>Middle</td>
<td>K&amp;S Livestock</td>
</tr>
<tr>
<td>2</td>
<td>8-24</td>
<td>54</td>
<td>Atropine</td>
<td>Proximal, Middle, Distal</td>
<td>K&amp;S Livestock</td>
</tr>
<tr>
<td>3</td>
<td>8-24</td>
<td>53.3</td>
<td>None</td>
<td>Proximal, Middle, Distal</td>
<td>K&amp;S Livestock</td>
</tr>
<tr>
<td>4</td>
<td>8-24</td>
<td>62.3</td>
<td>None</td>
<td>Middle, Distal</td>
<td>K&amp;S Livestock</td>
</tr>
<tr>
<td>5</td>
<td>8-12</td>
<td>57</td>
<td>None</td>
<td>Middle, Distal</td>
<td>Colorado State University</td>
</tr>
</tbody>
</table>
During each surgery, a 20 cm midline incision starting about 2 cm below the xiphoid process is made in the abdominal wall. A section of the small bowel is pulled through the incision and the surgeon identifies the proximal, middle, and distal regions by traversing its entire length. A 2 cm incision is made in the bowel wall and the MFS is inserted approximately 20 cm into the lumen past the incision (Figure 39). The incision in the bowel wall is sutured and the process is repeated until all sensors are in place. Once the MFSs are in place, the bowel is placed back inside the abdominal cavity, the abdomen is sutured closed, and the animal is left untouched in the dorsal recumbent position for approximately 16 minutes (Figure 41). During this time, the vital statistics are monitored to ensure viability of the animal, and the MFS data are recorded. Following the data acquisition, the sensors are removed and the animal is euthanized.

Figure 39. Surgical insertion of the MFS into the middle small bowel
Figure 40. MFS sensor fully inserted into the middle small bowel of pig 5. Notice the bowel has vigorously contracted around the sensor.

Figure 41. MFS sensors inserted into small bowel of the porcine model. The small bowel has been placed back inside the abdomen, the incision is sutured closed, and the MFS data are gathered.
Data from the experiments were used to find: 1) The mean force per porcine model; 2) The mean force per region location of the MFS (proximal, middle, or distal bowel; 3) The mean force per MFS balloon segment location.

All three of these calculations use the mean force experienced by a single MFS balloon segment while *in vivo* as the “base” measurement. This base measurement is denoted as $\bar{F}_{r,b,p}$, where $r$ is the region in the small intestine (proximal, middle, or distal), and $b$ is the balloon segment of the sensor (1 through 4), and $p$ is the porcine model (1 through 5). Note that Balloon 1 is always the trailing edge of the sensor and Balloon 4 is the leading edge, which is the edge that is inserted into the lumen first during surgery. $\bar{F}_{r,b,p}$ is calculated from data acquired from the interval of 6 to 11 minutes after insertion. The reason for using this interval is that exposing the intestine to room temperature air causes it to cool; therefore, allowing the sensors to rest in the abdomen for 6 minutes after replacing the intestine and suturing the incision enables the abdominal cavity to return to standard body temperature.

The mean contact force from myenteric activity acting on the MFS sensor is

$$F = \frac{1}{mnq} \sum_{r=1}^{m} \sum_{b=1}^{n} \sum_{p=1}^{q} \bar{F}_{r,b,p} \quad (3.24)$$

where $m$ is the number of regions tested, $n$ is the number of balloon segments per MFS, and $q$ is the number of pigs tested.
The mean force per porcine model gives a general understanding of the overall myenteric contractile strength of the small bowel of a particular pig. It is calculated by

\[
\overline{F}_{p_i} = \frac{1}{mn} \sum_{r=1}^{m} \sum_{b=1}^{n} \overline{F}_{r,b,p_i}
\]

where \( p_i \) is the pig id (i=1..5).

The mean force per region gives a general understanding of the overall myenteric contractile strength of the proximal, middle, and distal regions of the small bowel. It is calculated by

\[
\overline{F}_{r_i} = \frac{1}{nq} \sum_{p=1}^{q} \sum_{b=1}^{n} \overline{F}_{r,b,p}
\]

where \( r_i \) is the region of the small bowel (i=1..3 for the proximal, middle, and distal bowel respectively).

The mean force per MFS balloon segment gives the force distribution over the length of the MFS. It is calculated by

\[
\overline{F}_{b_i} = \frac{1}{md} \sum_{r=1}^{m} \sum_{p=1}^{d} \overline{F}_{r,b,p}
\]

where \( b_i \) is the balloon segment (i=1..4).

3.4.5 *In vivo* MFS Porcine Study Results

The mean myenteric contact force, \( \overline{F} \) from (3.24), based on data from all MFS balloon segments, regions, and pigs, is 1.9±1.0 N cm\(^{-1}\). The mean contact forces from myenteric contractions per pig, per region, and per MFS balloon segment are shown in Table 11. The distribution of the data for each
mean is illustrated by the box plots in Figure 42. As shown in the left plot of this figure, Pigs 1 through 4 have force values within one standard deviation of the mean. Pig 5, however, exhibits a significantly higher mean force of 3.7 N cm\(^{-1}\). Two possible reasons for this is that Pig 5 was purchased from a different institution than Pigs 1 through 4, and that it could be younger (see Table 10).

Illustrated by the middle plot of Figure 42 is an apparent increase in contact force from the proximal to distal region of the small bowel. A T-test at a 95% confidence level confirms a significant difference in the mean myenteric contact forces exerted by the proximal and distal small bowel (\(p = 0.02\)).

The leading edge of the MFS appears to experience lower force than the trailing edge; the differences, however, are not significant.

Table 11. Mean contact forces from myenteric contractions. \(\bar{F}_{p_i}\) is the mean force per porcine model from (3.25), \(\bar{F}_{r_i}\) is the mean force per region of the small intestine from (3.26), and \(\bar{F}_{b_i}\) is the mean force per MFS balloon segment from (3.27). All values have units of N cm\(^{-1}\).

<table>
<thead>
<tr>
<th>(\bar{F}_{p_i})</th>
<th>P1</th>
<th>1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P2</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>P3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>P4</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>P5</td>
<td>3.7</td>
</tr>
<tr>
<td>(\bar{F}_{r_i})</td>
<td>Proximal</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>2.3</td>
</tr>
<tr>
<td>(\bar{F}_{b_i})</td>
<td>B1</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>B4</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Figure 42. Box plots of myenteric force comparing the results from the five porcine models (left), the region of the bowel (middle), and the MFS balloon segments (right). On each box, the red central mark is the median, the blue edges of the box are the 25th and 75th percentiles, the black dotted whiskers extend to the most extreme data points not considered outliers, and outliers (red plus marks) are plotted individually.

The MFS measurements of the active forces generated by the small intestine presented here can also be found in the author’s published work [89].
Chapter 4: Conclusions

Following are specific conclusions drawn from each of the four primary components of our study: tribometry, mucosal adhesivity, passive biomechanical characterization, and active force characterization using the MFS.

4.1 Tribometry

A novel device for measuring the lumped in vivo coefficient of friction has been developed. Due to the small number of tissue samples tested (4 in vivo and 5 in vitro), the results at this stage are preliminary, yet they offer good proof-of-principle for the device. The results suggest that the COF of a polycarbonate sled against mucosa is slightly lower on living than excised tissue. As the sled repeatedly traverses the tissue, the COF appears to decrease after the first run, then stabilize between the second and third runs. This is true for both the live and excised tissue.
4.2 Mucus Adhesivity

Two experiments were conducted to measure the adhesivity of the mucosa. In an exploratory experiment, the adhesivity of mucosa to itself was measured. Several factors should be considered before using the results generated by this preliminary experiment for in vivo energy requirements of an RCE. For example, the results assume full separation of the entire inner surface of the bowel, yet the cross-sectional profile of the robot will affect the degree of mucoseparation. For example, a robot with a smaller profile will cause less separation, and therefore, the energy expenditure will be smaller. In addition, the adhesivity test probed two modalities, coplanar tack and ninety degree peel. As a robot travels within the lumen, the peel angle of the mucosa will depend on the profile of the leading edge of the robot. Furthermore, as evidenced by the full factorial study, it appears the adhesivity is rate dependent.

To the author’s knowledge, the full factorial study is the first study of porcine mucosal adhesivity to engineering materials. As such, the test apparatuses are used to first quantify the adhesivity of a commercially available, environmentally stable, geometrically uniform adhesive. The adhesivity of the mucosa is several orders of magnitude less than that of the commercial adhesive, which offers an intuitive feel for the adhesive strength of the mucosa. Also discovered is that separation via the tack modality requires much more energy, which provides an additional consideration for RCE designers who are interested in design optimization, however this may
be due to the bulk deformation and subsequent deformation of the viscoelastic mucosa, is not necessarily due only to adhesivity. The adhesivity of specific engineering materials may be a useful parameter for determining the efficiency of various drive mechanisms. The adhesivity of the mucosa, along with rheological, tribological, and other mechanical properties of the intraluminal environment, is an important component of a comprehensive model. Future work could investigate the adhesive dependence on rate, temperature, dwell time, and postprandial conditions. It should also be recognized that although care was taken to maintain hydration of the tissue, future work should investigate *in situ* measurements that are more representative of the RCE environment.

4.3 Biaxial Biomechanical Characterization

The in-plane biaxial biomechanical response of the small intestinal tissue exhibited hyperelastic, J-shaped behavior typical of soft tissues. Tests from pigs 1 and 2 did not indicate anisotropic behavior; however, the tissue from pig 3 was clearly anisotropic, with the circular direction exhibiting less stiffness than the longitudinal direction. One possible reason for this difference is that the maximum tension in tests 1 and 2 may be too high, causing plastic deformation of the elastin and collagen network and yielding results that are not physiological. The maximum tension in test 3 is about 7% and 14% lower than the thresholds in tests 1 and 2, respectively. The maximum tension values were determined by ramping tension until
macroscopic tearing was visible at the hook interface and then setting the threshold to 90% of that value in subsequent samples. Future work should refine the threshold determination technique so that deformation during testing is guaranteed to be physiological. The crimped fiber model developed by Kao et al. [64] fits the biaxial data marginally well but does not accurately capture all the characteristics of the small bowel tissue. This may be due to the higher elastin content in vascular tissue, which Kao used versus the low elastin content of the bowel tissue.

4.4 MFS

To the author’s knowledge, this is the first time the contact force exerted by the small intestine on a solid bolus has been measured on multiple porcine samples and in multiple locations. The mean force value, $\bar{F}$, is near the extreme of theoretical values from the literature. For example, work by Miftahof et al finds values in the range of 0.15 to 1.9 N cm$^{-1}$ [14], [24], [25]. Also significant is the discovery that the distal small bowel exerts 92% more contractile force against the MFS than the proximal small bowel. The reason for this is not known, though a possibility may be that the smaller diameter of the distal bowel provides for more optimal engagement of the actin and myosin filaments, and hence higher contraction strength against the MFS, which has a fixed diameter. Future work will investigate contractile force as a function of bolus diameter. Understanding the contact force exerted by the
myenteron throughout the small intestine provides an additional characteristic that RCE designers can consider for design optimization.
Chapter 5: Avenues of Future Research

There are multiple avenues this work could take. The most obvious are incremental improvements in the various protocols and test devices for further refining and generalizing the mechanical property measurements. Ultimately, the purpose of this work is to enable the creation of a unified model of the living small intestinal environment. The attributes of such a model would allow for simulation of the multiphysics RCE-tissue interactions that are presently poorly understood. Following is a discussion of each research component presented in this work and suggestions for additional research.

5.1 Tribology

Additional tribological experimental factors should be investigated. These include the COF as a function of rate, pressure, material, and geometry of the RCE. Presently, we measure a lumped COF, which includes the fluid shear and coulomb frictional properties. A more comprehensive study that investigates the contributions of each of these properties
separately would enable the development of a more complete model. To this end, the known rheological properties of the mucus could be used. Future work should be performed at body temperature as opposed to room temperature which is presently used.

5.2 Mucus Adhesivity

Results from the present study indicate that tack adhesivity may be rate dependent; future work could further probe this relationship. Peel angle could also be investigated. Adhesivity as a function of dwell pressure and duration could also be explored. In this study we investigated peel adhesivity to yield understanding of the energy requirements to gain passage through the collapsed small intestine. The separated tissue, however, comes together again at the trailing edge of the RCE. There likely is a “closing force” from the tissue that acts on the RCE and perhaps balances the adhesive peel force on the leading edge of the RCE. Another research possibility is to measure this so-called closing force.

5.3 Biomechanical Characterization

It is unknown if the presently used maximum tension value causes plastic deformation in the small intestine tissue. The literature suggests that the values used for biaxial stress in this study are well below the failure stress for small intestinal tissue [19]. Damage may be occurring, however, on a microscopic level at lower stresses. A histological study may need to be performed to determine if this microstructural damage occurring. Once
proper thresholds are determined and a suitable theoretical model is refined, a parametric study could be performed to understand the variability of the material parameters across:

- The proximal, middle, and distal regions of the small intestine
- The circumference of the small intestine
- Multiple porcine models

Even though the tissue is viscoelastic, the stress-stretch response is assumed to be independent of strain rate once the tissue is preconditioned, which is the case for other soft biological tissues [90], [91]. This assumption should be validated for small intestinal tissue.

5.4 MFS

The MFS in its present configuration provides a good (but not excellent) method for measuring the contact force from the myenteron. The advantages of the current system are low cost, ease of manufacture, and physical robustness. The device is, however, susceptible to environmental noise from fluctuations in temperature, ambient pressure, and creep of the elastomeric sensing surface. Although much more expensive, a solid state version of the device with in vivo transducers would significantly improve accuracy. Presently, the $R^2$ fit of the sensor model to the characterization data is about 0.86. It is anticipated that significant gains in model fit could be achieved with a solid state version of the MFS. If the present configuration is
used for future studies, a numerical or analytical model of the MFS sensor should be created and used to improve the sensor characterization.

The author has received IRB approval to test the MFS on a live human; indeed, a biocompatible version of the device and associated testing protocol are presently under development. Future work should carry this to fruition.

The present study of the contact force from the active myenteron is limited to a static, single diameter solid bolus. Future work could investigate the myenteric response to dynamic changes in bolus diameter, thus characterizing the response of tissue to RCE surgical manipulations. An untethered, ambulatory version of the device could measure myenteric response to a mobile bolus. This might be especially useful for characterizing forces due to capsule retention.

5.5 Unified Model

We have initiated a comprehensive program for characterizing the mechanical properties of the small intestine. Our aim was to support the multiple research groups investigating the feasibility of miniature, swallowable, \textit{in vivo}, untethered robots. This study has produced a starting point for future work that will focus on the creation of a unified analytical or numerical model of the \textit{in vivo} environment. It is anticipated that such a model will enhance the development of RCEs capable of traversing the gastrointestinal tract for the purpose of diagnosing pathologies, acquiring
biometrics, and performing next-generation minimally invasive surgical procedures.
REFERENCES


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[66] Samsom, Smout, Hebbard, Fraser, Omari, Horowitz, and Dent, “A novel portable perfused manometric system for recording of small intestinal


APPENDIX

There are numerous associated electronic files including software script, images, test notes, CAD models, etc. that are too expansive to include in the print version of this work. Following is a table of these files that indicates their location in the archived parent directory presently residing on the Advanced Medical Technologies Laboratory file server at:

\amd.colorado.edu\terrybs\working

This file server is accessible to those who have access to the University of Colorado Boulder network. Access, however, is limited to members of the lab.

<table>
<thead>
<tr>
<th>File or File Location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>.\Intestinal Crawler\PigStudies</td>
<td>Data and analysis code from pig studies</td>
</tr>
<tr>
<td>.\Intestinal Crawler\PigStudies/XXX_PigStudy</td>
<td>Specific pig study, where XXX is the date of the study. Matlab code that analyzes the associated pig study is located locally in their respective folders.</td>
</tr>
<tr>
<td>.\Intestinal Crawler\PigStudies\GlobalAnalysis</td>
<td>Matlab code that analyzes pig data across all pig studies.</td>
</tr>
<tr>
<td>.\Intestinal Crawler\VIs</td>
<td>Location of all Labview code for experiment control. This folder also contains several legacy programs.</td>
</tr>
<tr>
<td>.\Intestinal Crawler\VIs\MFSPressurize.vi</td>
<td>MFS system control and data acquisition software (see Figure 31 for MFS system). Primarily used for the water-filled, human version of the MFS (focus of future work).</td>
</tr>
<tr>
<td>.\Intestinal Crawler\VIs\SyringePumpSoftware.vi</td>
<td>MFS system control for the syringe pump (no data acquisition). Used with MFSSensorDataAcq.seproj for data acquisition.</td>
</tr>
<tr>
<td>.\Intestinal Crawler\VIs\MFSRadialCharacterization_cal.seproj</td>
<td>Data acquisition software for MFS radial contact experiment. See Section 3.4.2.2 for description of the experiment.</td>
</tr>
<tr>
<td>Directory Path</td>
<td>Description</td>
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<tr>
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<tr>
<td>\Intestinal Crawler\VIs\MFSSensorDataAcq.seproj</td>
<td>Data acquisition software for the MFS experiment (up to two MFS sensors, two manometers, and temperatures logged). Used in tandem with SyringePumpSoftware.vi.</td>
</tr>
<tr>
<td>\Intestinal Crawler\VIs\MFSSensorCharacterization.seproj</td>
<td>Data acquisition software used with the MTS Insight II tensile testing device (see MFS Validation.msm). Purpose of the software is gather data for the MFS characterization procedure (see Section 3.4.3.3).</td>
</tr>
<tr>
<td>\Intestinal Crawler\MTS Code\</td>
<td>Software for controlling the MTS tensile tester. This code was used to characterize the MFS and the mucosa.</td>
</tr>
<tr>
<td>\Intestinal Crawler\MTS Code\TackTest_PC_SS_PDMS.msm</td>
<td>MTS script used for performing the mucosa tack test on the polycarbonate, stainless steel, and polydimethylsiloxane.</td>
</tr>
<tr>
<td>\Intestinal Crawler\MTS Code\TapeTack_polyprop.msm</td>
<td>MTS script used for validating the tack protocol on polypropylene.</td>
</tr>
<tr>
<td>\Intestinal Crawler\MTS Code\MFS Validation.msm</td>
<td>MTS script used for characterizing the individual MFS sensors and used with the Labview code (see MFSSensorCharacterization.seproj).</td>
</tr>
<tr>
<td>\Intestinal Crawler\MMC Device Development</td>
<td>Files associated with the MFS development are stored here (the MFS was formerly called the MMC Sensor).</td>
</tr>
<tr>
<td>\Intestinal Crawler\MMC Device Development\Photos</td>
<td>Images of MFS development procedures and processes.</td>
</tr>
<tr>
<td>\Intestinal Crawler\MMC Device Development\Characterization Data</td>
<td>Contains multiple folders describing the evolution of the MFS. Subfolders are labeled CharTestXX, where XX is the test characterization number (chronologically). Much of the work in this folder is exploratory. Data acquisition software saves data to this folder by default.</td>
</tr>
<tr>
<td>\Intestinal Crawler\MMC Device Development\Characterization Data\SensorTracker.xlsx</td>
<td>Spreadsheet that tracks the various MFS builds and correlates the data from the characterization and testing of the sensors to CharTestXX folders described above.</td>
</tr>
<tr>
<td>\Intestinal Crawler\Mucus Adhesivity Development</td>
<td>Contains data and Matlab code from characterization and validation of the mucus adhesivity project. Data is exclusively from testing with commercial adhesives. See Sections 3.2.1 and 3.2.2.</td>
</tr>
<tr>
<td>\Intestinal Crawler\Papers</td>
<td>All publications associated with this work.</td>
</tr>
<tr>
<td>\Intestinal Crawler\SolidWorks</td>
<td>Location for all CAD parts, assemblies, and drawings associated with this work.</td>
</tr>
<tr>
<td>Directory</td>
<td>Description</td>
</tr>
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<tr>
<td>.\Intestinal Crawler\SolidWorks\Assembly, Apparatus, Test, Peristalsis.sldasm</td>
<td>Main assembly for the MFS. It also includes a grasper head model fixed to the trailing edge cap (see Section 3.4.1).</td>
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<tr>
<td>.\Intestinal Crawler\SolidWorks\Assembly, Characterization, MFS Radial Force.sldasm</td>
<td>Main assembly for the radial contact force test assembly (see Section 3.4.2.2).</td>
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<tr>
<td>.\Intestinal Crawler\SolidWorks\Assembly, Environmental Chamber, Custom.sldasm</td>
<td>Main assembly for the MFS environmental test chamber (see Section 3.4.3.3).</td>
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