A NOVEL DEVICE FOR GASTRIC CANCER SCREENING IN LOW AND MIDDLE-INCOME NATIONS

By

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To my Parents,

who, no matter the circumstance, have selflessly
supported me in all of my life's endeavors

and

To Cadbury and Keegan,

whose unconditional love I will always remember.

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CHAPTER 1

INTRODUCTION

1.1 Gastric and Esophageal Cancer

More than 1.4 million cases of gastric and esophageal cancer are diagnosed annually around the globe [1]. These two cancer types account for over ten percent of total incident diagnoses across the globe. Furthermore, over 70% of gastric and esophageal cancer incidents occur in low- and middle income nations, specifically in the pacific rim [2, 3]. Ongoing studies point to genetics, diet, bacterial exposure and the surrounding environment all playing roles in high gastric cancer incidents in places like Central America [4]. In places such as Japan, large scale screening programs have been shown to be effective in reducing the mortality rate of gastric and esophageal cancers through early detection [5, 6, 7, 8].

1.2 Gastric Cancer Tools and Screening Procedure

Screening for gastric and esophageal cancer usually involves the viewing of the upper gastrointestinal tract with a flexible endoscope by a physician. The flexible endoscope itself consists of an optical system paired with illumination to view the esophageal passage and gastric cavity. For movement, flexible endoscopes use a series of mechanical wires, called Bowden wires, that when actuated, allow the endoscope's tip to obtain two degrees of freedom. An additional channel is built into the endoscope to allow particular tools to operate within the patient during examination and therapy. An image of a flexible endoscope is shown in Fig 1.1. Prior to the procedure, a patient may choose to undergo full sedation,

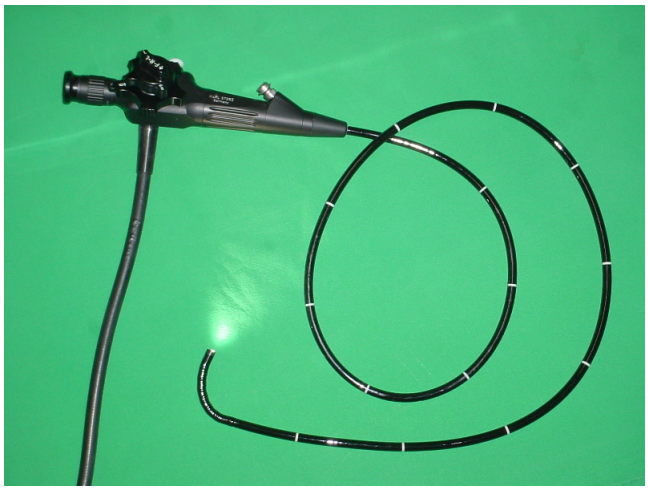

Figure 1.1: Image of Flexible Endoscope

have a localized anesthetic applied to the back of the throat to suppress the gag reflex, or have no anesthetic at all. Typically a full gastroscopy can be completed in under fifteen minutes, though this may increase in more complex cases.

While flexible endoscopes have been used in modern medical settings for decades, there are a few reasons why it is not a suitable tool in the establishment of a gastric cancer screening program in remote areas of low and middle-income nations. The first of these reasons is that many low and middle-income nations lack the ability to properly reprocess endoscopes after every use. This inability to correctly reprocess flexible endoscopes, whether due to lack of proper training, lack of sterilization tooling or lack of monetary funds, can lead to the transfer of harmful bacteria and viruses from those patients who are ill to those who are potentially perfectly healthy [9]. Such a situation would lead to instances where mass screenings could turn from being beneficial to being detrimental to a population [10]. Another reason flexible endoscopes may not be the optimal choice for screenings in remote areas of low- and middle-income nations is the costs associated when purchasing and operating the equipment. A single endoscopic system could require an initial investment of tens of thousands of U.S. dollars. When the system eventually needs repairs, each repair can cost an additional two

to five thousand dollars and take up to three months before being fully operational again. Lastly, system portability increases the difficulty of moving the system from one remote location to the next, especially when considering many of these nations have mountainous terrain. An example of this terrain is shown in Fig. 1.2.

Figure 1.2: Example of Terrain Surrounding a Remote Mountain Village in Honduras

1.3 Benefits of Capsule Based Endoscopy

With the outlined challenges of using a traditional flexible endoscopic system in remote areas of low and middle-income countries known, the question then becomes, "What system can be used to solve these issues?" Since 2001, capsule endoscopy has proven to be an effective method for viewing the lower gastrointestinal tract. Since capsule endoscopes are single-use items, they could prove useful in solving the sanitation dilemma as a disposable medical device. This would eliminate the need for reprocessing altogether and drastically reduce the transfer risk of bacteria and viruses between patients in low- and middle-income countries [11]. There are, however, difficulties associated with the use of endoscopic capsules for gastric cancer screening and limitations for their use within low- and middle-income countries. One of these difficulties is their lack of dynamic controllability [12]. When examining

the lower gastrointestinal tract, current endoscopic capsules use peristalsis, the digestive system's natural muscle contractions, for locomotion. Since the stomach is a much larger cavity, full exploration of it with a capsule cannot be accomplished using peristalsis. Therefore, if capsule technology is to be used in gastric cancer screening, some form of capsule motion control would need to be introduced. Another of these difficulties is the associated costs with endoscopic capsules. Per procedure, a typical examination of the lower intestine with an endoscopic capsule costs the patient around 500 USD [13]. This level of cost to the patient is unsustainable for majority of the population in low and middle-income nations. Any technology developed for gastric cancer screening in this region must be affordable for the local populous. Lastly, when traveling to and working in remote areas of low and middle-income countries, any platform for gastric cancer screening must be mobile, robust and use regularly available resources.

1.4 Platforms for Gastric Cancer Screening

There are platforms that either exist or are being developed which work toward solving some of the aforementioned issues. In 2010, Olympus Medical Systems Corp and Siemens Healthcare jointly started development of a wireless, magnetically guided endoscopic capsule (MGEC) for upper GI endoscopy [14]. This platform operates using the magnetic interaction between a small permanent magnet embedded in the capsule and a large magnetic guidance system (footprint of 1m x 2m) to control the capsule with 5 degrees of freedom (DoF). To reduce friction from the mucosa and to expand the stomach for easier viewing, the patient is asked to drink water prior to the procedure. Each MGEC is designed to be single-use and is disposed of after examination. While use of this platform is promising in modern medical settings, the costs associated with both the external driving unit and each individual capsule would prohibit its adoption in low-resource settings. In addition, any screening program's

ability to reach remote areas would be hindered by the limited portability of the magnetic guidance system due to its large footprint.

In 2011, another endoscopic capsule robot, the MASCE, was introduced by researchers at Carnegie Mellon University [15, 16, 17]. This capsule (18mm diameter, 31.5mm length in uncompressed state), also designed to operate in a fluid filled stomach, is operated through use of an external permanent magnet. For motion within the stomach, torque applied by an external magnet allows the capsule to roll across the stomachs mucosa. Use of the capsule requires an external system that consists of a large, rotating external permanent magnet and rotational patient bed. In the scenario of operation in a remote area, this setup limits the portability of the system [15].

Another wireless capsule system was proposed in 2013 by a lab at Scuola Superiore SantAnna in Pisa, Italy [18, 19]. This wireless capsule uses four motorized propellers mounted on the capsule aft end to navigate within the patients stomach. The capsule operates using onboard, battery-driven electromechanical parts, which in and of itself creates a significant risk of system failure. With operation in remote areas in mind, system reliability becomes a chief concern since repair of complex electrical systems in these locations could prove to be an impossible task. Additionally, the total cost of the system with its non reclaimable electronics could prove too expensive for use as a disposable unit in low-income countries [18].

Lastly, Medivators Inc. has recently released a disposable trans-nasal esophagoscope called the E.G. Scan II [20]. The E.G. Scan II system is comprised of a controller, processor box and disposable probe.This disposable probe has a tether diameter of 3.6mm and an optic capsule diameter of 6mm. It uses 4 light-emitting diodes (LEDs) for illumination and has a built in air channel for insufflation. While this system could prove to be a disposable diagnostic solution for certain markets, the system is designed to primarily operate in the esophagus, not the stomach. It is also worth noting that when the probe is disposed of after

each examination, the internal endoscopic camera within is disposed of as well. This raises overall procedural costs. All of these platforms are pictured below in Fig. 1.3.

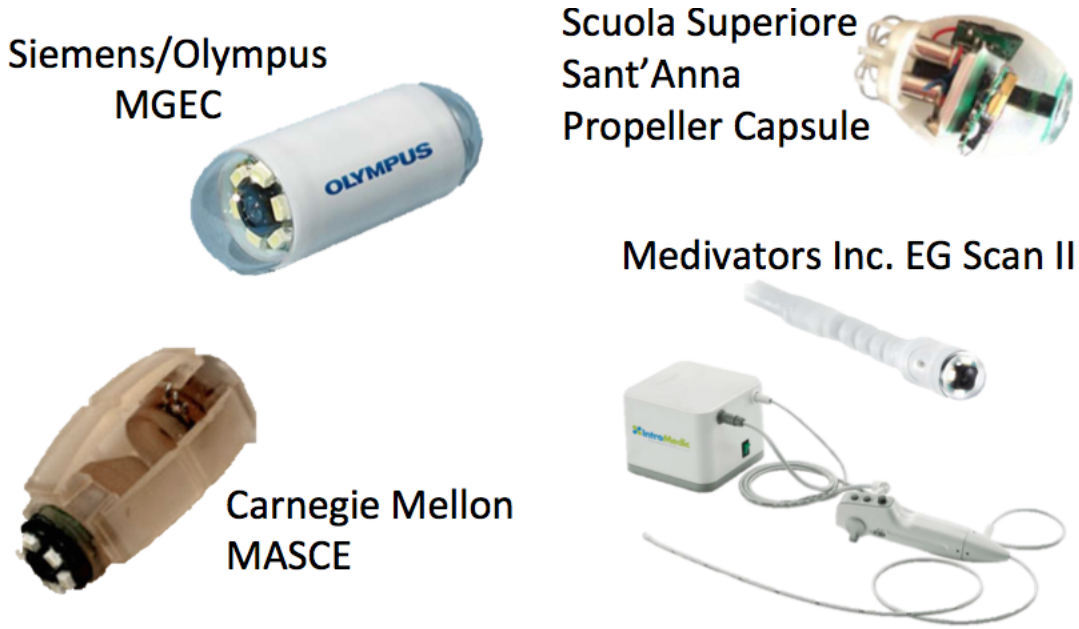

Figure 1.3: Other Gastric and Esophageal Screening Platforms [14, 15, 19, 20]

1.5 Hydrojet Endoscopic Capsule

Each of the previously mentioned platforms use different methods to dynamically control a capsule for gastric and esophageal endoscopy. In terms of usage in remote areas within low- and middle-income countries, each of these platforms also have major limitations such as overall costs, size and system complexity. For a platform to operate properly in a limited resource setting it will need to be affordable, easily reprocessed, mobile, robust and operate using available resources. The work presented in this document highlights the design, fabrication, and testing of a disposable, soft-tethered, swallowable endoscopic capsule, henceforth called the Hydrojet. The Hydrojet, as shown in Fig 1.4, has been designed to enable affordable gastric cancer screenings to take place in remote areas of low- and middle-income countries. If patients in a remote area are found to have any suspicious lesions or

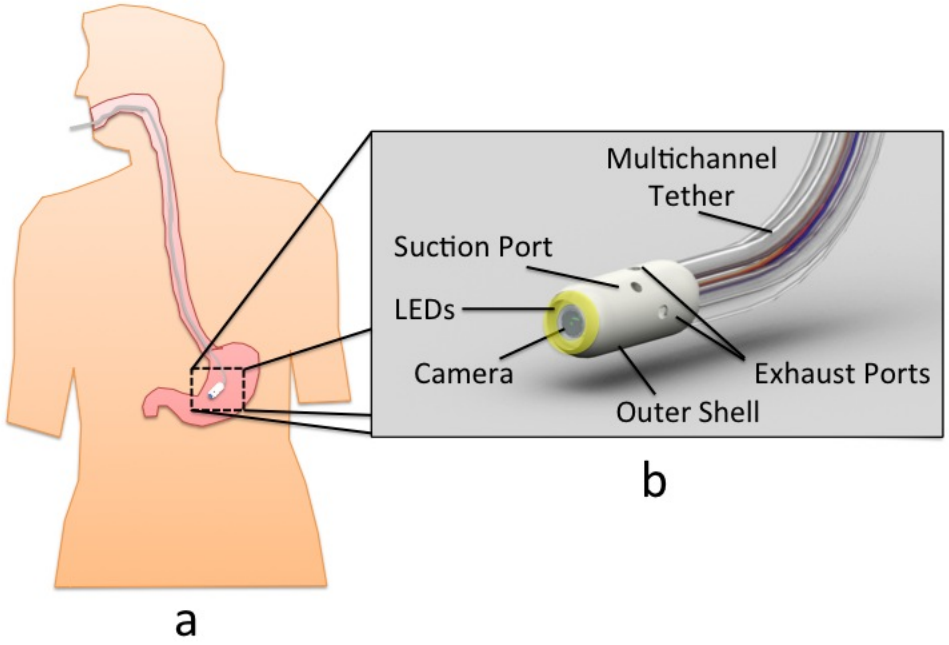

Figure 1.4: a) Hydrojet Within Human Stomach. b) Render of Hydrojet Endoscopic Capsule

any other noticeable physical discrepancies after a Hydrojet procedure, the physician would then be able to more reliably refer them to a less remote healthcare setting for a traditional gastroscopy. Pressurized water was chosen to control the capsule within the stomach as a resource is pressurized and ejected from the capsule to orient the view of the endoscopic camera. After completion of a cancer screening procedure, the Hydrojet outer shell and tether is disposed of and the capsules camera is reclaimed without needing further reprocessing. This capsule configuration has the potential to minimize procedural cost and reduce the risk of spreading disease through improper reprocessing of endoscopic tools. Additionally, since the setup needs to be easily transported from one location to the next, the entire system has been designed with portability in mind. This document presents the development of the Hydrojet platform in a chronological order. Section II will demonstrate the overall idea and operation of the platform. Next, Section III will discuss the design and fabrication process of the entire Hydrojet system. Section IV will show how we experimentally analyzed the system. Section

V gives a brief overview on a second generation of the platform under development. Lastly, Section VI finishes with some final thoughts and ideas for future work.

CHAPTER 2

PRINCIPLE OF OPERATION

2.1 Capsule Operation

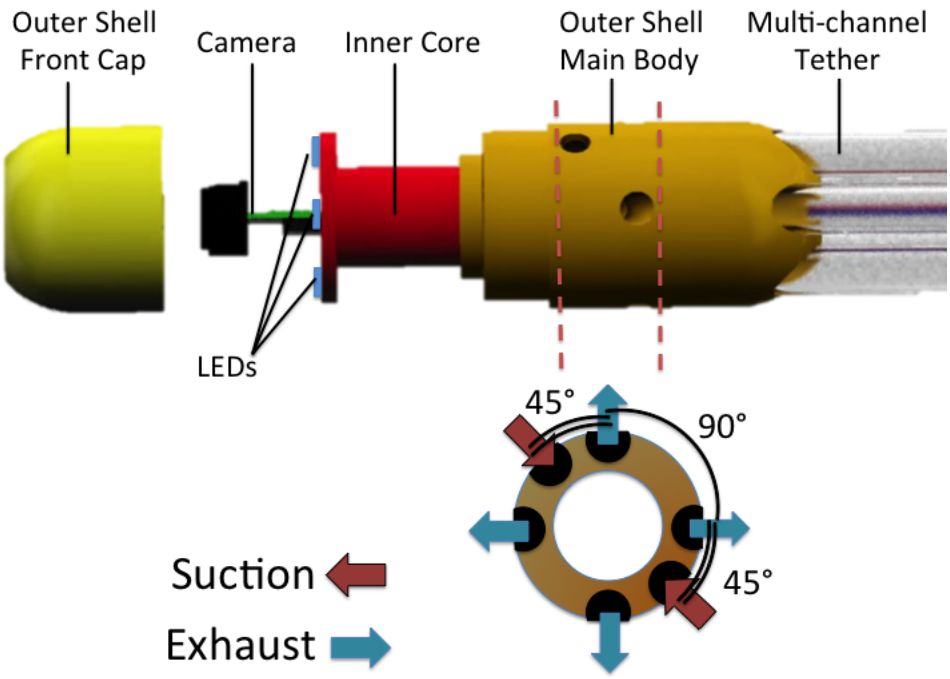

Figure 2.1: Exploded Diagram of Hydrojet Capsule Showing the Locations of Exhaust and Suction Ports

The Hydrojet platform is first composed of a swallowable capsule connected to a pressurized water supply system via a disposable, soft, multi-channel tether. Use of water jets as a propulsion method was influenced by the Omniegg underwater robot. Developed by a

group at MIT, the Omniegg was designed to use water jets to maneuver nuclear power plant pipe systems [21]. The capsule, as shown in Fig 2.1, is comprised of a disposable outer shell which has four pressurized water exhaust ports spaced at ninety degree intervals around the cylindrical body. Additionally two fluid suction ports are placed on the outer shell body opposite one another (180 degrees apart). The outer shell consists of an outer shell main body and an outer shell front cap. This two piece outer shell design enables the system to have a removable inner core in which all of the on-board electronics are housed. Oriented at 90 degrees relative to the capsule's axial direction, the exhaust ports allow for the Hydrojet to operate with two degrees of freedom when pressurized water is ejected from them. Selective activation of the exhaust ports and fluid exhaust pressure let the Hydrojet operate in a quasi-hemispherical region. To reduce or increase the radius of this hemispherical operating region, a third degree of freedom can be introduced by the user through feeding and retracting the device's multi-channel tether. The aforementioned suction ports allow for the user to control the amount of liquid introduced into the patient's stomach to both aid in maneuvering of the device as well as ensure patient safety. On the front side of the capsule, embedded in the capsule's cap, a viewing window is placed to allow the on-board camera to view the surrounding environment. When connected, the outer shell main body and front cap create a hermetically sealed environment for capsule's inner core. This environment allows the on-board electronics to operate without fear of exposure to the external environment. Limiting the exposure of the inner core during operation not only creates a safe working environment for the on-board electronics, since the capsule will be in an aqueous environment, but also permits the inner core to be reclaimed after each procedure without need of further reprocessing.

2.2 Multi-channel tether

The multi-channel tether consists of 6 individual tubes connected to the aft of the outer shell main body. Four of these tubes supply pressurized water to their respective Hydrojet exhaust ports on the main body. One tube, connected to a single port on the aft, provides acts as a fluid removal line for both suction ports. The last and central tube in the multi-channel tether houses electrical wiring for power and video transmission. This line connects to a connector mounted on the aft of the outer shell main body which, in turn, is directly connected to the capsule's inner core.

2.3 Water Distribution System

A system of fluid pumps, valves, flow meters and junction manifolds enables the monitoring and supply of pressurized water to the system. Fluid supplied to the system starts in a water reservoir and is fed into a propulsion pump for pressurization. This pressurized fluid is then fed into the first of two junction manifolds. This junction manifold, called the pressure manifold, has multiple binary, solenoid valves attached to it that control the pressure of the fluid as it continues downstream into the system. To decrease the downstream pressure, the user would activate either a single or multiple pressure controlling valves, which when activated would feed a fraction of the water flow back to the original water reservoir. In the first generation of designing the Hydrojet, only two pressure controlling valves were attached to the pressure control manifold. This leads to either a pressure reduction by a factor of two if one valve is activated, or by a factor of ten if both valves are opened simultaneously. As mentioned, the pressure control manifold is designed to have additional valves attached. Ideally, additional valves would allow for an even finer control of downstream water pressure by the user.

Once water has passed the pressure control manifold, it enters a flow meter known as the propulsion flow meter. This flow meter is used by the system to measure both the flow rate of water past the pressure control and also to monitor the amount of water introduced by the system into the patient's stomach. After exiting the propulsion flow meter, water then enters the second of the two system manifolds. This manifold, called the directional manifold, has four solenoid binary valves attached to it. These four valves each connect to one of the four water supply lines on the multi-channel tether. By selectively activating one or two of these valves, the pressurized water is directed to an exhaust port on the capsule allowing for the user to maneuver the system.

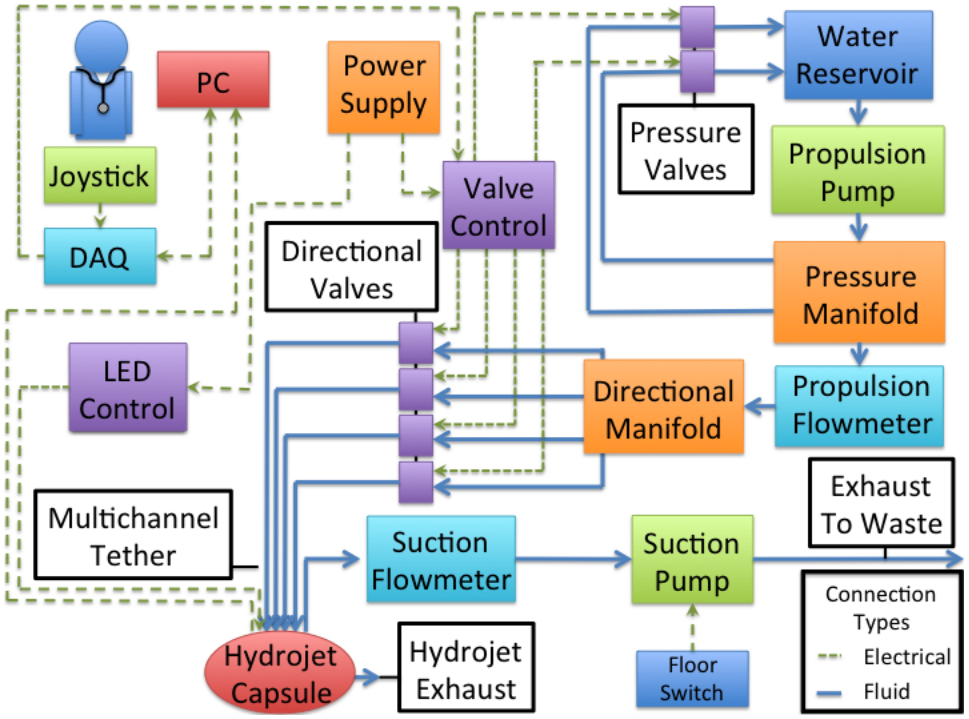

Figure 2.2: Illustration of Water Distribution System

Suction of fluid within the patient is accomplished via the previously mentioned suction ports and single suction line on the multi-channel tether. This tether line is connected to a second flow meter which monitors rate of suction and the amount of liquid removed by the

system. Past the flow meter is the suction pump itself which then feeds the removed fluid to a system waste reservoir.

All of the directional and pressure control valves are controlled by a valve control system, which is in turn supported by a personal computer, data acquisition system and power supply. Additionally the capsule's on-board camera and LEDs are also supported by an external power supply. Open loop control of the system by the user is accomplished via use of an external joystick and foot pedal in conjunction with images relayed by the capsule's vision system and by data presented to the user in a graphical user interface. Fluid exhaust pressure is controlled using a push button located on the joystick. Each push of the button cycles through the available pressure settings in a binary manner. The suction line, which is either off or on, is controlled via the previously mentioned foot pedal. The graphical user interface is displayed on the system's personal computer and provides the operator with which exhaust ports are active, what the current exhaust pressure setting is, the propulsion fluid flow rate, the total amount of liquid introduced into the patient, the fluid flow rate of the suction line, the amount of fluid suctioned from the patient and the net liquid introduced into the patient's body. The graphical user interface also alerts the operator if a previously defined safety threshold for fluid introduction has been broken. This alert allows the operator to safely cease propulsion and activate the fluid suction line until returning to a value safely under the established threshold. The video from the on-board camera is displayed on a secondary dedicated monitor. The entire layout of the water distribution system is illustrated in Fig 2.2.

CHAPTER 3

SYSTEM DESIGN AND FABRICATION

3.1 Medical Considerations and Design Requirements

Certain considerations had to be taken into account when designing the Hydrojet platform, both to create a functional device and to ensure the safety of the patient. First, considering that the Hydrojet is swallowed by the patient during device introduction, the Hydrojet capsule and tether must pass through the esophagus to reach the stomach cavity. The esophageal passage in a fully grown adult, as measured from the esophageal sphincter, is approximately 18-26 cm in length and 2-3 cm in diameter [22]. This is a limiting factor in the allowable diameter of the device. Standard flexible endoscopes can range in sizes based upon intended use and original manufacturer, but have been noted to be up to 1.1m in length and 12.8mm in diameter [23]. Both the Hydrojet capsule and multi-channel tether should ain to be no greater than these dimensions in diameter at their widest point and the multi-channel tether should provide a comparable length.

Once within the stomach, the Hydrojet would need to be able to maneuver and view regions of interest within the stomach in a fashion similar to flexible endoscopes. The stomach, on average, has a maximum width of 10 cm and a length of 34 cm at the greater curvature [24]. Non-distended the volume of the stomach is about 1000 cm^3 [25]. To operate within such a workspace, flexible endoscopes use Bowden wires to mechanically move the distal camera with two angular DoFs. To look backward to the cardia and the fundus,

flexible endoscopes are capable of retroflexion, a process where the tip of the endoscope is deflected 180 degrees by the user. To view these regions of the stomach the Hydrojet would need to accomplish a movement similar to retroflexion.

With patient safety in mind, any water jet exhausted by the capsule would need to be below a pressure of 3 bar so as not to risk tissue perforation [26]. The temperature of the capsule must remain at or below 34 degrees Celsius at all times during a procedure to ensure that the patient's mouth, esophagus or stomach mucosa is not damaged. In an event where the capsule becomes detached from the multi-channel tether, the capsule must be able to safely pass through the patient's lower gastrointestinal tract using peristalsis. This limits the size of the capsule it self to a diameter of 13mm and length of 31.5mm [27].

In the trials for the previously mentioned MGEC stomach capsule created by Siemens and Olympus, a protocol was used where, prior to the actual procedure, the patient consumes 1.3 liters of water [14]. Taking into account these medical trials, this volume of water will be considered the safety threshold which is not to be exceeded during Hydrojet operation. This will require a system that constantly monitors the amount of fluid introduced into the patient by the capsule and a system where the net amount of fluid introduced can be controlled by the operator.

A standard upper GI endoscopy typically lasts from 5 to 15 minutes [28]. The Hydorjet system must allow the operator to examine a patient in a similar time period. As a point of safety, however, the Hydrojet will also need to operate continuously for a period of time longer than the standard examination for certain extreme cases where additional time may be necessary. Using a factor of safety of five, the Hydrojet will be designed to at least operate continuously for 75 minutes (factor of 5 multiplied by the typical longest exam time).

With some remote areas of low and middle-income nations not being easily accessible, portability of the system becomes another factor consider. The footprint and weight of the system must be kept to a minimum and the system should preferably be in a form factor

that is easy to transport from one remote village to another. The system also should only use resources which are readily available and inexpensive in the region.

With the idea that this system will operate primarily in limited income areas, the price per procedure needs to be kept to a minimum (2-5 USD). A design where only inexpensively manufactured plastic parts are disposed and where expensive electronics can be easily reclaimed will both reduce sanitation issues and keep the price point low.

3.2 Capsule Fabrication

The capsule's outer shell was constructed via 3D printing (Objet Geometries Ltd, Model: OBJET 30) which used a durable plastic (Objet Verowhite Plus) as the building material. It was designed to have a diameter of 12 mm, length of 28 mm, and weight of 2.7 g. While the 3D printed plastic material is not biocompatible, it was deemed sufficient for the testing stage as only the feasibility of the device was being assessed at this stage. The design of the capsule, however, was made with the idea of eventually using an injection molding process, which would allow for the device to be readily replicated in mass quantities using a biocompatible plastic. In the center of the capsule's aft, a through hole (diameter 2 mm) was made for inserting the central line of the multi-channel tether. This line provides a direct connection for power and video transmission to and from the capsule's inner core. Around this central hole, five connection ports (diameter 3.4 mm) were created to allow insertion of the multi-channel tether's propulsion and suction tubes. On the outer shell main body's external surface, four exhaust ports (diameter 2 mm) were positioned in 90 degree intervals around the capsule's longitudinal axis. These exhaust ports were placed 16mm from the front of the capsule to align the exhaust jets with the capsule's theoretical center of mass when loaded with the inner core module. Approximately 12mm from the front of the capsule, two additional ports (diamter 2 mm) were placed to provide removal points for the suction line. The ports were spaced on opposites sides of the capsule from one another (180 degrees) in

hopes that when suction was activated by the operator, the suction force's effect on capsule motion would be negligible as the symmetrical placement would help to cancel one another out. The inner core module was also created using 3D rapid prototyping. It was designed to have a diameter of 5.4 mm and a length of 17 mm, and contains the on-board camera, LEDs, and a four-pole female connector on its aft. With these dimensions, the inner core was capable of being freely inserted and removed from a recess within the outer shell main body without ever contacting the external environment. To completely isolate it and create the hermetic seal around it, the capsule's front cap was also rapid prototyped using a 3D printer. The aft side of the cap mates with an o-ring mounted on the outer shell main body to create a water tight seal. On the front side of the cap, a recess (diameter 7 mm, depth 0.8 mm) was created to place a plexiglass cover to shield the inner core from the external environment while at the same time allowing the on-board camera to visualize the surrounding area. The capsule weight and size were designed to make it neutrally buoyant in water as well. The capsule and multi-channel tether are shown next to a traditional flexible endoscope in Fig 3.1.

3.3 Multi-Channel Tether Specifications

To connect the capsule to the water distribution and visual acquisition systems, six independent tubes, each measuring 1.1 m in length, were used. Five of these tubes (Tygon PVC Tubing, 3.18 mm outer diameter (OD), 1.59 mm inner diameter (ID)) are used by the water distribution system. The sixth tube (Miniature Clear EVA Tubing, 1.78 mm OD, 1.02 mm ID) nests in the center of the five larger tubes and provides the wired connections to the capsules electronics for power and video transmission.

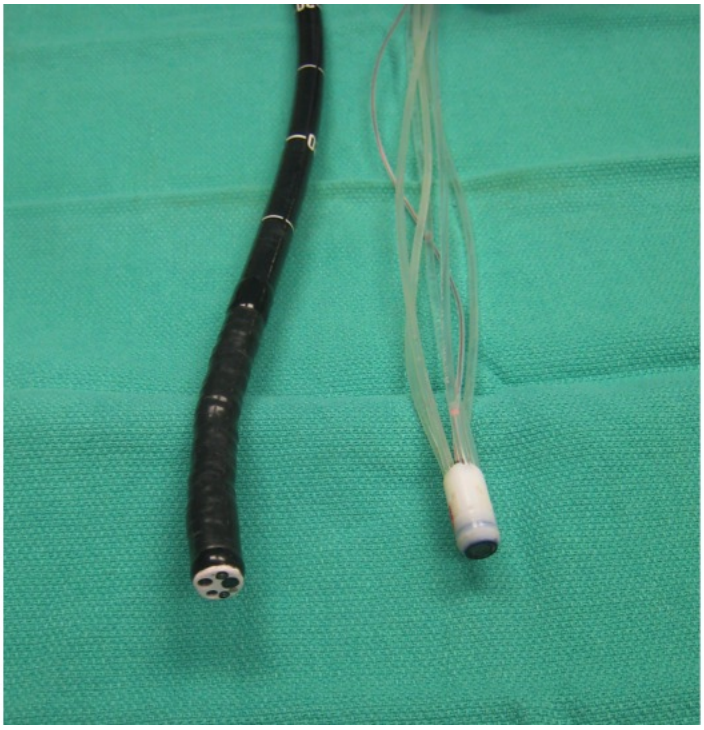

Figure 3.1: Diagram of Capsule Range of Motion Using Pivoting Technique

3.4 Water Distribution System Design and Construction

A positive displacement three-chamber diaphragm pump (ShurFlo, Model: 8030-863-239) was used to take in water from a reservoir and provide pressurized water to the system. Immediately downstream from the pump, pressurized water was fed into the system's first brass manifold which uses two of six available side outlets. These side outlets are connected by polyvinyl-chloride (PVC) tubing (6.35 mm OD, 3.18 mm ID) to their own respective stainless steel solenoid valves (McMaster-Carr, Model: 5077T144). Downstream from the pressure control manifold, an ultrasonic flow meter was attached to the system (Titan, Model: Atrato 740-V20-A) and connected directly to the systems data acquisition (DAQ) board (National Instruments, Model: NI-USB-6221) for monitoring the total amount of fluid expelled from the capsule. An ultrasonic flow meter was used in this instance as it only minimally inhibits the flow of water, thereby preserving the fluid pressure within the system

as much as possible. Further downstream is the systems second brass manifold which used four side outlets out of a possible six. The same model of valves (McMaster-Carr, Model: 5077T144) and PVC tubing (6.35 mm OD, 3.18 mm ID) were used to provide directional control to the Hydrojet. To activate both the pressure control and the directional control valves, power was regulated via a valve control box, which was comprised of multiple NPN transistor gates driven by the DAQ board. The valves were regulated via binary, On/Off signals due to their relatively slow commutation time (i.e., 20 ms). Pulse width modulation may prove to be useful in the future to control fluid exhaust from the capsule more precisely as is mentioned in [29]. Using a faster and more expensive valve, this system could be retrofitted with a pulse width modulation based valve, however, we hypothesized that three different levels of pressure, combined with the field of view of the camera and the adjustment of tether length, were sufficient to inspect the surface of the stomach, while minimizing the overall cost of the platform. The validity of this assumption was assessed in both ex vivo and in vivo trials described in section IV. Larger diameter PVC tubing (12.7 mm OD, 9.58 mm ID) was used between the reservoir, pump, flowmeter, and manifolds so as not to inhibit the max allowable flow rate to the Hydrojet capsule. To operate the suction line, another positive displacement pump (ShurFlo, Model: 8000-912-288) was used. A Pelton wheel flowmeter (Cole-Parmer, Model: W-32709-80) was attached upstream from the displacement pump and connected to the DAQ board to monitor the outflow of fluid from the patient during procedure. The choice of a Pelton wheel flow meter for measuring suction flow rate instead of using another acoustic based flow meter was due to a much lower price tag and the fact that in the suction line, we did not mind inhibiting the flow of water as much. All parts of the water distribution system were chosen with portability, form factor and cost in mind. The total cost of the listed components is under 6,000 USD. A picture of the complete water distribution system is shown in Fig 3.2.

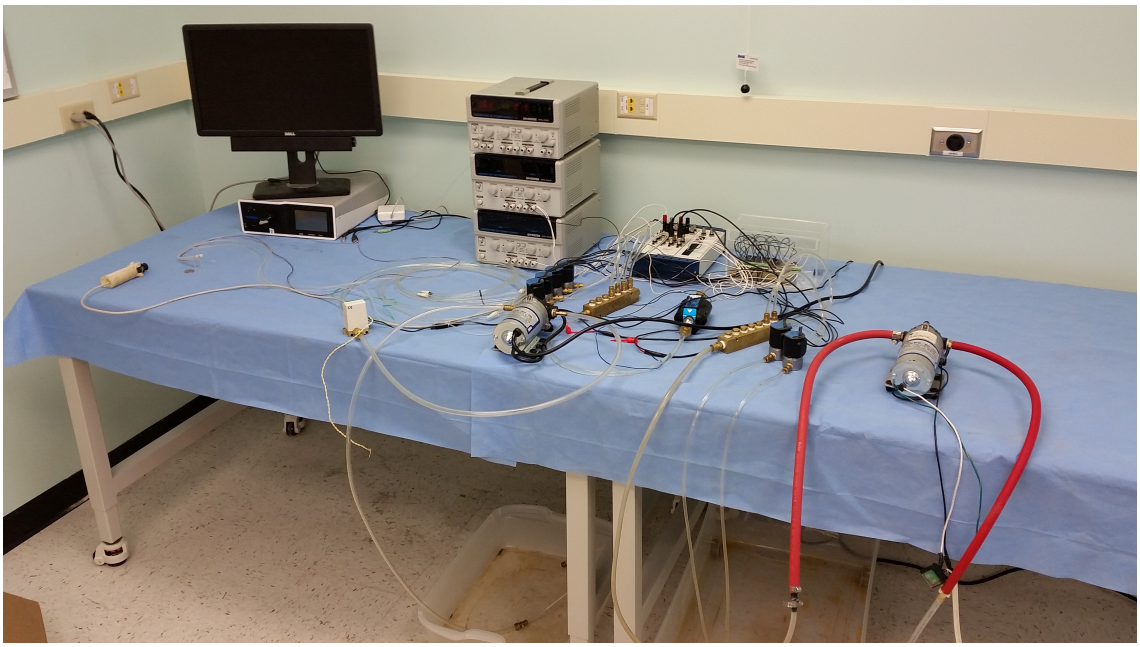

Figure 3.2: Image of Water Distribution System

3.5 Other Necessary Component

A Misumi Electronics ultra mini color camera (Model MO-B0804-62) was chosen to be used inside the capsule for its size (4.8mm diameter, 18.8mm length), cost (128 USD) and video quality (656x496 resolution, 30 fps). The cameras video signal is sent directly to the system operator's computer, where it is displayed on a dedicated secondary monitor. Four warm white LEDs (Nichia Corp, Model NS2L157ART-H3) provide illumination for the camera during the procedure. With their high current draw, the LED's power consumption and heat generation became a concern, so a separate pulse width modulation driver circuit was built to flash them at a rate above 120 Hz. This is in theory would not be seen by the camera, and thereby nor the operator, as the camera operates at a quarter of that frequency (30 HZ).

A thumb controlled joystick with a center select button was used to maneuver the Hydrojet during procedure. Connected directly to the system's data acquisition board, the

joystick uses an analog voltage signal to communicate with the software on the operator's personal computer attached to the system. The joystick was also mounted to an ergonomic 3d printed grip to enable better handling.

National Instruments LabVIEW platform was used to create the systems control program and the systems graphical user interface. The graphical user interface, shown in Fig. 3.3 relays information such as total time of operation, which control valves are currently open, the flow rate of water into the patient, the flow rate of water out of the patient, the net amount of liquid added to the patients stomach and the current pressure setting. The operator can press the joysticks center select button to cycle through the available pressure settings. In its basic state, both pressure control valves are open providing the lowest pressure possible to the capsule. With each click of the center select button, the software cycles using boolean algebra through different pressure control valve states, with each state representing a particular pressure control valve combination. In its current configuration the user may select either a low (both pressure control valves open), medium (one pressure control valve open) or high (no pressure control valves open) pressure of operation. Additional pressure control valves especially with differing exhaust diameters, would increase the amount of selectable states for the user.

3.6 Static Model Analysis

Prior to bench testing the system, static analysis calculations were performed. These calculations were done to obtain an estimation of force needed to propel the capsule to a particular orientation angle at various tether lengths. Tether length is originally measured from the esophageal sphincter as it is considered the point of origin within the stomach and acts as an anchor point for the tether. The possible orientation angles of the capsule were deemed to be of significance since, to successfully navigate the stomach, the capsule needs to be able to use the mucosa as a deflection wall. Approaching the mucosa at approximately a

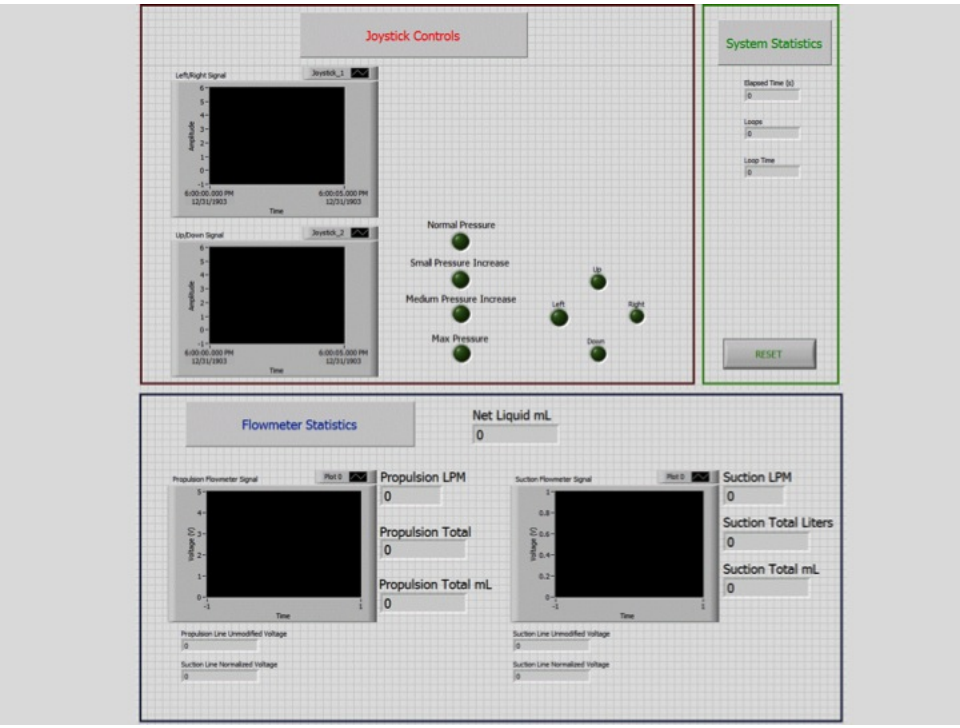

Figure 3.3: Image of the LabView Based Graphical User Interface for the Hydrojet System

90 degree angle allows for the capsule to pivot off the mucosal wall with minimal interaction as shown in Fig. 3.4. Introduction of additional tether length as the capsule is approximately perpendicular to the mucosal wall creates a physical pivot point where the tether contacts the mucosal wall. After this contact occurs, it is assumed the capsule is now operating on a newly created tether length. For example, this assumption means that the capsule will behave in a similar manner whether the tether is 6 cm past the esophageal sphincter or if 6 cm away from a pivot point on the mucosal wall.

To calculate capsule angular orientation, defined as the displacement from the vertical alignments as shown in Fig. 3.5, the method of elliptic integrals was used. To simplify the model, the multi-channel tether was considered to act as a single line. This simplification was calculated using an equivalent area moment of inertia method by first finding the area moment of inertia for each of the six independent tubes of the tether. Through usage of the parallel axis theorem around the centroidal axis of the central tube, the single area moments

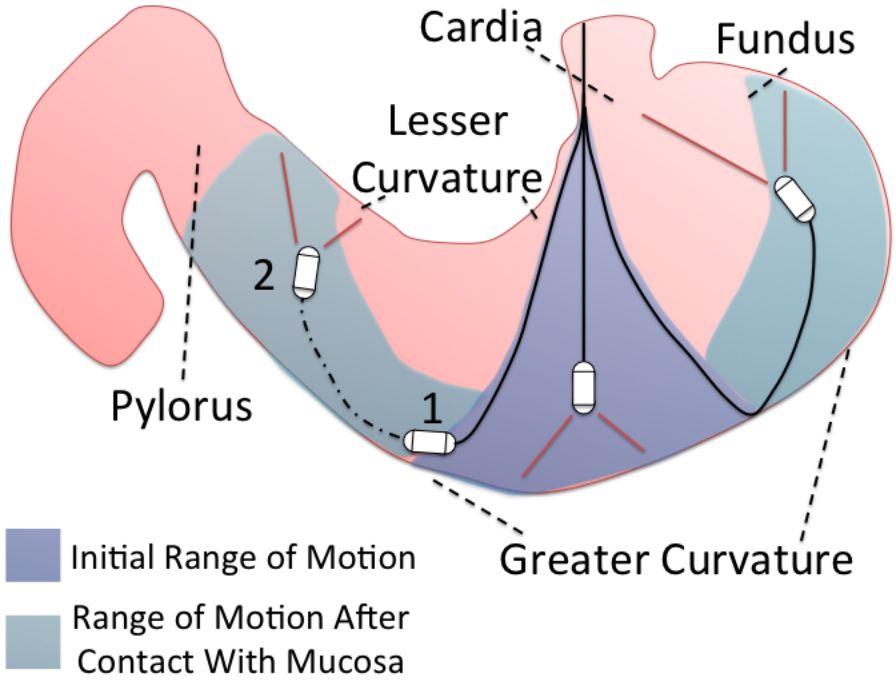

Figure 3.4: Diagram of Capsule Range of Motion Using Pivoting Technique

of inertia were summed to form one governing area moment of inertia. An equivalent dimensioned single tube was found by using the following circle packing equation for five circles within a circle,

$$D_o = d_{3o} + d_{3o}\sqrt{2(1 + \frac{1}{\sqrt{5}})}, \tag{3.6.1}$$

where d3o is the diameter of the outer multi-channel tubes (i.e., 3.18 mm). A packing of only five circles was used since the smaller central tube was capable of fitting within the interstitial space of the five outer tubes. By using this model, we obtained an equivalent single tube outer diameter of 8.59 mm, while an equivalent single tube inner diameter of 7.25 mm was derived from the previously found equivalent area moment of inertia.

It is worth mentioning that, in the current implementation, the single tubes can slide one against the other and reconfigure during bending. For this reason they offer a lower bending

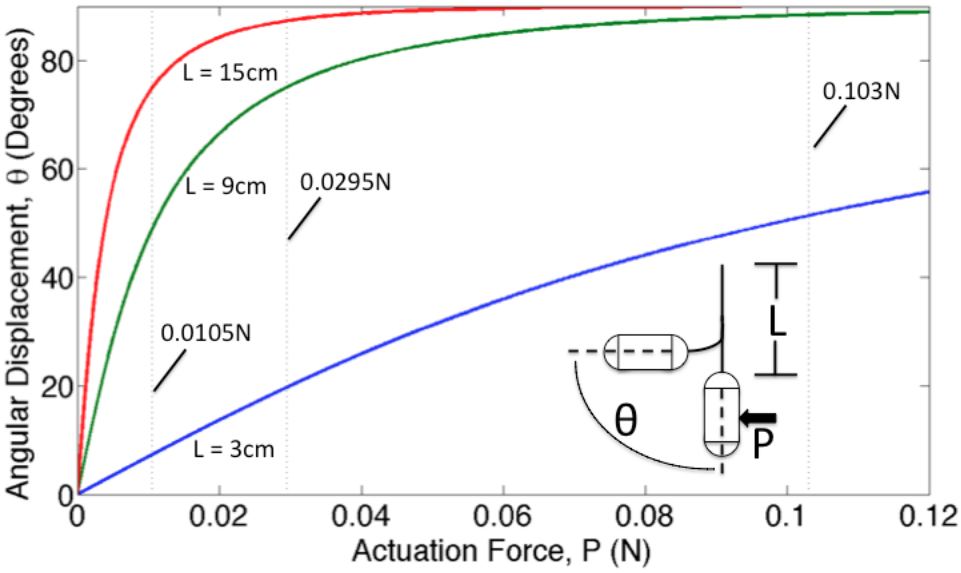

Figure 3.5: Forces Required to Achieve Particular Orientation Angles Using Single Tether Assumption

stiffness than a single multi-channel tube. Therefore, the modeling we propose here provides a worst-case estimation of the force required to achieve a certain orientation angle.

With dimensions for a single tube approximation available, the system will now be viewed as a flexible cantilever beam with a point load, representative of the water jet actuation, on it's end. Gravity will be ignored as an external force since in this model the capsule is submerged and as previously stated the capsule has been designed to be neutrally buoyant. The distance from the esophageal sphincter to the greater curvature is assumed to be around 15 cm, therefore the model will look at a beam (tether) lengths ranging from 3 cm to 18 cm in steps of 3 cm. To calculate the complete and incomplete elliptic integrals of the first kind, the non-dimensional variables λ, η, γ, and τ must be first be found using the the following equations.

$$\lambda = sin(\theta_0) - ncos(\theta_0) \tag{3.6.2}$$

$$\eta = \sqrt{1 + n^2} \tag{3.6.3}$$

$$\gamma = arcsin\sqrt{\frac{\eta - n}{\eta + \lambda}} \tag{3.6.4}$$

$$\tau = \sqrt{\frac{\eta + \lambda}{2\eta}} \tag{3.6.5}$$

In these equations, θ_0 is the desired final angle of bending at the cantilever tip and n ratio of the axial force on the cantilever tip to the transverse force on the tip. Since an axial force does not exist in this model, n is 0. Now the values of the complete elliptic integral of the first kind $F(t)$ and incomplete elliptic integral of the first kind $F(\gamma, t)$ can be found using software or elliptic integral tables. Next, the modular angle, α can be found using

$$\alpha = \frac{1}{\sqrt{\eta}}[F(t) - F(\gamma, t)] \tag{3.6.6}$$

With the modular angle known, the required force, P, for a given set of bending parameters can be found with

$$P = \frac{EI\alpha^2}{L^2} \tag{3.6.7}$$

where E is the Young's Modulus of the tube (4.5 MPa), I is the area moment of inertia of the tube and L is the tether length. The required forces to achieve particular angles on 3 cm, 9 cm and 15 cm tethers are shown in Figure 3.5.

CHAPTER 4

EXPERIMENTAL ANALYSIS

4.1 Overview

After fabrication of the device and initial calculations on possible motional capabilities, a series of bench-top tests were performed to determine items such as the amount of force exerted by the water jet exhaust on the capsule, the possible flow rates achievable by the system, actual range of motion attained by the capsule in an aqueous environment, reliability of the capsule during operation, thermal characteristics and overall portability. After these analyses were completed an ex vivo trial was conducted in an excised porcine stomach to assess maneuverability and to quantify an estimated time it would take an operator to use the Hydrojet for a procedure. Lastly, an In Vivo analysis was performed to test the insertion of the device orally into a living pig and to qualitatively examine movement within the stomach of a living creature.

4.2 Force Testing

Forces exerted by the expulsion of water were quantified using a load cell (ATI Industrial Automation, Model: NANO17, resolution 1/160 N). The capsule was connected to the load cell using a 3D printed adapter and a 130 mm steel rod of 4 mm diameter. Multiple tests were completed with the pressure set at low, medium and high settings, operating each

single exhaust port one at the time. The average forces exerted by the waterjets were 0.0105 ± 0.0013 N, 0.0295 ± 0.0012 N and 0.103 ± 0.0024 N on low, medium and high settings, respectively. These values are reported as vertical dashed lines in the plot in Fig. 3.5. The exhaust pressures were calculated to be 0.0334 ± 0.0041 bar, 0.0939 ± 0.0038 bar and 0.328 ± 0.0076 bar for low, medium and high settings. These values are well below the aforementioned safety threshold of 3 bar. We also confirmed experimentally that, when two exhaust ports are activated at the same time, the force drops by a factor of two. The average thrust force from each waterjet when two exhaust ports are simultaneously activated were found to be 0.0048 ± 0.0008 N, 0.0138 ± 0.0013 N and 0.0496 ± 0.0015 N for low, medium and high, respectively. An example of the capsule exhausting a water jet in air is shown in Fig. 4.1.

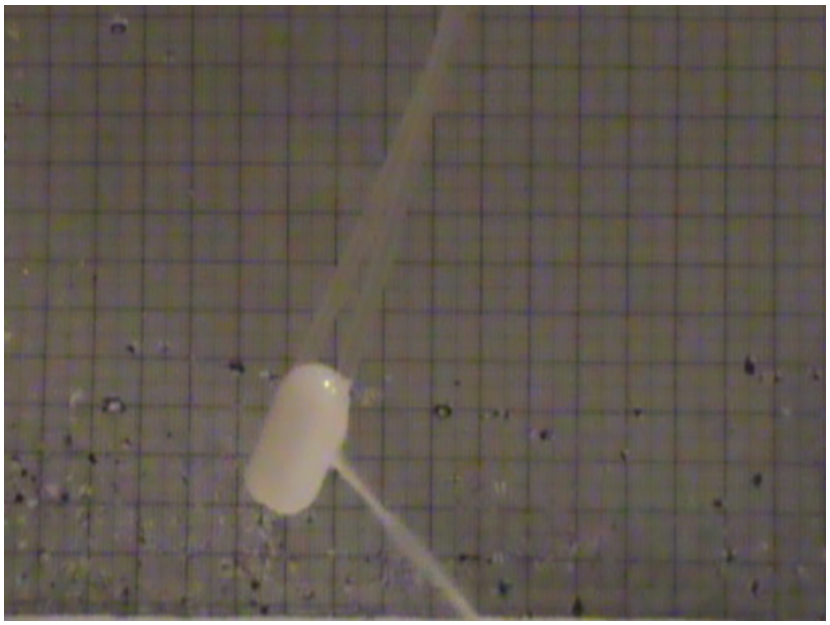

Figure 4.1: Water Jet Exhausted in Air

4.3 Flow Rate Testing

Using the system flow meters, the volumetric flow rate of the Hydrojet exhaust ports was found to be 0.328 L/min, 0.576 L/min and 1.07 L/min respectively for low, medium and high pressures. Using Bernoullis equation, exhaust velocities were found to be 2.43 m/s, 3.86 m/s and 5.54 m/s respectively. With the suction line having a fluid removal rate of approximately 0.5 L/min, extensive use of high pressure would require resting periods solely for suction. Using the real-time data acquired by both flow meters on the suction and propulsion lines, the operator would be alerted when period of resting suction would be required.

4.4 Capsule Range of Motion Analysis

It is probably worth highlighting the difference between the capsules range of motion versus the capsules range of vision before devling to deep into this experiment. The capsules range of motion is defined as the reachable locations of the capsules center of mass during operation. The capsules range of vision is defined as the workspace that can be visualized by the operator through the camera mounted in the Hydrojet capsule. Therefore, the range of vision is a larger region than the range of motion and is determined by the capsules range of motion, the capsules possible angular orientation at a given location and the field of view of the onboard camera.

The capsules range of motion and angular orientation were quantified using a 5-DoF magnetic tracking module (Northern Digital Inc. (NDI), Model: Aurora Tabletop Transmitter, 1.2 mm positional nominal root mean square error (RMSE), 0.5 degree rotational nominal RMSE, 40 Hz update rate) inserted into the capsule at the center of mass and orientated along its longitudinal axis. Rotation about this axis is the only DoF not recorded during the trials. Using a gastric overtube (Guardus, Model: PN00711149) to simulate an esophagus, the capsule with tracker was inserted into a tank of water until a tether length of 3 cm was

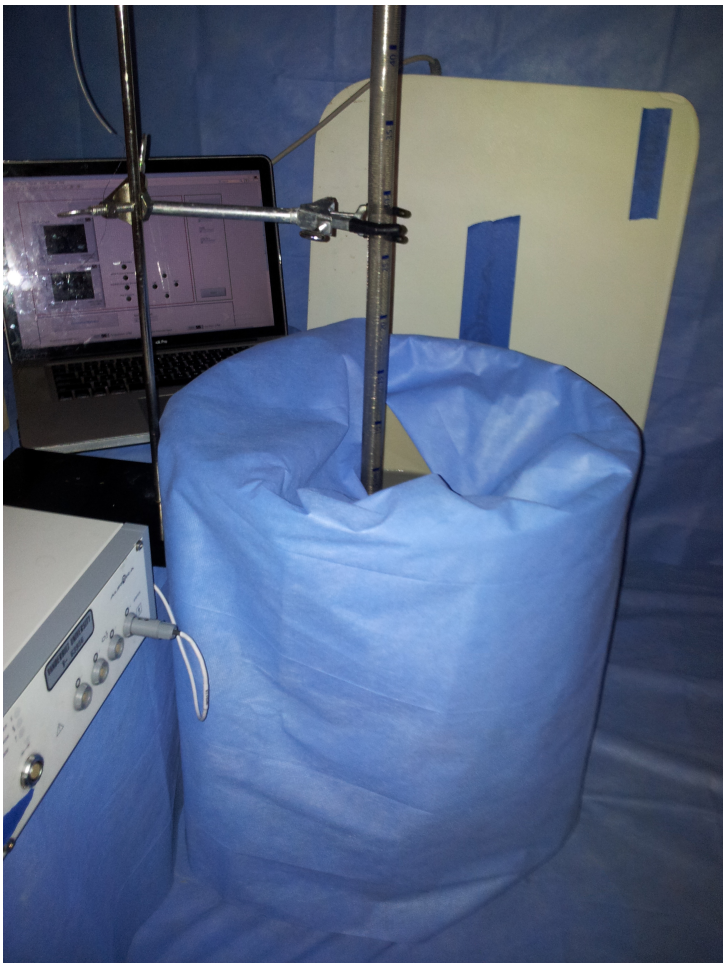

Figure 4.2: Range of Motion Experimental Setup

measured exiting from the overtube and into the tank.The capsule was then propelled in all possible directions on low, medium, and high water pressure settings. This experimental setup is shown in Fig. 4.2. After capturing a full range of motion for a 3 cm tether, the capsule was further introduced into the tank in steps of 3 cm additional tether lengths up to 15 cm and the test was repeated each time. Overall displacement of the capsule center of mass under a medium exhaust setting is reported in Fig. 4.3 . While the capsule was propelled in all possible directions, initial pre-bending in the tether either aided or hindered capsule motion depending on whether the capsule was moving with or against the moment

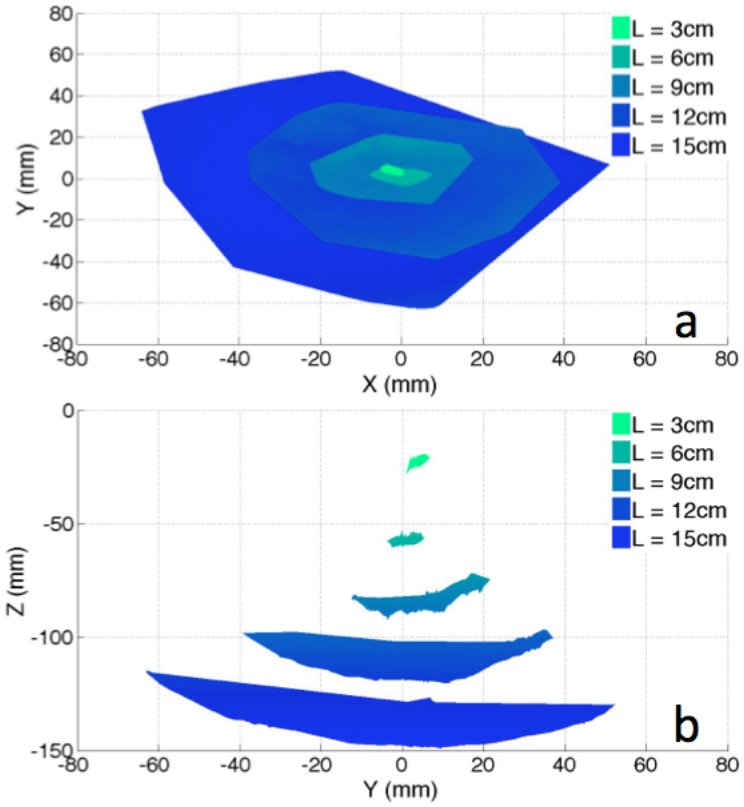

Figure 4.3: Capsule Range of Motion on Medium Pressure Exhuast

created by pre-bending. When operating the capsule on high pressure, the motion became unstable past a 9 cm tether length.

From the data acquired by the 5-DoF magnetic tracker, the capsules angular orientation as defined in Fig. 3.5, at maximum bending was extracted and then compared to the values estimated by the previously calculated single-tether model. The comparison of these values is shown in Table 4.1. As anticipated, the single tether assumption led to an underestimation of maximum bending angles with an average absolute error of 5.59 $\pm$ 6.46 degrees, which constitutes a percentage error of 13.5% $\pm$ 19.7% across all tether lengths and pressure settings. The large error at the 3-cm tether length is most likely due to the limited resolution of the magnetic tracker. If the 3- cm tether length is disregarded, the average absolute error becomes 3.76 $\pm$ 2.96 degrees with a percentage error of 6.25% $\pm$ 6.75%.

Table 4.1: Capsule Orientation: Comparison of Model Predicted Orientation Angle vs Maximum Measured Orientation Angle

Tether Length	Actuation Force (N) 0.0105		0.0295		0.103	
	Model	Measure	Model	Measure	Model	Measure
3 cm	8.3°	17.2°	19.4°	44.4°	49.8°	50.6°
6 cm	25.4°	36.9°	53.4°	61.9°	81.0°	87.8°
9 cm	47.0°	55.4°	73.5°	78.1°	88.1°	94.3°
12 cm	63.0°	65.6°	82.8°	86.3°	>90°	Unstable
15 cm	73.3°	75.5°	86.9°	87.2°	>90°	Unstable

4.5 Reliability Anaylsis

To determine the Hydrojets ability to operate for extended periods of time without structural failure, the capsule was subjected to a reliability test. In this examination, the capsule was submerged in a tank of water and operated at random by software with both camera and LEDs turned on. The Hydrojet system was monitored approximately every 30 minutes. After 6 hours of continuous operation, the capsule was removed from the test bench and examined, showing no signs of water leakage into the inner core and no degradation of either the on-board camera or LEDs.

4.6 Thermal Analysis

Thermistors (Digikey Corp, NTC 50k 1used to determine the Hydrojets operating temperatures. Two points on the capsule were measured during a total of 3 hours of operation. One sampling point was next to the vision module, while the other was at the connection with the multichannel tether. The capsule was submerged in 22 degrees C water at the beginning of the trial and remained submerged for the entire process. After approximately 79 minutes the capsule reached a steady state temperature of 34 degrees C at the front and

33 degrees C at the aft. This temperature profile meets the 34 degrees C limit previously mentioned as temperature safety threshold.

4.7 Portability Analysis

Once assembled, the entire system weighed 17.58 kg and required a footprint area of 0.3136 m^2. This weight and footprint could be designed to be split across two carrying cases retrofitted for the system.

4.8 Ex Vivo Analysis

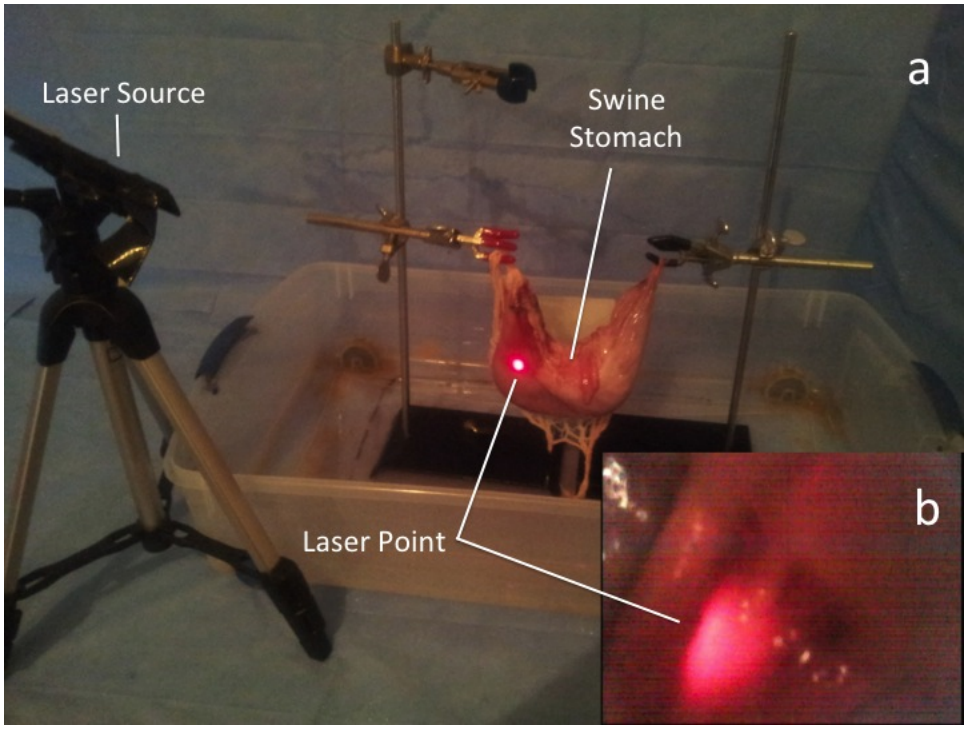

Figure 4.4: Image of Ex Vivo Analysis Setup

Ex vivo testing of the Hydrojet was performed in an excised porcine stomach aiming at visualizing the cardia, the fundus, the greater curvature, the lesser curvature, and the pylorus. These landmarks are typically observed during gastric cancer screening procedures

[30]. To ensure the capsule properly identifies the points from within the stomach, a series of external laser beams were projected at these particular points. The beams were visible both externally by the operator and internally by the Hydrojet, as represented in Fig. 4.4. For each trial, the operator was timed as he used the Hydrojet to identify the five anatomical landmarks. Identification of a point of interest was confirmed when the operator saw its respective laser point using the on-board camera. Unlike the suturing of markers or the injection of ink into the stomach wall, use of laser beams allowed for a qualitative assessment of landmark location by the operator without physically compromising the integrity of the porcine stomach. Prior to the ex vivo trial, the placement of landmark points was confirmed by an experienced gastroenterologist. The capsule along with the excised porcine stomach can be seen in Fig. 4.5.

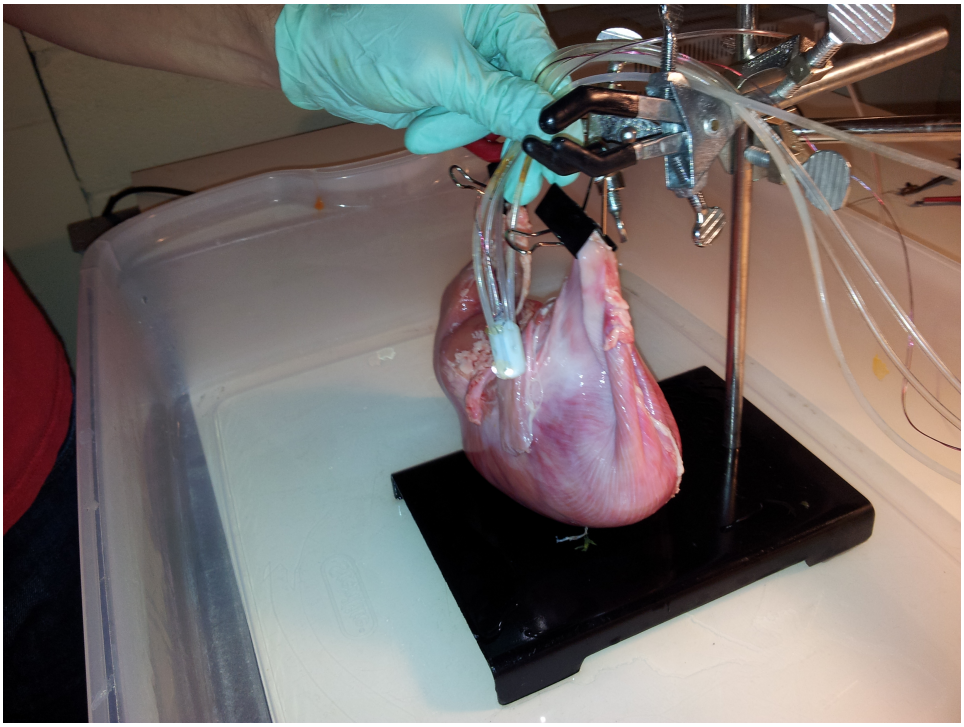

Figure 4.5: Hydrojet with Excised Porcine Stomach

A single operator controlled the Hydrojet for a total of six complete trials. The operator was allowed to experiment with capsule movement for 20 minutes prior to the trial. A trial

was deemed completed once all five points of interest were identified. The average time of trial completion was 6m 15s ± 1m 41s. In every trial, all the five landmarks were identified by the operator. These results fall within typical time ranges of a completed gastroscopy procedure. During each trial, it was also recorded that an average of 1.35L ± 0.4L of water was introduced into the porcine stomach by the capsule. During the procedure fluid was capable of being suctioned at a rate of 0.5L/min ± 0.02L/min. This rate allowed for the platform to operate without exceeding our 1.3 L safety threshold. No trauma to the excised porcine stomach was found after conclusion of the trials. It is worth mentioning that the operator often used the mucosa as a deflection wall to visualize certain landmarks such as the pylorus, the fundus, and the cardia, thus confirming the feasibility of the inspection strategy described in Fig. 3.4.

4.9 In Vivo Analysis

After ex vivo validation, an in vivo qualitative feasibility trial on a porcine model (55-kg female Yorkshire swine) was conducted at Vanderbilt University in accordance with all ethical considerations and the regulations related to animal experiments (IACUC protocol M/14/014). The aims of this study were to show capability of capsule introduction into a living subjects stomach and to qualitatively observe device maneuverability once within the gastric cavity. An attending physician at Vanderbilt (more than 1,000 lifetime flexible endoscopies) was involved in this trial to provide a feedback on usability. To ease device introduction since the animal was under intravenous sedation thus with reduced esophageal peristalsis a gastroesophageal overtube was used during the entire procedure (Guardus, Model: PN00711149). Along with the Hydrojet, a gastroscope (Olympus Corp., Model: GIF180) was inserted through the overtube to visualize capsule operation. Capsule and gastroscope operation were accomplished by two different users.

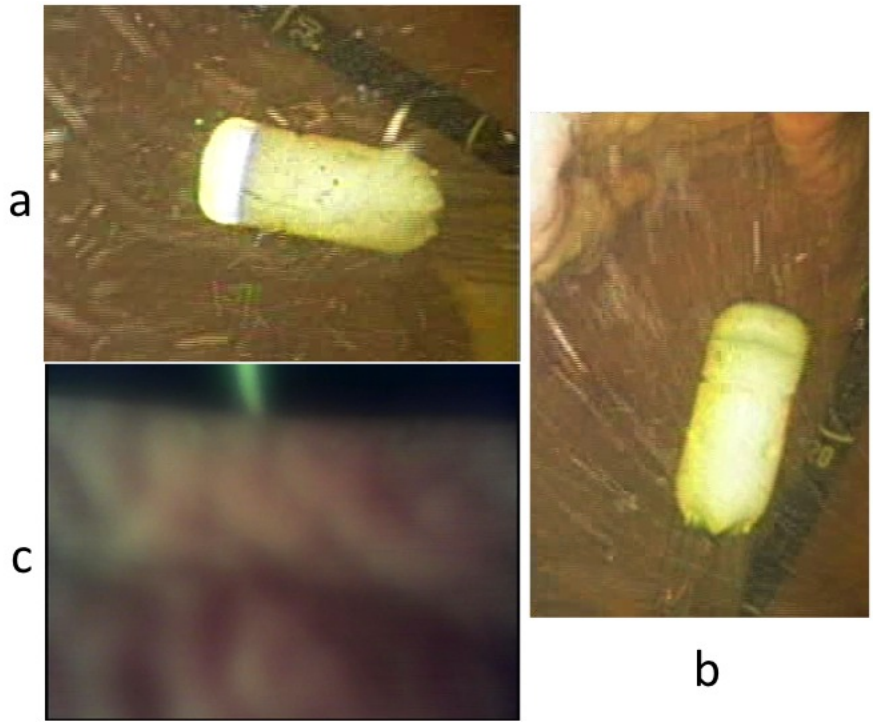

Figure 4.6: In Vivo Images: a) Capsule Operating with LEDs on, b)Capsule Operating with LEDs off, c) Image of Mucosa Taken by On-Board Camera

The capsule was successfully introduced through the esophagus into the subjects stomach using the gastroesophageal overtube. Once within the stomach, the capsule was able to maneuver and relay images using the on-board camera. An example of this image, along with images of the capsule during In Vivo operation are shown in Fig. 4.6. The mobility achieved by varying the water pressure level at the nozzles and by adjusting the tether length was deemed qualitative comparable to a standard gastroscope. Three consecutive frames representing the Hydrojet motion as observed by the retroflexed gastroscope are shown in Fig. 4.7. It is worth mentioning that the flow caused inside the stomach by the lateral waterjets, which can be observed in Fig. 4.7 , did not hamper the visualization of the mucosa by the Hydrojet capsule. After the conclusion of the in vivo analysis, the subject was sacrificed and the stomach excised for further analysis. No evidence of significant trauma to the swine was observed either during or after the experiment.

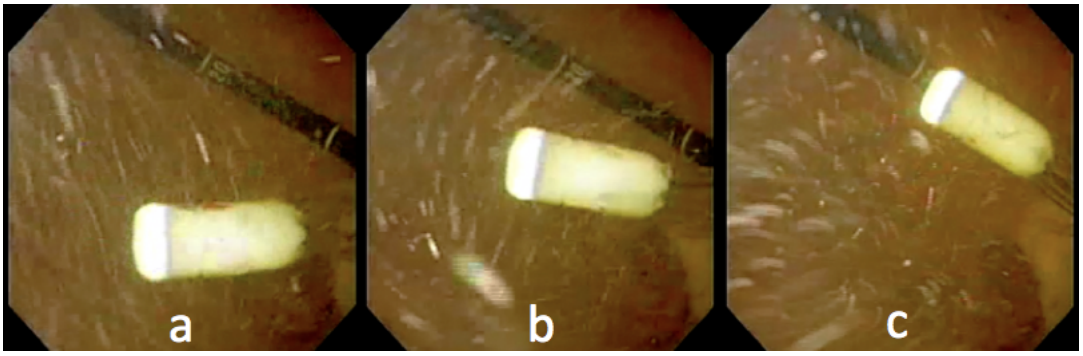

Figure 4.7: Sequential Frames of Capsule During In Vivo Procedure

CHAPTER 5

FURTHER DESIGN

5.1 Second Generation Design

After extensive testing, the initial design of the Hydrojet had to be re-evaluated in large to part due to the acquisition of a more compact endoscopic camera from Medigus Ltd. The micro Scoutcam 1.2 (diameter 1.2mm) [31] was smaller than the currently used Misumi camera by a factor of four, which ideally would allow for an overall smaller capsule design. There were limitations, however, associated with creating a new Hydrojet capsule around the Medgius micro scoutCam. First, the camera is not wired by the user but comes with its own tether that cannot be detached from the camera head. This leads to an issue concerning the multi-channel tether. In the first generation design, the electrical wiring in the central line of the multi-channel tether contained wiring which was disposed of along with the tether after each procedure. With the Scoutcam having a permanently attached transmission line, this could no longer be the case. Another issue with the Scoutcam tether is that, with a 0.8mm diamter, it is larger in diameter than the previously used wires, which were approximately 0.3mm. Therefore, if the camera were to be placed inside the multi-channel tether, the central tube of the multi-channel tether would need to be larger. With the capsule ideally becoming smaller in diameter, it would be counter intuitive to have to enlarge the supporting multi-channel tether. Lastly, the shape of the Scoutcam's lens is convex and it is recessed within it's camera head. The capsule's front cap uses a plexiglass cover to protect the

electronics yet allow vision from within the central core of the capsule. With a gap between the plexiglass cover and main camera lens, the image would become out of focus and lose quality.

With the troubles in mind, a second generation capsule was fabricated around the usage of the Scoutcam. The central tether line was increased from the previous 1.78 mm to 3.18mm to hold the Scoutcam's transmission line. To offset this and reduce the overall multi-channel tether diameter, the outer 5 tubes were reduced from 3.18 mm to 2.2 mm. The pressurized water flow rate would drop due to this reduction, but since the capsule and tether are both smaller and lighter it was thought that the maneuverability would not suffer. This led to the multi-channel tether having a total outer diameter of 7.62 mm. Redesigned around the new tether size, the second generation capsule was able to be reduced from the original 12mm to 9mm, a 25% reduction. As previously mentioned however, this new design was not entirely disposable, as the inner core module no longer existed and instead the camera was directly mounted into the center of the capsule. Additionally the plexiglass cover was removed from the front of the capsule. The Scoutcam's lens became the new front of the capsule, but was also exposed to the external environments within the stomach. Also, as previously stated, the multi-channel tether was no longer disposable. The capsule however still had an outer shell main body and front cap which could still hermetically seal the central cavity of the capsule. This design was kept as it was hoped that in the future, perhaps the camera could be modified with the aid of Medigus to be detachable from its transmission line and also be modified to allow the use of the front cap plexiglass once more. Now at 9mm diameter however, the capsule was much easier for a patient to swallow. The second generation with the Medigus micro Scoutcam is pictured below in Figs. 5.1, 5.2, and 5.3.

This design still requires extensive testing, but an In Vivo examination was performed to see if the reduction of tether diameter further inhibited the oral insertion of the capsule. During this trial, insertion did indeed prove to be more difficult with the smaller multi-

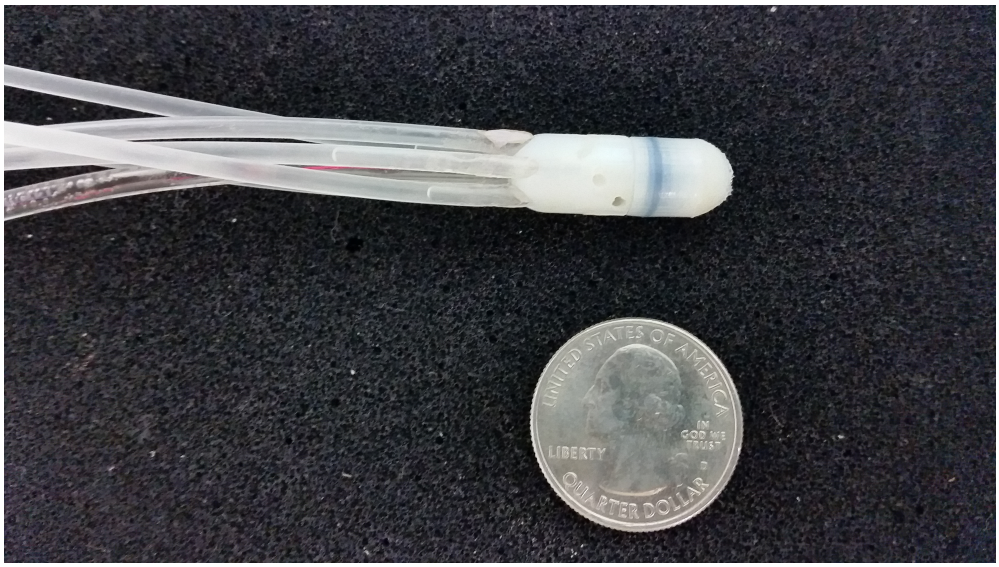

Figure 5.1: Top View of Second Generation Hydrojet

channel tether and eventually a second "capsule inserter" device had to be built to aid in introducing the capsule into the porcine stomach. Once inside, movement was also limited, but further tests are required to determine this Hydrojet generation's full capability.

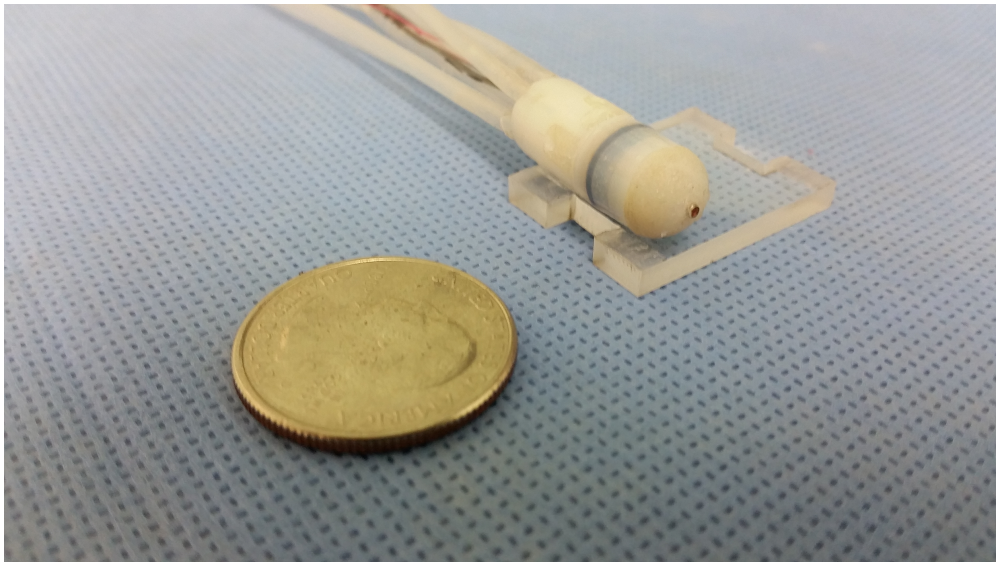

Figure 5.2: Isometric View of Second Generation Hydrojet

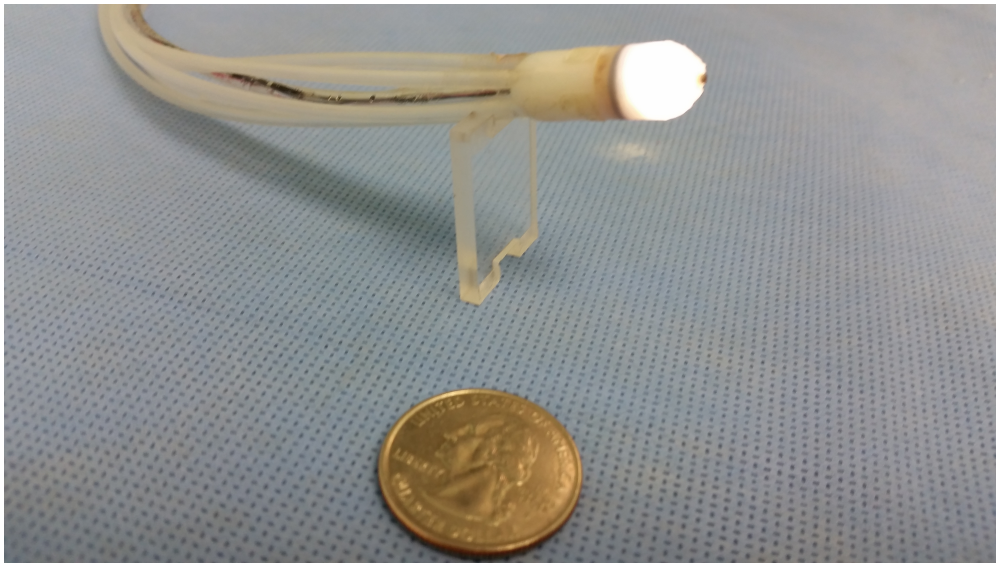

Figure 5.3: View of Second Generation Hydrojet with LEDs Activated

CHAPTER 6

CONCLUSION

This document first introduced the need to find a method for mass gastric cancer screenings in low- and middle-income countries, since majority of gastric cancer mortalities occur there and screening programs in the first world have been shown to lower the mortality rate. To accomplish this goal, we looked to endoscopic capsule technologies and compared some of the currently existing and developing technologies on the market. While these technologies hold promise, none of them are particularly suitable for remote areas of third world nations, either due to system complexity, lack of portability or having a high cost per procedure. This led to the design and eventual fabrication of the Hydrojet endoscopic capsule system. The ease of disposability of the capsule and multi-channel tether, along with the re-usability of the Hydrojets internal camera without needing further reprocessing, would allow it to be used inexpensively in low- and middle income countries. Since water is typically a readily available resource, the capsule's propulsion system was chosen to be hydraulically driven with pressurized water jets. These water jets allow the operator to move the capsule within the stomach to enable viewing of any necessary landmarks. A model to predict capsule orientation at differing exhaust forces and tether lengths was derived by simplifying the multi-channel tether to an equivalent single tube tether and using elliptic integrals functions.Bench trials were performed to determine the force of water expelled from the capsule at various pressure settings, the capsules range of motion, the long term reliability of the capsule in

operation underwater, and the capsules temperature over extended periods of operation. Ex vivo assessment of the Hydrojet platform was performed using a porcine stomach to quantify the total time needed to visualize anatomical landmarks typically adopted in gastric cancer screening procedures. An In Vivo qualitative analysis was completed using the Hydrojet to confirm the feasibility of introducing the capsule into a living subject and to assess capsule maneuverability once inside in the stomach. Lastly, a new caspule design was accomplished using a smaller camera which allowed for the capsule diameter to be reduced by 25%. The overall cost of the platform is estimated to be below 6,000 USD, with a projected cost per procedure related to the disposable part of the Hydrojet of 2-5 USD. With the entire platform occupying a footprint of 0.157 m2 and weighing 17.58 kg, we can envisage integration into a couple of carry-on sized luggage containers, thus allowing portability in remote regions of low- and middle-income nations.

6.1 Future Work

There is much work left to be done to have a complete endoscopic system. First, refinement of the Hydrojet's pressure control system would allow for a more precise movement of the capsule within the body and allow the operator to view area's within the gastric cavity with higher ease. One solution to this method is to add additional binary solenoid valves with differing exhaust diameters. This would in effect operate like a hydraulic gear system. This setup however would still limit movement to only certain points along the range of motion arc. A more elegant solution would probably be to use faster valves controlled whose exiting flow rate could be controlled via pulse width modulation, much like the Omniegg underwater robot mentioned earlier. An even more elegant solution similar to a pulse width modulation driven fluid valve may be to use an air over liquid system. This system feeds air through a proportional valve into a pressure vessel containing water. As the air pressure increases in the vessel a higher flow rate of water is evacuated downstream into the capsule

exhaust. This type of pressure control system may increase the price of the platform some but could provide smoother transitions between changing flow rates and eliminate the worry of rust forming in the valves which supply water to the capsule inside the patient. After having traveled to Honduras and seeing the how the unreliable their electric service is and how hearing how often electrical surges can occur, the system needs to have robust surge protection added and also needs to be able to be hooked into other power sources such as car batteries, etc.

The second generation design of the Hydrojet holds promise with its size, but the capsule must return to completely isolating the electronic technologies within to accomplish to the goal of being disposable. This means that a detachable camera transmission line and a viewing window that can work in conjunction with the Medigus micro scoutCam camera lens are a must when moving forward with this design. The issue of capsule insertion into a living animal is something that needs to be solved as well. One possible solution is to move towards an actual multi-channel single tube tether instead of having 6 independent lines. This would increase the stiffness of the tether, which may inhibit motion some, but should allow for easier insertion and retraction of the capsule. This single tube tether also might make capsule movement more predictable as movement can no longer be subject to how lines interact with one another.

Additional In Vivo trials should take place to quantitatively evaluate the system inside a living creature. This evaluation should include an image comparison with a standard endoscope as well a time trial to see how long it takes an operator to view all the necessary landmarks. With success in these trials, hopefully, the platform could later move on to clinical trials in a low-income nation. It is my hope that eventually this platform will eventually allow gastric cancer screenigns to those who would otherwise not have access to such medical care.

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