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Towards Noninvasive Functional Gastrointestinal Assessment with Multi-Electrode Surface Potential Recordings

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Towards Noninvasive Functional Gastrointestinal Assessment with Multi-Electrode Surface Potential Recordings

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Bioengineering

by

Armen Alex Gharibans

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Professor Larry L. Smarr

2017
The dissertation of Armen Alex Gharibans is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

2017
DEDICATION

To my parents.
The two most important days in your life are
the day you are born and the day you find out why.

—Mark Twain
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ABSTRACT OF THE DISSERTATION

Towards Noninvasive Functional Gastrointestinal Assessment with Multi-Electrode Surface Potential Recordings

by

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Professor Todd P. Coleman, Chair

Rates of diagnosis for gastrointestinal (GI) medical conditions have increased markedly in recent years. However, many such diagnoses are in broad, idiopathic categories. Current measures to assess GI function are mostly invasive, which leads to a relative scarcity of expertise and limited clinical visits with rarefied specialists. There is a need for a noninvasive and easily administered technique that provides robust and actionable information to clinicians. Even though the electrogastrogram (EGG) has existed for decades, its use as a diagnostic and
research tool has been limited due to inconsistent results that are difficult to interpret.

Recent studies have characterized the occurrence of spatial gastric myoelectric abnormalities that are ignored by typical approaches relying on time-frequency analysis of single channels. Here, we present the high-resolution EGG, which utilizes an array of cutaneous electrodes to estimate the direction and speed of gastric slow-waves. We verified the approach using a forward electrophysiology model of the stomach, demonstrating that an accurate assessment of slow-wave propagation can be made. Also, our experimental results of propagation direction and speed were consistent with serosal recordings of slow-waves described in the literature.

Next, we introduce an approach for artifact removal along with a system for robustly recording the EGG signal in an ambulatory setting for continuous 24-hour intervals. We validated the signal processing techniques with simultaneous EGG and invasive manometry recordings. The 24-hour recordings in free-living subjects revealed daily patterns in gastric motility and apparent gastric emptying after meals.

Finally, we aim to determine the clinical utility of our developed methods. We show that the HR-EGG can detect spatial abnormalities in a patient population with well-characterized gastroparesis. We also provide a case study demonstrating the ability of the ambulatory EGG in identifying gastric outlet obstruction.

The approaches described in this dissertation are non-invasive, full-automated, and inexpensive, enabling use in the development of finer diagnoses and continu-
ous symptom monitoring for gastrointestinal research and clinical applications. By overcoming the limitations of current methods, these tools may unveil new classes of abnormalities, which could lead to a better diagnosis of diseases and inspire novel drugs and therapies, ultimately improving clinical outcomes.
Chapter 1

Introduction

1.1 Motivation

Gastrointestinal (GI) problems are the second leading cause for missing work or school after the common cold [Brun and Kuo, 2010], giving rise to 10 percent of the reasons that a patient visits their primary care physician [Gikas and Triantafillidis, 2014]. Subjective guess-and-check approaches are routinely used to sort out problems. If symptoms persist after multiple rounds of iteration, which happens approximately 50% of the time [Gikas and Triantafillidis, 2014], patients are referred to GI specialists. In up to half of the referred patients, further investigations fail to identify abnormalities that readily explain symptoms [Tack and Wald, 2015]. These “functional” GI disorders are poorly understood, highly prevalent and have significant individual, health care, and socioeconomic consequences [Moayyedi and Mason, 2002].
GI disorders cost the United States $142 billion annually, and trends are moving in a more ominous direction for all age groups. Symptoms of dyspepsia, defined as upper abdominal pain or discomfort with nausea, bloating, and early satiety, are reported by up to 20% of children and adolescents [Hyams et al., 1996], which often results in adverse social and psychological outcomes. In addition, approximately 40% of geriatric patients report at least one GI complaint during routine physical exams, and the rapidly aging United States population is predicted to place tremendous pressure on GI specialists [Hall et al., 2005].

Functional GI disorders are characterized by chronic and recurring symptoms because of abnormal functioning of the GI system. Since clinical tests typically do not identify abnormalities in patients with functional GI disorders, the standard for diagnosing and treating these disorders is based on the Rome criteria, which is a symptom-based assessment [Drossman, 2006]. Some clinicians may order unnecessary diagnostic procedures in an attempt to find something “real” [Drossman, 2003], resulting in increased costs and possibly inappropriate care [Longstreth and Drossman, 2005].

One of the primary features of functional GI disorders is altered motility. Motility refers to the muscular activity of the GI tract, which is controlled by the enteric nervous system. Normal motility patterns are highly-coordinated contractions (i.e. peristalsis) that propel food through the GI tract. Motility in functional GI disorders can be rapid, slow, or disorganized, and sometimes consists of muscular spasms. Abnormal GI motility can result in pain or other symptoms [Kellow
and Phillips, 1987].

Most clinical tools to assess GI motility function are invasive (e.g. manometry) or require radiation (e.g. gastric emptying scintigraphy). This hinders complete understanding of the state of the GI system in health and disease, since tests are only offered by a limited number of specialists and cannot be easily repeated. Novel, objective approaches to understand and diagnose functional motility disorders are critical to improve patient care, offer effective and personalized therapies, and reduce treatment costs.

Although the ECG is remarkable in how it serves as a first step in providing actionable information about the state of the heart, the same cannot be said about gastroenterology. The GI system has analogous myoelectric cells that generate electrical rhythms, and the abnormal aspects of GI function have physiologic underpinnings analogous to that of the heart (e.g. tachygastria, bradygastria, conduction block, abnormal initiation). However, the electrogastrogram (EGG), the analogous clinical waveform from electrodes recorded over the abdomen [Parkman et al., 2003], does not correlate with GI symptoms or invasive measures and is seldom used clinically [Abid and Lindberg, 2007]. Modern engineering tools, such as temporal and spatial signal processing techniques, have not yet been applied to EGG recordings. Understanding the underlying physiology and addressing the limitations of the EGG with innovative approaches could provide tremendous value in the diagnosis and treatment of GI disorders.
1.2 Gastrointestinal Physiology

1.2.1 Stomach Anatomy

The stomach is located in the upper abdominal cavity in humans (i.e. below the heart and above the navel) in between the esophagus and duodenum, which is the first part of the small intestines. Specifically, it extends from the upper left quadrant downwards, forwards and to the right [Netter, 2010]. At birth, the capacity of the stomach is merely 30 mL, but it expands to approximately 1500 mL by adulthood.

The stomach is anatomically divided into three regions: the fundus, body (also referred to as the corpus), and antrum (see Figure 1.1 top). The fundus is the upper curvature of the organ and its primary function is the storage of gas and extra food as necessary. By a mechanism called receptive relaxation, the fundus can expand to allow for the stomach to receive food without increasing intragastric pressure. This also protects the gastric muscle walls from excessive stretching. The body of the stomach physically and chemically breaks down food during digestion. The antrum is the region closest to the small intestines, where food is further broken down and pushed into the duodenum through the pyloric sphincter, which acts as the gate-keeper for the stomach.

The wall of the stomach contains several muscle layers pointed in three different directions, referred to as the longitudinal, circular, and oblique muscle layers (see 1.1 middle). The smooth muscle layers engage to propel food through
Figure 1.1: Stomach anatomy with a cutout depicting the lumen, mucosa, and the muscularis of the stomach. The interstitial cells of Cajal synapse with the circular muscle layer and myenteric neurons (from [Koch and Stern, 2004] with permission).

The gastrointestinal tract through a process of coordinated muscle activity called peristalsis. The gastric components of the enteric nervous system lie in between the smooth muscle layers. The neurons of the myenteric plexus have synaptic interactions with afferent neurons, interneurons, and post-ganglionic parasympathetic neurons.

The interstitial cells of Cajal (ICCs) are pacemaker cells that involuntarily depolarize and repolarize about every 20 seconds to set the gastric myoelectrical
rhythmicity [Thomsen et al., 1998]. An important anatomical and functional relationship exists between the ICCs and myenteric neurons (see Figure 1.1 bottom). These cells are incorporated between smooth muscle layers and form a network throughout the stomach wall with synaptic contacts to smooth muscle cells.

The vagus nerve, which connects many organs in the body to the brain with intrinsic and extrinsic neurons, innervates the stomach [Andrews, 1986]. The vagus nerve, along with hormones and intraluminal content, modulate both the contractile activity and relaxation in different regions of the stomach.

1.2.2 Electrical Activity of GI Smooth Muscle

Slow-waves

The involuntary contractions in the stomach and small intestines mostly occur rhythmically. The frequency of the contractions is determined primarily by slow-waves of membrane potential in the smooth muscle that are controlled by the ICCs. The slow-waves are not action potentials, but rather changes in the resting membrane potential that propagate axially. The amplitude of the slow-waves typically varies between 5 and 15 mV and the intrinsic frequency is different in various parts of the gastrointestinal tract. For example, in humans the frequency of the stomach is around 3 cycles per minute (cpm), while the duodenum oscillates between 8-12 cpm, and the terminal ileum, which is the distal end of the small intestine, at 8-9 cpm.
The slow-waves are a result of an intricate interaction between the pacemaker ICCs and smooth muscle cells. The ICCs are most abundant in the proximal corpus along the greater curvature of the stomach. These cells undergo cyclic changes in membrane potential that are caused by ionic channels that periodically open, producing inward currents. The electrical wave quickly propagates along the circumference, forming a ring of excitation that travels slowly down the stomach towards the small intestines. This phenomenon is the electrical basis of gastric peristaltic contractions.

The details of gastric slow-wave propagation for a healthy human adult have been determined using high-resolution mapping of the serosal surface and are depicted in Figure 1.2 [O’Grady et al., 2010]. The slow-wave originates in the pacemaker region and propagates for only a limited distance towards the fundus, which is mostly quiescent due to its primary purpose for food storage. In the corpus, the slow-wave front organizes into a circumferential ring traveling in the axial direction of the stomach. There is no longer any transverse propagation component after this band has organized. After 2-3 seconds of propagation, the amplitude drops by about 50 percent and the velocity by approximately 66 percent. This results in a slow propagation velocity of 3 mm/s in the corpus, which leads to the accumulation of several slow-wave fronts with a spacing of 60 mm. Within the antrum, the slow-wave propagation front transitions to approximately double the amplitude and speed, leading to an accordingly wider spacing of the propagating waves in the distal stomach. The gastric slow-wave activity terminates in the
pyloric sphincter.

Figure 1.2: Origin and propagation pattern of normal electrical slow-waves on the human stomach surface.

Although the highest density of ICCs are found in the corpus of the stomach, the rest of the stomach also has ICCs, except for the fundus. Therefore, other regions can also generate slow-wave activity, such as the antrum. The intrinsic frequency of the ICCs in the corpus is higher compared to any other part of the stomach. This results in the slow-waves being generated and propagating through the antrum before the antral ICCs can generate their own slow-waves. Alterations in the ICC frequency in any region of the stomach in disease can give rise to gastric arrhythmias and propagation abnormalities. Also, slow-waves require ICCs for propagation, and will decay in amplitude and disappear within a few millimeters in a region of the stomach lacking ICCs.
Spike Potentials

The slow-waves in the gastrointestinal tract do not directly cause smooth muscle contractions. The slow-waves excite intermittent spike potentials, which in turn lead to the muscle contractions [Suzuki, 2000]. Spike potentials occur automatically when the resting smooth muscle membrane potential becomes higher than -40mV. These are true action potentials and the greater the slow-wave potential, the higher the frequency of the potentials, which can occur anywhere between 1 and 10 spikes per second.

The spike potentials last much longer in gastrointestinal smooth muscle compared to the action potentials in large nerve fibers. Nerve fibers exclusively operate with sodium channels, while the gastrointestinal smooth muscle also consist of calcium-sodium ion channels that allow many calcium ions to enter the cells along with a relatively small number of sodium ions. These calcium-sodium ion channels are much slower (10 to 40 times) to open and close compared to sodium ion channels, which accounts for the long duration of the gastrointestinal action potentials.

Changes in Resting Membrane Potential

Under normal physiological conditions, the resting membrane potential is about -56 mV on average. Depolarization (i.e. when the membrane potential increases) results in the muscle fibers becoming more excitable, while hyperpolarization (i.e. the potential decreases) has the opposite effect.
Factors that depolarize the membrane include: stretching of the muscle, stimulation by acetylcholine, stimulation by parasympathetic nerves that secrete acetylcholine at their endings, and stimulation by several gastrointestinal hormones. Factors that hyperpolarize the membrane include: the effect of norepinephrine or epinephrine on the fiber membrane, and stimulation of the sympathetic nerves that secrete mainly norepinephrine at their endings.

1.2.3 Control of Gastrointestinal Function

Enteric Nervous System

The gastrointestinal system has a nervous system of its own called the enteric nervous system [Furness and Costa, 1987]. It lies entirely in the wall of the gut, starting in the esophagus and extending all the way down to the rectum. The enteric system consists of approximately 100 million neurons and has two plexuses. The myenteric plexus is the outer plexus that lies in between the longitudinal and circular muscle layers and controls peristalsis. The submucosal plexus lies in the submucosa and is responsible for local blood flow and gastrointestinal secretions.

Although the gastrointestinal tract is coupled to the central nervous system, it is the only organ in the body that can function completely independently of the brain via the enteric nervous system. The enteric nervous system does not automatically follow instructions it receives from the central nervous system, nor does it necessarily send information it receives back to the brain. The enteric
nervous system can process signals from sensory receptors and activate and control a set of effectors self-sufficiently.

**Autonomic Nervous System**

While the enteric nervous system can function on its own, gastrointestinal functions are also significantly activated and inhibited by the parasympathetic and sympathetic systems [Jänig, 1989]. The sensory nerve endings in the gut wall send afferent signals to the enteric nervous system, sympathetic nervous system, spinal cord, and brain stem.

The part of the peripheral nervous system that effects the function of internal organs, such as the gut, is called the autonomic nervous system. Unlike the nerves that control skeletal muscle, autonomic nerves do not connect the central nervous system directly to the organs. An autonomic signal from the brain is transmitted by at least two separate nerve cells, while a signal from the brain to a skeletal muscle requires only one. Due to this physiological mechanism, skeletal muscle exhibit an “all or none” response to a signal from the brain, while autonomic signals can be modulated (e.g. amplified or weakened) at autonomic synapses. Also, the autonomic nervous system contains regional aggregates of nerve cell bodies called ganglia. Preganglionic nerves transmit signals to the ganglia, while postganglionic nerve cells convey signals away from the ganglia to effectors at the organs.

The parasympathetic innervation to the gastrointestinal tract consist of two parts: the cranial and sacral. The cranial parasympathetic nerve fibers are
almost completely contained in the vagus nerve. The vagus nerve innervates the esophagus, stomach, small intestines, and the first half of the large intestine. The sacral parasympathetic nerves originate in the spinal cord and pass through the pelvic nerves to the distal half of the large intestine all the way through the rectum. The role of these fibers is to execute defecation reflexes. The plexuses contain most of the postganglionic neurons of the gastrointestinal parasympathetic system. Stimulation of the parasympathetic nerves typically enhances activity of the entire enteric nervous system, which in turn increases the activity of most gastrointestinal functions.

The sympathetic fibers that innervate the gastrointestinal tract originate between the T5 and L2 vertebrae in the spinal cord. Unlike the parasympathetic system, the sympathetic system consists of short, fast-conducting preganglionic nerves and long, slow-conducting postganglionic nerves. Due to this physiological difference, the sympathetic responses are slower and more diffuse compared to the fast and precise parasympathetic responses. Parasympathetic responses are often targeted to individual organs, while sympathetic responses typically effect the entire body. For example, the sympathetic response leads to rapid beating of the heart, pupil dilation, and an elevation in blood pressure in a stressful situation. Usually, this type of response also inhibits the activity of the gastrointestinal tract, which is not critical in a fight or flight situation. On the contrary, the parasympathetic system has many of the opposite effects.
Other Gastrointestinal Nerves and Reflexes

Many afferent sensory nerve fibers also innervate the gut [Furness and Costa, 1987]. These sensory nerves can be stimulated by excessive distention of the gut wall, inflammation of the gut mucosa, and even the presence of certain chemical substances within the gut. Signals transmitted through these fibers can then lead to excitation or inhibition of gastrointestinal movements. Other sensory signals from the gut can travel to multiple areas of the spinal cord and even the brain stem. For example, 80% of the nerve fibers in the vagus nerves are afferent rather than efferent. These afferent fibers transmit sensory signals from the gastrointestinal tract into the brain medulla, which in turn initiates vagal reflex signals that return to the gastrointestinal tract to control many of its functions.

The gastrointestinal system consists of several reflexes. There are reflexes within the enteric nervous system in the gut wall. These include reflexes that control gastrointestinal secretion, peristalsis, mixing contractions, and local inhibitory effects. There are also reflexes in between various parts of the gut. These reflexes can transmit signals over long distances to various areas of the gastrointestinal tract. One example includes the gastro-colic reflex, which is characterized by signals from the stomach to the large intestine after a meal to cause evacuation of the colon. Another example includes signals from the colon and small intestine to inhibit stomach motility and stomach secretion. Finally, there are reflexes between the gut and central nervous system. Reflexes from the stomach and duodenum to
the brain stem and back to the stomach via the vagus nerve can control gastric motor and secretory activity. Pain reflexes can cause general inhibition of the entire gastrointestinal tract. Defecation reflexes travel from the colon and rectum to the spinal cord and back again to produce the powerful colonic, rectal, and abdominal contractions required for defecation.

**Fasting Motility**

During fasting there are repeated patterns of gastric and intestinal contractions and quiescence, known as the migrating motor complex (MMC) [Sarna, 1985]. A full cycle of the MMC has three unique phases and it typically lasts between 90 and 120 minutes. Phase I is predominantly quite with little to no contractions. Phase II is characterized by highly variable and uncoordinated contractions. Finally, Phase III consists of a period of about 5 to 10 minutes of very coordinated peristaltic contractions in the stomach and small intestines. The phase III contraction pattern typically starts in the stomach and migrates distally through the small intestines. This process repeats itself during the interdigestive state. The phase III contractions clear nondigested items from the stomach and are associated with hunger sensation, which may mediate food intake [Deloose et al., 2012].

**Postprandial Motility**

The MMC phases during fasting are interrupted by food intake. The gastrointestinal tract immediately switches to a postprandial motility pattern, which
includes the relaxation of the fundus, known as receptive relaxation, and coordinated antral contractions (see Figure 1.3) [Kelly, 1980]. The purpose of the relaxation is to allow for gastric filling while maintaining a constant intragastric pressure. The gastric accommodation due to the relaxation is coordinated by a vago-vagal reflex pathway, and allows the stomach to act as a food reservoir.

Figure 1.3: A healthy stomach’s response to ingestion of food. The fundus relaxes to accommodate the food, while grinding and emptying is modulated by antroduodenal coordination and pyloric and duodenal resistances (from [Koch and Stern, 2004] with permission).

After the consumption of the meal, peristaltic contractions take place in the corpus and antrum, initiated at the pacemaker region along the greater curvature of the stomach. As the contractions propagate towards the pylorus, the pylorus closes, resulting in retropulsion of the food back towards the corpus (see Figure
1.3). This process grinds the food down to small particles. Once the particles are about 1-2mm in diameter, they are pushed through the pylorus into the duodenum. Therefore, the pylorus functions as a “gate-keeper” for the stomach and plays an important role in the control of gastric emptying.
1.3 Clinical Tools for Motility Testing

1.3.1 Gastric Emptying Scintigraphy

Gastric emptying rate is a measure of how quickly the stomach empties its contents after a meal. The gastric emptying test is commonly administered when patients report upper GI symptoms and an endoscopy does not reveal any abnormalities (e.g. an ulcer, inflammation, or obstruction). Gastric emptying time is defined as the amount of time between food entering the stomach and completely leaving the stomach. When food enters the stomach, several functions need to take place for normal gastric emptying into the small intestines. The fundus of the stomach needs to expand to be able to allow the food to enter the stomach without an increase in pressure, referred to as gastric accommodation or receptive relaxation. A pressure gradient between the proximal and distal stomach must exist to transport the food in the correct direction. Finally, coordinated wave-like contractions of the smooth muscle need to occur to break down and propel the food. Abnormal gastric emptying can be a result of any of these processes going awry.

The most common technique for measuring gastric emptying time is gastric emptying scintigraphy. During the test, the patient is asked to consume a standardized, radioactively-labelled (technetium-99m) meal, and the abdomen is imaged for four hours [Abell et al., 2008]. The meal consists of fat-free liquid egg-white substitute, 2 slices of bread, 30g of strawberry jam, and 120mL of water.
The meal is a total of 255 kcal with a composition of 2% fat, 24% protein, 2% fiber, and 72% carbohydrate. The patient is asked to consume the meal within 10 minutes, and imaging starts immediately after completion of the meal. After the acquisition of four hours of images, a region of interest is manually drawn around the stomach, and the contents of the stomach are estimated for every image in the study and plotted. The gastric counts are typically corrected for physical decay and attenuation. It is reported that the patient has rapid gastric emptying if less than 35% of the meal is remaining in the stomach after 1 hour. Delayed gastric emptying is present if retention is above 60% at 2 hours or 10% at 4 hours.

1.3.2 Wireless Motility Capsule

The wireless motility capsule is an ingestible device containing sensors that can measure luminal pH, pressure, and temperature, with capabilities of wireless data transmission to a data logging unit that is worn on the patient’s body. The wireless motility capsule is currently the only motility test that is administered in an ambulatory setting. The measurements can be used to estimate gastric emptying time, since there is a sharp increase in pH when the capsule travels from the antrum of the stomach to the duodenum. Small bowel transit time can also be determined by a sudden change in pH. The temperature sensor can be used to determine when the pill exits the body, from which whole gut transit time can be calculated. The pressure sensor may be useful for assessing motility patterns, although peristalsis cannot be measured since it only has one pressure sensor and
the capsule is not stationary [Kloetzer et al., 2010].

The patient is asked to fast the night before the test and to stop gastric acid suppressants for a week. After ingestion of the test meal, which is a standardized nutrient bar and 50 mL of water, the patient is required to fast for the following 6 hours, after which they can return to normal daily activities while avoiding strenuous activity. The patient is asked to keep a diary during the test, noting events such as meals, bowel movements, and sleep. If the evidence of the capsule leaving the body is not conclusive, an x-ray is usually taken to confirm.

A gastric emptying time determined by the capsule of greater than 5 hours is considered abnormal. A study has shown a correlation between the motility capsule and scintigraphy gastric emptying times of 0.82 [Kuo et al., 2008]. Healthy subjects have a mean gastric emptying time of 4.7±4.5 hours, a small bowel transit time of 25±14 hours, and a mean whole gut transit time of 29±14 hours [Sarosiek et al., 2010]. The upper limit in the normal range for colon transit time and whole gut transit time has been found to be 59 and 71 hours, respectively [Rao et al., 2009, Camilleri et al., 2010].

1.3.3 Manometry

Antroduodenal manometry is a technique that measures both gastric and small intestine contractions simultaneously at multiple locations using a catheter inserted through the mouth, nose, or g-tube opening (if present). Recording the amplitude at each location enables the assessment of both neural control and mus-
cle response of the stomach and small intestines.

Subjects are asked to fast at least 8 hours prior to placement of the catheter, which can be placed with fluoroscopic guidance or endoscopically. Medications affecting motility are stopped at least 48 hours prior to the procedure. Two types of catheters can be used to record pressure: water profused and solid-state. The water profused catheters are one-time use, lower cost, and have fewer pressure sensors (typically 4 to 5 in the antrum with 1-2cm spacing and 3 to 4 in the small bowel with 10-15cm spacing). Solid state catheters allow for higher-resolution recordings with more pressure sensors and have a higher fidelity response to pressure changes, but are more expensive and must be sterilized between uses.

A typical protocol for the study is as follows. Fasting antroduodenal motility is recorded for 3-4 hours, during which the investigator is looking for the presence and coordination of the interdigestive phase III migrating motor complex. If it is not observed, intravenous erythromycin is administered to induce a phase III migrating motor complex. Finally, a meal is consumed by the patient and the postprandial activity is recorded for 1-2 hours. Due to the difficulty administering and interpreting antroduodenal manometry, it is only offered at a limited number of highly-specialized tertiary motility centers.

Various patterns of antroduodenal motility have been linked to upper abdominal symptoms. Postprandial antral hypomotility, which is defined as a lack of increase in antral contractions after a meal, has been associated with delayed gastric emptying and symptoms of nausea, abdominal pain, and vomiting [Thumshirn
et al., 1997]. Pseudo-obstruction results in a reduction in the orderly movement of contents out of the stomach and through the small intestines [Mann et al., 1997]. Antroduodenal manometry can differentiate between myopathic and neuropathic pseudo-obstruction. Characteristics of myopathic pseudo-obstruction include low amplitude contractions with normal propagation, while neuropathic pseudo-obstruction results in uncoordinated contractions at normal or increased amplitude. Studies have shown that the results of antroduodenal manometry change the diagnosis and treatment of 15% to 20% of patients with upper gastrointestinal symptoms [Verhagen et al., 1999a, Soffer and Thongsawat, 1996].

1.3.4 Electrogastography (EGG)

Electrogastography (EGG) is a noninvasive technique for recording the gastric myoelectric activity using electrodes placed cutaneously on the abdominal surface overlaying the stomach. The simplicity and safety of EGG make it attractive for diagnosing abnormalities in gastric motility and emptying. EGG was first reported in the 1922 paper by Alvarez [Alvarez, 1922], but most of the progress in the field has occurred in the last couple decades.

When there is little smooth muscle contractility during the fasting period, the electrical events on the surface of the stomach mainly reflect depolarization and repolarization of the ICCs. Additional gastric myoelectrical activity occurs when stronger circular muscle contraction occurs (e.g. when vagal efferent activity and release of acetylcholine from the postganglionic cholinergic neurons are elicited
in response to ingestion of a meal). Thus, compared with fasting, the amplitude of the EGG wave is generally greater in the postprandial condition depending on the specific meal ingested. Figure 1.4 illustrates a stronger electrical activity in the postprandial period when the additional gastric myoelectrical activity of the spike potentials are linked to the migrating gastric pacesetter potential. Although there may be several simultaneous wavefronts present on the surface of the stomach, the cutaneous recording of EGG reflects a summation of all the source potentials resulting in a signal with a frequency that matches the frequency of wave generation.

![Figure 1.4](image.png)

**Figure 1.4**: Migration of pacesetter potential plus plateau-action potential activity in the postprandial period. The corresponding cutaneous EGG signal is also shown (from [Koch and Stern, 2004] with permission).

A typical electrode configuration for recording the EGG is shown in Figure 1.5. The measurement electrode is placed half-way between the xiphoid process
and umbilicus, the reference electrode is placed 4-6cm to the subject’s left, and the ground electrode is placed on the subject’s right. These three electrodes produce a single voltage time-series.

![Surface electrodes](image)

**Figure 1.5:** Commonly used electrode placement for recording the electrogastrogram. Electrodes 1 and 2 are a bipolar pair of recording electrodes and electrode 3 is the ground (from [Koch and Stern, 2004] with permission).

Since the recorded gastric signal is relatively weak and noisy, visually determining the frequency and amplitude of the signal is difficult. Therefore, spectral analysis using the fast Fourier transform (FFT) is commonly used for objective quantification of the data [Abell and Malagelada, 1988]. The dominant frequency of the EGG signal in each window of data (e.g. 4 minutes) is one of the main parameters used to assess abnormalities. The dominant EGG frequency for a normal subject is around 3 cycles per minute (0.05 Hz). Frequencies above this are labeled as tachygastria and below are considered bradygastria, both of which are considered abnormal in both the fasting and postprandial state. A quantitative
measure often used is the percentage of time throughout the recording that the dominant frequency is in the normal range. If the dominant EGG frequency is close to 3 cpμ for greater than 70% of the recording, the subject is considered normal [Parkman et al., 2003]. Another spectral feature of the EGG that is used to determine abnormal gastric function is the dominant power before and after eating a meal. The dominant power of the EGG for a healthy subject should increase after a meal, reflecting an increase in motility.
1.4 Review of Single-Channel EGG Studies

Gastroparesis

Gastroparesis is a disorder characterized by delayed gastric emptying in the absence of obstruction, resulting in food remaining in the stomach for a prolonged period. The predominant symptoms associated with gastroparesis are nausea, vomiting, and abdominal pain. EGG dysrhythmias, specifically bradygastria (i.e. dominant frequency below 2 cpm), have been observed in patients with gastroparesis [Geldof et al., 1986]. Another study suggested that gastric myoelectrical pattern recorded by the EGG can differentiate between mechanical obstruction and idiopathic causes of gastroparesis. Patients with gastric outlet obstruction had a relatively high amplitude and very regular 3cpm activity, while patients with idiopathic gastroparesis had primary 1 to 2 cpm activity and low 3cpm activity [Brzana et al., 1998].

Diabetic Gastropathy

Diabetic gastropathy effects patients with both type-1 and type-2 diabetes. This disease includes several neuromuscular dysfunctions of the stomach, including abnormal gastric contractility, tone, and myoelectrical activity. The common symptoms associated with this disorder include nausea, vomiting, bloating, early satiety, and various levels of abdominal pain. The cause of diabetic gastropathy is still not well understood, but it involves abnormalities in multiple interact-
ing cell types including the extrinsic nervous system, ICCs, enteric nervous system, immune cells, and smooth muscles. Patients with diabetic gastropathy can also have cyclic vomiting syndrome (CVS), migraine headaches, and delayed gastric emptying. Patients with diabetic gastropathy and CVS have more abnormal EGG frequencies compared to patients with diabetic gastroparesis with no cyclical symptoms [Christensen et al., 2008]. Interestingly, studies have shown that hyperglycemia slows gastric emptying, while hypoglycemia accelerates it [Schvarcz et al., 1997, Horowitz et al., 2002]. The primary treatment options for diabetic gastropathy include prokinetics, antiemetics, nutritional support, and pain control.

### Nausea and Vomiting in Pregnant Women

Nausea and vomiting are common in pregnancy, effecting approximately 80% of all pregnant women [Lee and Saha, 2011]. Koch et al. found that the EGG in pregnant women with nausea showed gastric dysrhythmias, while those without nausea had normal slow waves [Koch et al., 1990a]. Riezzo et al. observed EGG abnormalities in symptomatic women that vanished after voluntary interruption of the pregnancy [Riezzo et al., 1992]. A study that looked at the effect of meal content on nausea in pregnant women found that meals with mainly protein content reduced nausea and dysrhythmic activity more than fat and carbohydrate meals with similar caloric content. Also, liquid meals decreased dysrhythmias more than solid meals [Jednak et al., 1999]. The effect of pregnancy hormones on the EGG has also been studied. It was found that progesterone resulted in an increase of
bradygastrias, while simultaneous administration of progesterone and estradiol at typical pregnancy levels induced both bradygastrias and tachy gastrias in nonpregnant women [Walsh et al., 1996].

**Functional Dyspepsia**

Functional dyspepsia is a medical condition characterized by upper abdominal fullness, recurrent pain in the upper abdomen, and early satiety in which an organic cause cannot be found. Patients may also experience bloating, belching, nausea, or heartburn. A study showed that about half of these patients have disordered gastric myoelectrical activity [Chen et al., 1999]. Another study found that the EGG was abnormal from 36 to 60 percent of functional dyspeptic patients with an ability to detect a dysfunction of gastric motility in approximately 93 percent of the patients [Lin et al., 1999]. Compared to healthy control subjects, dyspeptic patients also exhibited a higher dominant power and a greater percentage of tachy gastrias [Riezzo et al., 2001]. In a study that assessed a population with irritable bowel syndrome (IBS), the EGG was abnormal only if concurrent dyspepsia was also present [Leahy et al., 1999].

**Motion Sickness**

A rotating optometric drum can be used as a provocative stimulus to produce an illusion of self-motion, and the resulting central sensory conflict induces nausea in approximately half of control subjects. In a study where gastric my-
oelectrical activity was measured along with autonomic nervous system activity, the nausea from the rotating optometric drum led to an increase in sympathetic nervous activity, decrease in parasympathetic nervous system activity, and an increase in tachygastrias [Hu et al., 1991]. Another study found that the onset of nausea and increase in vasopressin release was preceded by gastric dysrhythmias measured by the EGG. It has been hypothesized that gastric dysrhythmias may directly induce a sensation of nausea or increase levels of vasopressin by vagal afferent signaling [Koch et al., 1990b].

Maturation of EGG in Neonates

The studies on gastrointestinal motility on neonates concern the development of the electrical and mechanical activity of the gut [Berseth, 1996]. There are a lot of conflicting results in the literature. One study found no differences between preterm and full-term infants [Koch et al., 1993], while another study found the gastric electrical activity to be immature at birth, suggesting a development process from 1 week to 6 months [Chen et al., 1997]. Riezzo et al. observed a clear maturation pattern of gastric motility. An abnormal EGG pattern and delayed gastric emptying time was present in preterm infants of 28-32 weeks of age. The 3 cpm activity became dominant at approximately 32 to 36 weeks of gestational age, and by that time, the gastric emptying time was similar to that of full-term infants [Riezzo et al., 2000b]. The gastric electrical activity and emptying have also been studied along with the intestinal permeability in preterm newborns. Both electri-
cal and motor activities were shown to be completely developed at birth, while the intestinal epithelial barrier evaluated by lactulose/mannitol tests improved during the first week of life [Riezzo et al., 2009].

**Pediatric GI Disorders**

The noninvasiveness of EGG makes it particularly attractive for assessing pediatric GI disorders, where minimal intervention is desired. Abnormal EGG tracings, specifically a higher percentage of tachygastria and reduce postprandial amplitude, have been observed in children with dyspepsia compared to healthy children [Riezzo et al., 2000a, Chen et al., 1998]. EGG abnormalities were accompanied by delayed gastric emptying, which were present in two-thirds of the dyspeptic children. Gastric dysrhythmias were present in 62 percent of children with CNS disorders and vomiting, and 32 percent of patients exhibited both gastroesophageal reflux and gastric dysrhythmias [Ravelli and Milla, 1998]. Abnormal gastric myoelectrical activity may play a role in the development of cyclic vomiting syndrome (CVS), since children with CVS have a characteristic periodicity potentially due to an abnormality that can be detected by the EGG [Chong, 1999]. While symptomatic children showed both preprandial and postprandial episodes of tachygastria, asymptomatic CVS children only had postprandial tachygastria. Abnormal EGG patterns and higher tachygastria activity were also associated with delayed gastric emptying.

Chronic idiopathic intestinal pseudo-obstruction (CIIP) is an uncommon
disorder of intestinal neural or muscular function. It is characterized by recurring episodes of intestinal obstruction without an evident anatomical cause. Symptoms also include vomiting and intolerance of enteral feeding. In this population, patients with neuropathic dysmotility typically have a persistent tachygastria, while those with myopathy have no dominant frequency [Devane et al., 1992].

**Chronic Renal Failure**

In studies including patients with chronic renal failure, there were observed gastric myoelectrical abnormalities, particularly bradygastrias and tachygastrias, especially during episodes of nausea. After renal transplantation the gastric dysrhythmias resolved and normal myoelectrical function was restored [Ravelli et al., 1992, Ravelli, 1995].

**Food Content**

The volume of food along with its composition and caloric content is assumed to be a physiological stimulus that can activate or modulate both mechanical and hormonal stomach activity. It is well established that ingestion of a meal results in an increase in EGG amplitude [Shimada et al., 1998]. This response is due to increased gastric electrical activity and antral contractions, which are influenced by the chemical and physical characteristics of the meal [Levanon et al., 1998]. In one study, it was shown that the postprandial to preprandial EGG power ratio increased more for a 350-kcal versus 250-kcal muffin-based meal, and the 350-kcal
meal had a longer emptying time [Gonlachanvit et al., 2001].

Osmolarity of the meal can also affect the stomach myoelectrical response. Hypertonic glucose solutions can evoke tachygastria myoelectrical patterns as well as significantly delay gastric emptying compared to distilled water [Syrkiewicz-Trepiak et al., 2010]. Gastric motility and emptying can also be affected by the viscosity of foods. In a study of healthy individuals, pectin increased viscosity of food and accelerated gastric emptying, while up to 4.5 grams of guar gum did not affect gastric emptying or intestinal transit times [van Nieuwenhoven et al., 2001].

**Drugs**

Prokinetic agents are a type of drug that enhances gastrointestinal motility, and are used to treat irritable bowel syndrome, gastroparesis, functional dyspepsia, gastritis, and acid reflux disease. Both domperidone [Koch et al., 1989] and erythromycin [Yoon et al., 2012] seem to induce normal gastric myoelectric activity together with an improvement in upper gastrointestinal symptoms and emptying time. However, the effects of these two drugs on general symptoms of dyspepsia are often limited. Trimebutine maleate, when associated to a proton pump inhibitor, may improve gastric motility by reducing periods of tachygastria and bradygastria in patients with gastric ulcer, but it does not improve gastric emptying [Kamiya et al., 1998]. A study found that cisapride improved gastric dysrhythmia in patients with diabetic gastroparesis [Chang et al., 1998], but this drug was taken off the market because of severe cardiac side effects. Another study revealed that
prokinetic drug treatments (itopride hypochloride, mosapride, and levosulpiride) are useful in improving dyspepsia symptoms via improved gastric electrical activity [Lim et al., 2012]. A study on the effects of a proton pump inhibitor, omeprazole, on gastric electrical activity and gastric emptying showed an improvement in gastric myoelectrical activity but no difference in gastric emptying. The improvement in myoelectrical activity may be one of the mechanisms involved in its success in relieving symptoms in patients with functional dyspepsia [Kamiya et al., 2011].

1.5 Acknowledgements

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Chapter 2

Pitfalls of Single-Channel EGG

Unlike the 12-lead electrocardiogram (ECG), which has proven to be a valuable diagnostic tool, the EGG is not used often in the clinic. This is due to several challenges that have affected the reliability of the recordings and have been difficult to overcome. First, the amplitude of the recorded signal is on the order of 50-200 \( \mu V \), which is relatively weak compared to the cardiac myoelectric signal [Chang et al., 1996]. The EGG signal is contaminated by signals from the heart, respiration, movement, and other gastrointestinal organs [Mintchev et al., 2000]. Some of this noise can be successfully removed using digital filters, since they occur at different frequencies than the gastric slow wave (approximately 3 cpm). On the other hand, movement artifacts are difficult to avoid since recordings often last over an hour (this limitation is addressed in Chapter 4). Secondly, there is a significant amount of inter-subject variability in stomach anatomy. As a consequence, standard electrode placement using anatomical landmarks has not
yet been established. Finally, recent studies from high-resolution serosal electrical mapping have shown the existence of spatial dysrhythmias that cannot be detected using a single channel EGG measurement.

There have been contradictory reports in the literature about the correlation between traditional EGG parameters and abnormalities in gastric emptying. Some investigations have reported no relation [Koch et al., 1989], while others have reported a strong positive correlation [Abell et al., 1991]. Overall, normal EGG does not assure normal gastric emptying (sensitivity < 50%), but an abnormal EGG may predict delayed gastric emptying (specificity 78%-92%) [Parkman et al., 1997, Pfaffenbach et al., 1997, Geldof et al., 1986, Lin et al., 1999, Chen et al., 1996]. In other words, while subjects with an abnormal EGG typically have delayed gastric emptying, there are patients with a normal EGG who can still have slow emptying. This limitation is an important reason why EGG has not been widely adopted clinically.

2.1 Anatomical Variability

The source of the EGG signal is the myoelectrical activity on the stomach surface, and we record that signal with electrodes placed on the abdominal surface. The signal conducts through abdominal tissue, which contains muscle, fat, and skin. The conduction of the signal through this volume attenuates the signal, and the attenuation is a function of distance [Plonsey, 1969]. Therefore, to record an
EGG signal with the highest signal-to-noise ratio, the electrodes should be as close to the stomach as possible.

**Figure 2.1:** Coronal views of torso and stomach reconstructed from volumetric CT images of 4 subjects showing the high degree of anatomical variability. Red dots indicate the traditional EGG electrode placement location.

The first step in determining the optimal placement of EGG leads is to evaluate the distribution in the anatomical parameters across a wide range of subjects. To assess this, we reconstructed the stomach and torso with volumetric CT scans from 29 subjects with a wide range of BMI (25 ± 4, range 18 to 36). Figure 2.1 shows an example of the 3D reconstruction of the stomach and torso for four of the subjects, with red dots indicating the commonly used single-channel EGG electrode placement. The following parameters were calculated from the volumetric reconstructions: a) the horizontal position (X) of the antrum of the stomach relative to the xiphoid process, b) the vertical position (Y) of the antrum of the stomach relative to the xiphoid process, c) the distance (Z) from the abdominal surface to the antrum of the stomach, d) the minimum angle of the stomach with respect to the positive x-axis, e) the maximum angle of the stomach with respect to the positive x-axis, and f) the volume of the stomach.
The results from this study are shown in Table 2.1. Regarding the position of the stomach relative to the xiphoid, the Y dimension had the most variability between subjects with a range of 17.4 cm (see Figure 2.2). Surprisingly, the volume of the stomach was highly variable between subjects, with an average of $510 \pm 522$ mm$^3$ and a range of 136 to 2694 mm$^3$. It should be noted that the subjects included in this study were not healthy and were all experiencing upper gastrointestinal symptoms.

Standardization of the lead placement for EGG has proven difficult due to high anatomical variability between subjects. We quantified the variability between subjects by reconstructing volumetric CT scans. We found a wide variety in stomach shape, size, and position. In some cases, the traditional single-channel EGG lead placement resulted in electrodes that were quite far from the stomach. In the following section, we will quantify the sensitivity of the EGG signal to placement of the electrodes.

### 2.2 Sensitivity to Electrode Placement

According to the American Motility Society, healthy subjects exhibit gastric activity at the normal frequency (2.0 - 4.0 cpm) for greater than or equal to 70% of the recording. This value was chosen heuristically based on the results from the EGG recordings of 189 asymptomatic subjects from four studies [Parkman
Table 2.1: Anatomical parameters measured from 3D CT reconstructions across 29 subjects.

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<th>Y (CM) FROM XIPHOID</th>
<th>Z (CM) FROM SURFACE</th>
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<th>MAX ANGLE (DEGREES)</th>
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<td>$25 \pm 4$</td>
<td>$-5.0 \pm 1.5$</td>
<td>$-11 \pm 4$</td>
<td>$3.2 \pm 1.3$</td>
<td>$166 \pm 23$</td>
<td>$227 \pm 14$</td>
<td>$510 \pm 522$</td>
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</table>
et al., 1996, Lin et al., 1999, Chen and McCallum, 1992, Pfaffenbach et al., 1995].

This suggests that normal subjects can have dysrhythmias up to 30% of the time, but this is more likely due to signal noise and low amplitude [Camilleri et al., 1998]. Researchers have detected fewer frequency deviations on serosal recordings compared to cutaneous EGG, implying that some of the cutaneously acquired dysrhythmias are artefactual [Couturier et al., 1972, Verhagen et al., 1999b]. Also, in an analysis of 10 healthy subjects, a study showed that shifting the measurement electrodes 10 cm away from the antrum resulted in a drop (approximately 17%) in the percentage of normal frequency activity during the recording, sometimes even dropping below the 70% normal cutoff [Pfaffenbach et al., 1995]. To test the sensitivity of electrode placement, we assessed how EGG electrode placement can affect determination of percent slow-wave time in the 2-4 cpm frequency band by

**Figure 2.2**: The distribution of the position of the antrum relative to the xiphoid process for 29 subjects.
using a high density 100 channel array in subjects with wide-ranging BMI.

**Figure 2.3:** (a) Heat map of EGG activity generated from 100 electrode array (10 by 10, 2cm spacing) in a single subject. The red and blue bipolar electrode pairs are 5cm apart. Spectrogram computed from (b) traditional (red) and (c) optimal (blue) electrode pairs.

Seventeen subjects (12M/5F) were enrolled in our study with an average age of 46 years (range 21-79 years) and an average BMI of 26 (range 19-36). EGG was simultaneously recorded from 100 electrodes placed in a uniform 10x10 grid (2cm x 2cm spacing) extending from the sternum (at the top) to the umbilicus or below (at the bottom). The reference and ground electrodes were placed outside of the array on the subject’s right side, above the hip bone. The locations of the umbilicus and xiphoid relative to the array were documented as anatomical references. Each subject was asked to fast prior to the start of the EGG recording. After 30 minutes of recording, each subject consumed a standardized meal and the
Table 2.2: Improved detection of gastric slow-wave with optimal lead placement.

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>AGE</th>
<th>BMI</th>
<th>GENDER</th>
<th>OPTIMAL % 2-4 CPM</th>
<th>TYPICAL % 2-4 CPM</th>
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<td>58</td>
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<td>M</td>
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<td>72</td>
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<tr>
<td>MEAN</td>
<td>46</td>
<td>26</td>
<td></td>
<td>93 ± 8</td>
<td>68 ± 17</td>
</tr>
</tbody>
</table>

An average EGG potential map was computed using the data from all the electrodes throughout the entire recording (see Figure 2.3a). The EGG potential map represents the area of the array that has the highest EGG power in the 0.04-0.06 Hz frequency band. It was produced by re-referencing the data to each electrode in the array and calculating the mean EGG power relative to all other electrodes. The region of the potential map with the highest power corresponds to the region closest to the stomach.

For each subject, an optimal electrode pair was automatically determined by calculating the bipolar pair with the highest EGG signal-to-noise ratio in the study continued for 1.5 more hours for a total of 2 hours.
array. Signal-to-noise ratio was defined as the average power in the 0.04-0.06Hz frequency band divided by the average power in the 0.06-0.15Hz frequency band. The results from the optimal electrode pair were compared to those from the typical single-channel EGG placement (one electrode halfway between the xiphoid and umbilicus and the second 4-6 cm to the subjects left).

The percentage of the recording that the dominant frequency is between 2 and 4 cpm is a commonly used EGG metric, where a value below 70% is considered abnormal. Figure 2.3 illustrates the effect of electrode placement on the time-frequency analysis of the data for a representative subject using the fast Fourier transform. The data from electrodes at a slight distance away from the optimal pair (about 5 cm) resulted in a dramatic change in the spectrogram and an incorrect classification of this asymptomatic subject.

Using the optimal electrode pair, the percent 2-4 cpm activity was well over 70% for all 17 subjects (93 ± 8 %). This number dropped significantly (p = 3.7E-6) when calculating the same value using the traditional EGG electrode placement (68 ± 8 %) (see Table 2.2), where more than half of the subjects (9 out 17) fell below the 70% threshold. Statistical significance was determined by a two-sided test for the null hypothesis that the two independent samples have identical average values. This effect was particularly pronounced for the high BMI subjects. The variability in the distance between the optimal and typical electrode pairs (range X: -8 to 13 cm, range Y: -6 to 7 cm) can be seen in Figure 2.4.

The presented evidence shows that EGG frequency is very sensitive to elec-
trode placement. Blind placement of the electrodes with reference to the umbilicus may result in significant deviations in EGG metrics and lead to erroneous conclusions. The use of multiple electrodes or stomach localization is necessary for accurate detection of the EGG signal.

2.3 Fails to Measure Spatial Abnormalities

High-resolution electrical mapping of the serosal surface during surgery has recently been carried out to understand normal gastric slow-wave activity [O’Grady et al., 2010]. This technique involves positioning a spatially dense electrode array directly on the surface of the stomach to allow for the recording and reconstruction of patterns of electrical activation [Du et al., 2009]. The finding for normal subjects, in brief, was that the gastric slow-waves originate in the pacemaker region of the corpus, quickly form circumferential bands around the stomach, propagate slowly
in the axial direction, and eventually terminate in the pylorus (see Figure 1.2). Due to the slow speed of propagation, multiple wavefronts typically exist on the stomach surface at any given time.

Using the same technique, the researchers also evaluated the gastric slow-waves in subjects with gastroparesis [O'Grady et al., 2012] and chronic unexplained nausea and vomiting [Angeli et al., 2015] in order to define, quantify, and classify abnormalities with spatiotemporal detail. They observed aberrant initiation and conduction of the slow-waves, which occasionally led to premature termination and colliding wavefronts. The crucial finding was that half of the subjects exhibited spatial abnormalities that occurred at the normal 3 cpm frequency. This suggests that single channel EGG recordings are unable to detect such abnormalities. Results from a recent study [Buist et al., 2006] further emphasize this point by modeling both normal slow-wave propagation and a conduction block resulting in colliding wavefronts. It revealed that a single channel EGG recording on the abdominal surface would be unable to detect the irregularity.

2.4 Closing Remarks

Although abnormal EGGs have been reported with nausea, vomiting, early satiety, dyspepsia, gastroparesis, motional sickness, pregnancy, and eating disorders (see Chapter 1), it is not often used clinically because of its lack of reliability. There is more controversy regarding the clinical indications for EGG than any
other gastric motility test. This chapter enumerates several pitfalls of the EGG methodology. Estimating the frequency of a single channel recording of EGG via fast Fourier transform is too sensitive to the placement of electrodes. The inter-subject variability of stomach anatomy is more than the precision required for EGG electrode placement, which explains why a standard electrode configuration has not been established that can be used across all subjects. Although abnormal EGG has been shown to predict abnormal gastric emptying, normal EGG does not necessarily indicate normal gastric emptying. This may be because there exists a class of abnormalities (aberrant initiation and conduction) requiring spatial resolution to detect that would otherwise appear normal when only examining the frequency of the signal from only one channel. These limitations of the EGG are addressed in this dissertation to improve its diagnostic ability and clinical usefulness.

2.5 Acknowledgements

Chapters 2, in part, is currently being prepared for submission for publication of the material. Gharibans, Armen; Kunkel, David; Mousa, Hayat; Coleman, Todd. The dissertation author was the primary investigator and author of this material.
Chapter 3

High-Resolution Electrogastrogram: A Method for Determining Gastric Slow-Wave Direction and Speed

There have been attempts at extracting EGG spatial information from multiple surface electrodes in the past [Chen et al., 1999, Wang et al., 2003]. By placing four electrodes along the axis of the stomach, the amount of frequency coupling between channels can be evaluated, with the notion that coupling between channels reflects normal wave propagation. This method, however, does not measure true wave propagation and therefore does not accurately estimate propagation velocity.
Moreover, this approach is dependent on the placement of electrodes, particularly the reference. If the reference electrode is positioned in a region with strong gastric signal, phase shifts will not be observed. Given the amount of inter-subject variability in stomach anatomy, standardizing electrode placement becomes challenging [Burdan et al., 2012, Cheng et al., 2007].

In addition to the potentials recorded by surface electrodes in the EGG, the gastric electrical currents also produce a magnetic field that can be measured with a magnetometer, known as the magnetogastrogram (MGG). The relationship between the EGG and MGG is analogous to that of the electroencephalogram (EEG) and magnetoencephalogram (MEG) utilized for studying the activity of the brain. The MGG has been used to detect gastric slow-wave frequency and propagation with promising results [Bradshaw et al., 2009, Bradshaw et al., 2016]. A key feasibility distinction between the two modalities is that the MGG requires measuring the signal with large, expensive equipment in a controlled environment, while the EGG has the potential for ambulatory monitoring [Lindberg et al., 1996].

In this chapter, we address the spatial limitations of the EGG by presenting the high-resolution electrogastrogram (HR-EGG), a method for determining gastric slow-wave propagation direction and speed from an array of skin-mounted electrodes.
3.1 Methodology

3.1.1 Spatial Sampling

In order to accurately map the potentials on the abdominal surface, the layout and size of the electrodes need to be considered. The abdominal surface potential is a continuous field that is discretely sampled at each electrode location. The recorded potentials are a smeared version of the current sources generated by the interstitial cells of Cajal on the stomach surface. This is due to the conduction of the signal through the tissue (i.e. fat, muscle, and skin) separating the electrodes and the source. While volume conduction limits the spatial resolution of HR-EGG compared to serosal recordings, it makes it feasible to discretely sample the abdominal potentials. The separating tissue acts as a natural anti-aliasing spatial filter, enabling accurate sampling of the potentials with a reasonable number of electrodes [Nunez and Srinivasan, 2006].

The discrete sampling of continuous time-series data has been well-characterized [Bendat and Piersol, 2011]. The key concept is the Nyquist criterion, which states that for lossless digitization, the sampling rate should be at least twice the maximum frequency (i.e. \( f_s > 2f_{\text{max}} \) where \( f_s \) is the sampling rate and \( f_{\text{max}} \) is the maximum frequency of the signal). Once a time series has been aliased, there is no signal processing technique that can recover the lost information.

The Nyquist criterion for temporal sampling also applies to spatial sampling. The density and measurement area of the electrodes dictate the highest
spatial frequency that can be detected without spatial aliasing. The electrode is an analog filter that eliminates spatial frequencies with wavelengths shorter than its measurement diameter [Nunez and Srinivasan, 2006]. This is due to fact that the electrode averages the potentials within the region that is in contact with the gel or measurement area. Consider an array of electrodes that have uniform center-to-center spacing $d$ and electrode diameter $D$. Applying the Nyquist criterion to the edge-to-edge distance between neighboring electrodes results in the following constraint:

$$d - D < \frac{\lambda_{\text{min}}}{2}$$

(3.1)

where $\lambda_{\text{min}}$ is the shortest spatial wavelength of the signal [Nunez and Srinivasan, 2006].

The electrode spacing and measurement area is determined by a lower bound for the spatial wavelength of the cutaneous wave, which can be estimated by considering its slowest speed and highest frequency ($\lambda = \text{speed}/\text{freq}$). We assume that the slowest physiological serosal and cutaneous speeds are equivalent. After applying the appropriate values from the literature for healthy subjects (1.5 mm/s, 0.06 Hz) [O‘Grady et al., 2010], the minimum spatial wavelength ($\lambda_{\text{min}}$) of the cutaneous wave is calculated to be 25 mm. Therefore, to ensure that no spatial aliasing occurs, the edge-to-edge distance between electrodes should be less than 12.5 mm ($\lambda_{\text{min}}/2$). We chose an electrode diameter $D$ of 11 mm with a center-to-center spacing $d$ of 20 mm, which results in an edge-to-edge distance of 9 mm to
satisfy this condition.

### 3.1.2 Surface Laplacian

Typically, biopotentials are recorded with a differential amplifier, where the desired signal appears as a voltage between two input terminals. Differential amplifiers are able to reject the common mode signal from various sources of interference, yielding improved signal quality. A consequence of this recording scheme is that the local potentials are not accurately depicted. The surface Laplacian can provide a more realistic representation of local source distributions compared to conventional bipolar recordings by removing the effects of the reference electrode and eliminating volume conducted signals from distant regions [Nunez and Pilgreen, 1991]. The surface Laplacian has previously been applied for ECG mapping to provide better spatial resolution and resolve depolarizations in different regions of the heart [He and Cohen, 1992]. The surface Laplacian has also been shown to be more robust to ECG and respiratory interference when recording small intestine electrical activity [Garcia-Casado et al., 2013].

The surface Laplacian is the second spatial derivative of the surface potential estimated on the surface of a geometry that passes through the electrode locations. For a voltage $\Phi$ on a planar surface, it is defined by the expression:

$$\nabla^2_s \Phi_s = \frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial^2 \Phi}{\partial y^2}$$

A simple nearest-neighbor method of estimating the surface Laplacian of EEG data
was first published in 1975 by Hjorth [Hjorth, 1975]. This approach used a finite-difference approximation for the second spatial derivative of the scalp potential by averaging potential differences between a central and four surrounding electrode locations. Although there have been many advances since the first paper, the finite-difference approximation is practical and easy to implement.

The original method was improved by including eight electrodes positioned radially with respect to the central electrode position [Hjorth, 1980]. Involving a larger number of electrodes improves the possibility of obtaining a good approximation. Before averaging, the potential difference is divided by the corresponding electrode distance in order to represent the gradient. This is calculated using the following equation:

\[
v_0 = P_0 - 0.15 (P_1 + P_2 + P_3 + P_4) - 0.1 (P_5 + P_6 + P_7 + P_8)
\]

where, \(P_0\) is the potential measured at the central electrode, and \(P_1\) to \(P_8\) are the potentials measured at the radially neighboring electrodes, as seen in Figure 3.1. The weighting coefficient for each of the surrounding electrodes is proportional to the reciprocal of its distance to the center electrode. The method described by Equation 3.3 was used as a pre-processing step before the estimation of wave propagation.
Figure 3.1: Schematic used to illustrate the eight neighboring electrodes that are used to calculate the finite-difference surface Laplacian. The source activity is within a measurement area centered at electrode $P_0$.

### 3.1.3 Wave Estimation

Motivated by a realistic, multi-scale model of EGG [Du et al., 2010], we expected coherent spatial propagation of the surface potential in healthy subjects. We implemented a technique originally developed to compute the 2D component velocity from image sequences [Fleet and Jepson, 1990] to estimate features of stomach wave propagation on the abdominal surface. By using a data-driven approach that evaluates the temporal evolution of constant phase spatial contours, strong underlying assumptions are not made of the spatial properties of the cutaneous potentials.

Here, we provide the framework which forms the basis of the algorithm. The Hilbert transform is first applied to the surface Laplacian estimate at each
electrode location \((x, y)\), resulting in a characterization of instantaneous amplitude \(a(x, y, t)\) and phase \(\varphi(x, y, t)\):

\[
V(x, y, t) + i Hb[V(x, y, t)] = a(x, y, t) e^{i \varphi(x, y, t)}
\]  

(3.4)

In biological signals, contours of constant phase provide a better approximation to the motion field compared to those of constant amplitude, since the amplitude of the signal is proportional to the distance of the recording electrode to the source. Surfaces of constant phase satisfy the equation:

\[
\varphi(x, y, t) = c, \quad c \in \mathbb{R}
\]  

(3.5)

By assuming that the constant phase surfaces move along the motion field, we can differentiate the phase with respect to time using the total derivative:

\[
\frac{d\varphi}{dt} = \nabla \varphi \cdot \mathbf{v} + \frac{\partial \varphi}{\partial t} = 0
\]  

(3.6)

where \(\nabla \varphi\) is the spatial gradient of the instantaneous phase, \(\mathbf{v} = \left(\frac{dx}{dt}, \frac{dy}{dt}\right)\) is the wave velocity, and “\(\cdot\)” represents the dot product operator. Since the phase gradient is parallel to the velocity direction, the speed can be calculated as:

\[
\text{speed} (t) = \| \mathbf{v} (t) \| = \frac{\| \partial \varphi / \partial t \|}{\| \nabla \varphi \|}
\]  

(3.7)

where for any \(z \in \mathbb{R}^n\), \(\| z \|\) represents the 2-norm and \(\overline{\cdot}\) indicates the spatial average (i.e. across all electrodes) at a given time. The wave direction is then computed by:

\[
\text{direction} (t) = \text{ang} \left( \nabla \varphi \right)
\]  

(3.8)
where $\text{ang}(\cdot)$ is the element-wise arc tangent, choosing the quadrant correctly.

A quantity called phase gradient directionality, $\text{PGD}(t)$, is defined as a measure of how well the phase gradients align across the array [Rubino et al., 2006]:

$$\text{PGD}(t) = \frac{\|\nabla \varphi\|}{\|\nabla \varphi\|}$$

(3.9)

PGD can take on values between 0 and 1, where 0 represents phase gradients that are randomly distributed and a value of 1 signifies perfect spatial alignment.

Estimates at time points when the PGD is less than 0.5 are typically ignored, since velocity is only well-defined when phase gradients are coherent across the array [Rubino et al., 2006]. With a small number of sensors, it is possible that the PGD can be greater than 0.5 by chance, even when a spatial wave does not exist. We generated independent, identically distributed (i.i.d.) white Gaussian noise on a 3 by 3 sensor array across time (i.e. no spatial wave present) and eval-
Figure 3.3: (a) Plot of stomach anatomy and electrode configuration used for the forward model. The black circles represent electrodes (5 by 5 array). The blue line corresponds to the location of the 1D serosal solution that is expanded to a 2D mesh to match the stomach geometry. The pacemaker P, corpus C, and antrum A regions of the stomach are labeled. (b) Time snapshots over a 16 second period for the 1D serosal solution are shown. The pulses are generated in the pacemaker P region, have a decreased speed and amplitude in the corpus C followed by an increase of both in the antrum A, and eventually terminate in the pylorus.

uated the false positive rate of the PGD being greater than 0.5 by coincidence. Without an additional minimum duration constraint, up to a 50% of the samples would be considered a wave (see Figure 3.2). By further imposing criteria that the PGD must be above 0.5 for a certain duration of time, the likelihood of false positives can be drastically reduced. We defined a sustained wave as one having a PGD greater than 0.5 for at least 2 seconds, since the false positive rate for noise with this specification is near zero (see Figure 3.2). Values of wave propagation direction and speed in this paper are reported for instances that meet these criteria.
3.2 Experimental Methods

3.2.1 Model

A forward electrophysiology model of stomach was used to validate the wave estimation methodology. For simplicity, we ignored circumferential propagation of the serosal slow-wave and solved the following 1D wave equation using a finite difference approach:

\[ \frac{\partial^2 u}{\partial t^2} = c(x)^2 \frac{\partial^2 u}{\partial x^2} \]  

(3.10)

where \( c(x) \) is the wave speed that depends on the location on the stomach surface. Gaussian pulses with a width of 35 mm were generated every 20 seconds (0.05 Hz) in the pacemaker region of the stomach, as illustrated in Figure 3.3. The pulse width, in addition to the modulations of its speed and amplitude along the organoaxial direction of the stomach, were chosen to be consistent with the most recent description in the literature for healthy subjects [O'Grady et al., 2010]. Both the speed and amplitude were highest in the pacemaker region (6.0 mm/s, 0.57 mV), followed by a reduction in the corpus (3.0 mm/s, 0.25 mV), and finally increased in the antrum (5.9 mm/s, 0.52 mV). Mur’s boundary condition was used to ensure the pulses were absorbed into the pylorus rather than being reflected into the stomach. The Courant-Friedrichs-Lewy condition dictated the temporal step-size to guarantee a converged finite-difference solution. We expanded the 1D serosal solution onto a 2D mesh to match a realistic geometry of the stomach, using anatomical and physiological parameters described previously (see Figure 3.3) [Pal
The cutaneous potentials are essentially a weighted summation of the serosal slow-wave at every time point. Due to the electrical properties of physiological systems, a quasi-static assumption can be made even though the sources are time-varying [Plonsey, 1969]. By further assuming a volume that is linear, homogenous, and isotropic, the potential $\varphi$ at a field point $(x', y', z')$ due to a volume current source density $I_v(x, y, z)$ is given by [Liang and Chen, 1997]:

$$
\varphi(x', y', z') = \frac{1}{4\pi \tilde{\sigma}} \int_{V} \frac{I_v(x, y, z)}{r} dv
$$

(3.11)

where, $\tilde{\sigma}$ is the conductivity and $r$ is the Euclidean distance between the source point and the field point. The primed variables refer to the points on the abdominal skin while the unprimed variables correspond to those on the stomach surface. We chose a conductivity of 0.125 S/m, which is halfway between the mean conductivities of fat and the human trunk [Plonsey, 1969], the two primary constituents separating the stomach and skin. The distance $r$ depends on the stomach size and abdominal thickness, which was chosen to be 4 cm. The simulated cutaneous potentials were computed at locations that matched our experimental electrode layout (5 by 5 grid, 2 cm center-to-center electrode distance, 95 mm$^2$ electrode measurement area). Figure 3.3 depicts the stomach anatomy and its relation to the electrode configuration used in the forward model.
Figure 3.4: Depiction of electrode configuration on the abdominal surface. Electrodes are disposable pre-gelled Ag-AgCl electrodes with $95 \text{ mm}^2$ measurement area and $2 \text{ cm}$ spacing. The middle of the array is the reference and the ground electrode on the right hip.

3.2.2 Experimental Protocol

Ethical approval for this work was obtained from the institutional review board at the University of California, San Diego. Eight healthy subjects (5 male, 3 female, age = $26 \pm 4$ years, BMI = $22 \pm 3$) without gastrointestinal symptoms or discomfort participated in the study. Subjects were asked to fast overnight prior to the recording. Any excess abdominal hair was removed and the skin was prepped with NuPrep® to reduce electrode contact impedance. Conventional pre-gelled Ag-AgCl electrodes with a $95 \text{ mm}^2$ measurement area were placed on the abdominal surface using anatomical landmarks for consistency between subjects. The array was horizontally centered on the subject’s midline and the top row was positioned $5 \text{ cm}$ below the xiphoid. The electrodes were arranged in a $5 \times 5$ square grid with a $2 \text{ cm}$ center-to-center electrode distance, as seen in Figure 3.4.
The middle electrode of the array was assigned as the reference and the ground electrode was placed on the right hip bone. The BrainProducts BrainAmp 32ch EEG amplifier was used to acquire the signals at a sampling rate of 250 Hz. The test meal was a 250-kcal nutrient bar (CLIF Bar®: 5g fat, 45g carbohydrate, 10g protein, 7g fiber) along with 8 ounces of room temperature water. The duration of the recording was 30 minutes pre-prandial and 60 minutes post-prandial. The subjects sat in a comfortable recliner angled at 45 degrees and were asked to limit talking and bodily movement throughout the recording.

3.2.3 Data Preprocessing

Prior to wave estimation, the signals recorded from each electrode were down-sampled to 5 Hz and then bidirectionally filtered to avoid phase distortion using a finite impulse response band-pass filter with pass-band frequencies between 0.015 and 0.15 Hz. The surface Laplacian was then calculated at each interior electrode location using Equation 3.3.

3.3 Results

3.3.1 Simulated Data

To determine if the surface Laplacian method alters the estimates of direction and speed, we generated signals using a forward model with known parameters,
Figure 3.5: Results from a 60 second simulation of cutaneous potentials from the forward model on a 5 by 5 array. (a) The voltage from three channels with a dotted black line illustrating wave propagation. (b) Estimate of wave direction (mean: 187 degrees) and (c) speed (mean: 5.3 mm/s). (d) The PGD is above 0.9 throughout the simulation.
as described in Section III. The signals were subtracted from the center electrode
to replicate the use of a reference electrode in the experimental recording. The
surface Laplacian was then calculated and the output was used to verify that the
wave-estimation algorithm can estimate the correct direction and speed.

The simulation results are shown in Figure 3.5. The voltages from three
select simulated electrode sites from the horizontal axis illustrates the wave prop-
agation across the array. The wave estimation algorithm outputs direction, speed,
and PGD for every time point in the simulation, which is also displayed in Figure
3.5. The average estimated direction (187 degrees) and speed (5.3 mm/s) match
the model parameters. PGD is greater than 0.9 for all the time points, indicating
phase gradients with near perfect spatial alignment.

3.3.2 Experimental Data

By generating a series of time snapshots, a sample wave can be visualized
(Figure 3.6). In the time window shown, the wave originated on the right side of the
array and propagated slowly to the left at a speed of approximately 4 mm/s. The
snapshots display local potentials as calculated by the surface Laplacian, which
are spatially interpolated for better visualization. The amplitude of the signal was
about 100 $\mu V$, as indicated by the color bar.

A two-minute segment of the surface Laplacian time series from three elec-
Figure 3.6: Individual time snapshots of the voltages for a 20 second segment from Subject 1. Voltage is presented in white-blue color (blue representing positive voltage) and time (in seconds) is labeled above each plot. The snapshots are interpolated for visualization purposes. This particular wave took approximately 20 seconds to propagate across the array at about 180 degrees relative to the positive x-axis.

trodes parallel to the wave propagation direction is displayed in Figure 3.7. A phase delay between the electrodes that is characteristic of wave propagation is indicated by a black dotted line. The output of the wave estimation algorithm is also displayed with a shared time axis. The instantaneous wave direction and speed estimates for sustained waves are displayed in blue, while time points not meeting the sustained wave criteria are red. Sustained waves are defined as having a PGD greater than 0.5 for at least 2 consecutive seconds. The waves in this two-minute window have a bearing of 180 degrees relative to the positive x-axis at a speed of about 4 mm/s. Time-points between subsequent slow-waves typically had lower PGD values and did not meet the sustained wave criteria, indicated by the red dots approximately every 20 seconds in Figure 3.7. The data used to visualize
Figure 3.7: (a) Voltages of three channels from a 120 second segment of data from Subject 1 data. Wave propagation observed by the phase delay between the channels is depicted by the black diagonal dotted line. A plot is shown of the (b) direction, (c) speed, and (d) PGD as computed by the wave estimation algorithm at every time point. A PGD threshold is used to detect sustained waves (above 0.5 for at least 2 seconds). Blue indicates a sustained wave while red is used for points that do not meet the criteria.
Figure 3.8: PGD as a function of frequency for the band-pass filtered data (bandwidth 0.04 Hz) from Subject 1. The star indicates the maximum PGD, which is at 0.05 Hz.

the wave propagation in Figure 3.6 corresponds to the data from the 30-50 second interval in Figure 3.7. Note that the start and end of a representative slow-wave is observed at about 30 and 50 seconds, respectively.

To quantitatively confirm that the gastric electrophysiology was the source for the coordinated spatial activity, we computed the mean PGD as a function of frequency, as shown in Figure 3.8. The plot was constructed by calculating the average PGD for the dataset after applying various band-pass filters (bandwidth = 0.04 Hz) that swept through a frequency range from 0.02 to 0.17 Hz. The peak PGD value in this case occurred at 0.05 Hz, which corresponds to the normal stomach slow-wave frequency [Parkman et al., 2003].

Histograms of wave direction, speed, and PGD reveal overall distributions of the wave propagation parameters for the entire recording (Figure 3.9). Only
time points of direction and speed during sustained waves were used to generate the histograms. For this particular subject, the waves propagated at 186 ± 27 degrees (subject’s left to right) and 3.2 ± 0.9 mm/s throughout the recording. An average phase map was also computed for sustained waves by spatially unwrapping the phase at each time point and then subtracting the phase value of a reference electrode at that time prior to averaging (Figure 3.9b). The white arrow shows the direction of propagation, which is along the negative phase gradient. Figure 3.9c and Figure 3.9d capture the variability in the wave parameters throughout the recording.

Wave propagation was observed in all eight of the subjects. Summary statistics for the various wave parameters are shown in Table 3.1. The mean wave direction and speed for all the subjects were 181 ± 29 degrees and 3.7 ± 0.5 mm/s, respectively. On average, 41% of the time points met the sustained wave criteria. There were no statistically significant differences in slow-wave propagation between male and female subjects. To quantify that the observed wave phenomena were not be generated by noise, we designed the test statistic as the fraction of time that the PGD is greater than 0.5 for 2 seconds or longer. With generation of i.i.d. white Gaussian noise, we used a non-parametric bootstrapping method to develop the distribution of the test statistic under the null hypothesis. Examples of the false positive rate of i.i.d. white Gaussian noise are shown in Figure 3.2. With this, we calculated a p-value using the histogram from the bootstrap, which was
Figure 3.9: (a) A histogram of the PGD values from every time point throughout the recording for Subject 1. (b) The mean phase map, computed using the instantaneous phase for time points meeting the sustained wave criteria. The white arrow indicates the propagation direction of the waves based on the direction of the negative phase gradient. (c) Polar histogram showing the estimated direction of propagation for sustained waves. (d) Histogram of the estimated speed for sustained waves.
Table 3.1: Wave propagation and EGG parameters across subjects

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>GENDER</th>
<th>WAVE DIRECTION (DEG)</th>
<th>WAVE SPEED (MM/S)</th>
<th>SUSTAINED WAVE (%)</th>
<th>% 2-4 CPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>186 ± 27</td>
<td>3.2 ± 0.9</td>
<td>53*</td>
<td>99.4</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>156 ± 29</td>
<td>4.8 ± 1.6</td>
<td>57*</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>185 ± 40</td>
<td>3.4 ± 1.3</td>
<td>43*</td>
<td>98.9</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>173 ± 35</td>
<td>3.6 ± 1.4</td>
<td>32*</td>
<td>98.9</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>182 ± 48</td>
<td>3.8 ± 1.6</td>
<td>34*</td>
<td>96.6</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>131 ± 48</td>
<td>3.2 ± 1.3</td>
<td>33*</td>
<td>96.6</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>224 ± 44</td>
<td>4.0 ± 1.3</td>
<td>36*</td>
<td>98.9</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>211 ± 35</td>
<td>3.9 ± 1.4</td>
<td>36*</td>
<td>100</td>
</tr>
<tr>
<td>MEAN</td>
<td></td>
<td>181 ± 29</td>
<td>3.7 ± 0.5</td>
<td>41 ± 10</td>
<td>98.7 ± 1.4</td>
</tr>
</tbody>
</table>

* p-value < 10^{-4}

less than 10^{-4} for all subjects.

A commonly reported EGG metric, the percent of 2-4 cycles/minute activity, is also shown in Table 3.1. This value was calculated by generating a spectrogram (4 minute windows, 75% overlap) using the short-time Fourier transform of a single bipolar channel with the strongest gastric signal for each subject, and evaluating the percentage of time the dominant frequency was within the 2-4 cpm range. A value over 70% is indicative of a normal EGG, and all the subjects were above 95%.

3.4 Discussion

The optimal number and layout of the electrodes remains an open question that deserves further attention. We note that strict application of the Nyquist criterion requires a priori knowledge of the spatial spectra along with the source
distributions. Such information is not generally available, in part because knowledge of an adequate number of electrodes for the gastric signal would first require oversampling of the potential distribution to determine the highest spatial frequencies present in the data.

There may be concern that propagation of the potential from the source to the electrode may lead to phase delays that distort the estimated wave parameters. It has been shown that a quasi-static assumption can be made to describe the potential field in the human body [Plonsey, 1969]. Since the capacitive component of the tissue impedance is negligible in the frequency range of internal bioelectric events, electromagnetic propagation effects can be neglected. This allows us to make true gastric slow-wave speed estimates.

The surface Laplacian is critical in resolving the reference issue and yielding local potentials that can be used to estimate wave propagation. The signal recorded at an electrode position is a spatial average of the active current sources within the volume. The signal depends on several factors, including the volume geometry and conduction properties, as well as the location of the reference electrode. Each current source contributes to the signal based on its orientation, strength and electrical distance to the electrode. Two nearby electrodes record similar signals since they record the average activity in overlapping volumes of tissue. The surface Laplacian effectively reduces the volume that each electrode averages, culminating in improved spatial resolution [Nunez and Pilgreen, 1991]. The surface Laplacian emphasizes superficial localized sources, while suppressing deep sources along with
shallow sources that are widespread and coherent. This property allows us to detect accurate gastric slow-wave propagation from the abdominal surface.

In this chapter, we calculated the surface Laplacian using a finite-difference approach. Other surface Laplacian estimation methods have been developed for the brain that fit surface potential maps to spline functions [Perrin et al., 1987] and incorporate more realistic scalp surfaces using MRI [Babiloni et al., 1996]. We investigated the use of more sophisticated surface spline Laplacian derivations, but did not observe any significant differences in the wave estimation parameters. Unlike the scalp, our electrode configuration for the stomach is fairly planar and therefore the finite-difference method was chosen for its simplicity.

Although our forward model had simulation parameters such as propagation speed and electrode location chosen to mimic the physiology and experimental recordings, it had several simplifying assumptions. In particular, we applied a 2D approximation of the stomach geometry and did not incorporate the ionic components of smooth muscle cells and the interstitial cells of Cajal. Nonetheless, our findings verify that the wave speed and direction can be accurately estimated, and that the surface Laplacian does not distort the estimation of wave parameters.

It is well established that the normal gastric slow-wave frequency in humans is between 0.04 and 0.06 Hz [Parkman et al., 2003]. Selectively band-pass filtering the signal to narrow 0.04 Hz bands and sweeping across frequencies enabled us to confirm that the peak wave detection occurred at 0.05 Hz. The average PGD was used as a metric to identify when waves were present, since a higher PGD indicates
the presence of waves. The peak of the PGD spectrum occurred near 0.05 Hz for all subjects, confirming that the stomach was the source of the detected wave propagation described in this chapter.

Gastric contractions are initiated and coordinated by slow-wave activity, and the results from this study generally agree with existing descriptions of human gastric motility. MRI studies of contraction wave propagation in healthy stomachs have demonstrated a contractile displacement rate between 1.8-2.7 mm/s [Kwiatek et al., 2006, Schulze, 2006, Marciani, 2011]. Using invasive serosal electrical measurements, O’Grady et al. observed a mean slow-wave propagation speed of 8.0 mm/s in the pacemaker region, a drop to 3.0 mm/s in the corpus, followed by an increase to 5.7 mm/s in the antrum for normal subjects [O’Grady et al., 2010]. The average speed recorded in our study was 3.7 ± 0.5 mm/s. The variability for each subject can be seen Table 3.1, with the distribution for a representative recording shown in Figure 3.9d. These results suggest that the HR-EGG reflects slow-wave activity in both the corpus and antrum, which is where most spatial abnormalities have been detected during invasive recordings [O’Grady et al., 2012, Angeli et al., 2015]. Higher gastric slow-wave speeds of 7.4 mm/s were reported in a recent MGG study for normal subjects [Bradshaw et al., 2016]. Further investigations are required to resolve the differences between these modalities.

An important consideration is that the stomach is a three-dimensional organ, and its angle of elevation relative to the plane of the electrode array may skew the results. Also, no obese (BMI > 30) subjects participated in this study. It is
possible that a significant amount of fat tissue separating the stomach and electrodes will present a challenge in detecting wave propagation. A future study that includes imaging and/or modeling is required to determine how an individual’s stomach and torso anatomy affects the speed estimated from electrodes placed on the abdominal surface.

The slow-wave direction estimates in our study were consistent with the expected stomach orientation. Although there is a considerable amount of inter-subject variability, the stomach typically lies in the left superior quadrant, terminates across the median line and can descend below the plane of the umbilicus [Netter, 2010]. The average gastric slow-wave direction for our subjects was $181 \pm 29$ degrees, consistent with the aforementioned anatomical description. Nonetheless, a study with stomach localization relative to the electrodes can more quantitatively confirm that our direction estimates align with the principal stomach axis in normal subjects.

The slow-wave propagation was detected in both the fasting and post-prandial states for all the subjects in our study. There were no significant differences in the speed and direction of the waves in the two states. We chose a 250-kcal nutrient bar along with eight ounces of water since that is similar to the standardized meal given with tests of gastric motor function. Further investigation is necessary to determine the consequence of test meals with different volume and composition on wave propagation parameters.

Traditional EGG spectral analysis relies on using large windows of the
recording (typically 4 minutes), due to the slow nature of the signal. This can be limiting, since gastric electrophysiological abnormalities may occur at a shorter time scale. Estimating the wave properties at every time sample, as shown in Figure 3.7, allows for the detection of instantaneous episodes of abnormalities. Moreover, the methodology described in this chapter is fully automated and not susceptible to human bias. The summary statistics for wave direction, wave speed and PGD in Table 3.1 demonstrate that the HR-EGG can be used to estimate the gastric slow-waves properties for normal subjects. Statistical signal processing, including state space models, can be used in the future to describe the dynamics of wave propagation across time.

3.5 Acknowledgements

Chapter 3, in full, is a reprint of the material as it appears in IEEE Transaction on Biomedical Engineering 2017. Gharibans, Armen; Sanggyun, Kim; Kunkel, David; Coleman, Todd, IEEE, 2017. The dissertation author was the primary investigator and author of this paper.
Chapter 4

Robust Ambulatory Monitoring of Gastric Myoelectrical Activity

There is a need for reliable, non-invasive systems and methods to accurately measure GI function outside of the hospital or clinical setting. Studies have shown that ambulatory manometry recordings are superior to stationary manometry, because they allow for improved detection of inter-digestive abnormalities as well as assessment of the relationship between abnormalities and transient symptoms during typical physiological conditions [Jebbink et al., 1995, Bortolotti et al., 2000]. Moreover, it is common for patients to experience white coat syndrome, characterized by the increased level of anxiety experienced with being in the clinic [Middeke and Lemmer, 1996], especially in the presence of a physician or nurse [Mancia et al., 1987]. This is particularly problematic for GI measurements, since GI activity is affected by the sympathetic/parasympathetic balance in the body.
[Geeraerts et al., 2005, Homma, 2006]. Although ambulatory manometry recordings are possible, a recent study showed most patients have a strong preference for noninvasive testing over manometry [Mugie et al., 2013].

GI smooth muscle contractions are initiated and coordinated by underlying, rhythmic bioelectrical events, termed slow-waves. In humans, the slow-wave is generated by the stomach three times per minute (0.05 Hz) and propagates along the stomach's longitudinal axis towards the small intestines. This results in a ring-like smooth muscle contraction wave (i.e. peristalsis) that physically breaks down food and propels it down the GI tract. These events have been recorded noninvasively using skin-mounted electrodes, called the electrogastrogram (EGG) [Abell and Malagelada, 1988, Chen and McCallum, 1991, Riezzo et al., 2013]. The EGG has not seen widespread clinical adoption due to its poor correlation with gastric emptying tests, manometry, and diagnosed disease status, in part because results are found to be inconsistent and suffer from poor signal quality [Verhagen et al., 1999b]. Motion artifacts in the EGG signal are especially problematic, giving rise to high exclusion rates even in non-ambulatory patients [Abid and Lindberg, 2007]. Another limitation of EGG is that data is typically binned into several-minute windows for spectral analysis of slow-waves, and so artifacts have an amplified impact by rendering large time periods uninformative [Verhagen et al., 1999b]. Previous attempts of ambulatory EGG recordings reported problems with significant interference in the signal from typical movements throughout the day [Lindberg et al., 1996, Hocke et al., 2001].
Biopotentials recorded from the body surface including the EGG or electroencephalogram (EEG) are relatively weak, generally within the range of 50-200 $\mu$V. Therefore, the signals must be significantly amplified, which makes them susceptible to noise and artifacts superimposed on the signals of interest. Artifacts can be broadly divided in two classes: stereotyped and non-stereotyped [Onton et al., 2006]. Stereotyped artifacts in the EEG generally arise from eye movements, eye blinks, and the ECG from the heart, which have stereotyped projections onto the electrodes (i.e. their origin remains in the same location in the body). Non-stereotyped artifacts can originate from motion of the electrode, the cable (deformations of the cable insulation act as a piezoelectric movement transducer), and changes at the electrode-skin interface (skin potentials change with pressure on the skin), as well as large muscle movement [Webster, 1977].

There is a large body of work aimed at removing artifacts from the EEG, with independent component analysis (ICA) being one of the popular approaches [Urigüen and Garcia-Zapirain, 2015]. The location of the electrodes on the torso along with the low-frequency of the EGG signal creates unique challenges compared to the EEG. While stereotyped artifacts dominate the EEG, the EGG consists mainly of non-stereotyped artifacts. Analog or digital filters (e.g. band-pass and low-pass filters) can be used to remove most stereotyped artifacts from the EGG, since they occur at higher frequencies. Motion artifacts, though, can span across all frequencies, and cannot be completely removed by filtering alone. Also, ICA cannot successfully remove non-stereotyped artifacts, because they introduce var-
ious unique spatial patterns into the data that compromises ICA decompositions [Onton et al., 2006]. In practice, these types of artifacts are manually removed prior to ICA analysis [Delorme et al., 2007, Mognon et al., 2011], but such manual intervention limits the number of subjects and duration of use for which these techniques can be employed.

Here, we present a fully automated and computationally efficient statistical approach for removing artifacts from the EGG signal. This enables robust ambulatory EGG recordings of arbitrary duration, which can be assessed in real-time, without incurring deletion of data. We validate the approach using simultaneously recorded manometry recordings and demonstrate an ambulatory EGG system, with which we are able to describe gastric dynamics not previously seen.

4.1 Methods

4.1.1 Artifact Rejection Methodology

The Linear Minimum Mean Squared Error (LMMSE) Estimator

Suppose we have the following measurement $y$:

$$ y = x + n $$

(4.1)

where $x$ is the underlying signal of interest and $n$ is zero-mean white Gaussian noise. The goal is to estimate $\hat{x}$ given $y$. The minimum mean squared error
(MMSE) estimate of $x$ given $y$ is given by:

$$g(y) = E[x|y]$$  \hspace{1cm} (4.2)

In practice, this may be difficult to compute, because $g(y)$ could have a complicated form and $f_{x|y}(y)$ might be difficult to calculate. Instead, we can use a simpler function $g(y)$ to estimate $\hat{x}$, for example a linear function of $y$:

$$\hat{x}_L = g(y) = ay + b$$  \hspace{1cm} (4.3)

We then want to minimize the mean squared error:

$$\min \ E[(x - \hat{x}_L)^2]$$  \hspace{1cm} (4.4)

and the resulting estimator is called the linear MMSE estimator.

The optimization problem can be written as the following:

$$\min_{a,b} \ E[(x - ay - b)^2]$$  \hspace{1cm} (4.5)

We can expand the objective function:

$$f(a, b) = E[(x - ay - b)^2]$$

$$= E[x^2 + a^2y^2 + b^2 - 2axy - 2bx + 2by]$$  \hspace{1cm} (4.6)

$$= E[x^2] + a^2E[y^2] + b^2 - 2aE[xy] - 2bE[x] + 2abE[y]$$

This is a convex optimization problem since it is a quadratic function of $a$ and $b$. Therefore, there exists a global minimum and we can simply take the derivatives with respect to $a$ and $b$ and set them equal to zero to find the optimal $a^*$ and $b^*$.
that minimize the function.

\[
\begin{align*}
\frac{\partial f(a, b)}{\partial a} &= 2aE[y^2] - 2E[xy] + 2bE[y] = 0 \\
\frac{\partial f(a, b)}{\partial b} &= 2b - 2E[x] + 2aE[y] = 0
\end{align*}
\] (4.7)

\[
\begin{align*}
aE[y^2] + bE[y] &= E[xy] \\
aE[y] + b &= E[x]
\end{align*}
\] (4.8)

\[
b^* = E[x] - aE[y]
\] (4.9)

\[
a^* = \frac{E[xy] - E[x]E[y]}{E[y^2] - E[y]^2} = \frac{\text{Cov}(x, y)}{\text{Var}(y)}
\] (4.10)

The following property was used to simplify the numerator of \(a^*\):

\[
\text{Cov}(x, y) = E[(x) - E[x])(y - E[y])] = E[xy] - xE[y] - E[x]y + E[x]E[y]
\] (4.11)

\[
\]

The following property was used to simplify the denominator of \(a^*\):

\[
\] (4.12)

\[
\]
We can then plug in $a^*$ and $b^*$ to evaluate the estimate $\hat{x}_L$:

$$\hat{x}_L = a^*y + b^*$$

$$= \frac{\text{Cov}(x,y)}{\text{Var}(y)}y + \mathbb{E}[x] - \frac{\text{Cov}(x,y)}{\text{Var}(y)}\mathbb{E}[y]$$

$$= \mathbb{E}[x] + \left(\frac{\text{Cov}(x,y)}{\text{Var}(y)}\right)(y - \mathbb{E}[y]) \quad (4.13)$$

Equation 4.13 is the solution to the LMMSE estimator.

**Using the LMMSE Estimator to Remove Artifacts from the EGG**

Since the artifacts typically have much higher amplitude compared to the EGG (50-200 $\mu$V), we can use the LMMSE filter to estimate the artifacts in the signal, and subsequently subtract it from the observed data to extract only the EGG component in the signal. In our recordings, the EGG signal, artifact, and noise characteristics are non-stationary (i.e., they vary significantly throughout the recording). In order to accurately estimate the artifacts, we can adapt the processing to the local characteristics of the data by using relevant information in the neighborhood region centered around that time point. A similar approach has been previously proposed for image processing, where the filter is adapted at each pixel [Lee, 1980].

We can formulate the problem as follows:

$$y = x + e \quad (4.14)$$

where, $y$ is the observed signal, $x$ is the artifact, and $e$ is the EGG signal. Within
a window of size \( n \) samples the local mean and variance of \( y \) can be computed:

\[
E[y]_i = \frac{1}{2n+1} \sum_{k=i-n}^{i+n} y_k \quad (4.15)
\]

\[
\text{Var}(y)_i = \frac{1}{2n+1} \sum_{k=i-n}^{i+n} (y_k - E[y]_i)^2 \quad (4.16)
\]

By choosing \( n \) to be the average EGG cycle duration (i.e. inverse of the average EGG frequency), we can assume the following:

\[
E[e] = 0 \quad (4.17)
\]

\[
\text{Var}(e) = \sigma_e^2 \quad (4.18)
\]

Now, we can apply the LMMSE estimator derived above:

\[
\hat{x} = E[x] + \left( \frac{\text{Cov}(x,y)}{\text{Var}(y)} \right) (y - E[y]) \quad (4.19)
\]

For our problem,

\[
E[y] = E[x] \quad (4.20)
\]

\[
\text{Cov}(x, y) = \text{Cov}(x, x + e)
\]

\[= \text{Cov}(x, x) + \text{Cov}(x, e) \quad (4.21)\]

\[= \text{Var}(x) \]

The following property was used in Eq. 4.21:

\[
\text{Cov}(x, x + e) = E[(x - E[x])(x + e - E[x] + e - E[e])]
\]

\[= E[(x - E[x])(x - E[x] + e - E[e])]
\]

\[= E[(x - E[x])^2] + E[(x - E(x))(e - E[e])]
\]

\[= \text{Cov}(x, x) + \text{Cov}(x, e) \quad (4.22)\]
Therefore, the LMMSE estimator for the artifacts in our signal becomes:

\[
\hat{x} = E[x] + \frac{\text{Cov}(x, y)}{\text{Var}(y)} (y - E[y]) \\
= E[y] + \frac{\text{Var}(x)}{\text{Var}(y)} (y - E[y]) \\
= E[y] + \frac{\text{Var}(y) - \sigma^2_e}{\text{Var}(y)} (y - E[y])
\] (4.23)

Because the variance of the observation is the sum of the variances of the artifact and the EGG, both non-negative, the variance of the recorded signal should be greater than or equal to the EGG variance. In certain windows of the real data, the local variance can have a calculated value less than the EGG variance. When this happens, the local variance is set to \(\sigma^2_e\). In other words, the local variance is expressed more precisely as:

\[
\text{Var}(y) = \max \{\text{Var}(y), \sigma^2_e\}
\] (4.24)

The value of \(\sigma^2_e\) is not exactly known, so a slight variant of the LMMSE estimator can be used:

\[
\hat{x} = E[y] + \max \{0, \text{Var}(y) - \sigma^2_e\} \max \{\text{Var}(y), \sigma^2_e\} (y - E[y])
\] (4.25)

where \(\sigma^2_e\) is calculated by taking the mean of all values of the local variance of \(y\) over the entire time series.

In practice, the LMMSE estimator filters out EGG in regions without artifact and leaves the data unchanged in the vicinity of artifacts. The artifacts can then be simply removed from the raw data as follows:

\[
e = y - \hat{x}
\] (4.26)
4.1.2 Simultaneous Manometry and EGG Recordings

Manometry was used to record GI contractions by measuring pressure at several points inside the stomach in ten subjects (age: 7-15 years, gender: 3M/7F). All subjects had a healthy enteric nervous system, characterized by having at least one Phase III migrating motor complex during fasting. Manometry was performed with a flexible catheter comprising of eight water-perfused channels, with four channels (1 cm spacing) positioned in the antrum of the stomach and one in the pylorus (see Figure 4.1a). The recording duration was between six to eight hours, with at least four hours of fasting followed by two hours postprandial. Multichannel EGG was simultaneously recorded with a five-by-five array of skin-mounted electrodes positioned over the stomach during the manometry study. The radio-opaque markers on the manometry catheter at the pressure measurement sites were used to confirm appropriate placement of the EGG electrode array (see Figure 4.1b).

The EGG was recorded at a sampling rate of 250 Hz and downsampled to 5 Hz prior to artifact removal and analysis in order to speed up computational time. Although one of the electrodes was chosen as the reference during the recording, the channels can be re-reference after the recording to any of the other channels by simple subtraction of the time-series. A spectrogram with four minute windows and 75% overlap was computed from every pair of measurement electrodes, and the pair with the highest signal-to-noise ratio was correlated with the manometry channels.
Figure 4.1: (a) Outline of the stomach depicting the placement of the manometry catheter. The red dots indicate the locations where the pressure is measured. (b) An x-ray image showing the position of the EGG electrode array relative to the manometry channels.

Signal-to-noise ratio was defined as the average power between 0.04 and 0.06 Hz divided by the average power between 0.06 and 0.15 Hz. The motility index, a measure of contractile activity, was calculated from the manometry recording for four minute windows with 75% overlap to match the EGG spectral analysis. Motility index was defined as the natural logarithm of the area under manometric pressure peaks above a threshold pressure of 9 mm Hg [Parkman et al., 1998].

4.1.3 Ambulatory EGG Recordings

We have developed a system that is capable of robustly recording the EGG activity in an ambulatory (i.e. unrestricted) setting. Figure 4.2 illustrates the components of the system, which includes the hardware, electrodes, and smartphone application. The hardware consists of a low noise, eight channel biopotential am-
plifier with a 24-bit analog to digital converter (Texas Instruments ADS1299), microSD card slot for local storage of data for offline analysis, and an accelerometer for tracking subject movement. The battery and microSD card capacities can be chosen to satisfy the duration requirements of the recording. In our tests, a 3.7V 1800mAh battery provided power for at least 24 hours.

![Diagram of wearable system](image)

**Figure 4.2:** A wearable system including (a) hardware and skin-mounted electrodes, and (b) a smartphone application for logging events, which enables (c) recording of the gastric electrical activity outside of the clinic.

Up to eight electrodes with a common reference and ground can be spatially arranged in any configuration on the torso and connected to the board. The
shortest possible electrode cable length (10 cm) was used to limit motion artifacts from cable movement. Off-the-shelf Ag-AgCl electrodes that are typically used for long-term monitoring in cardiology are also appropriate to use for ambulatory EGG recordings. A smartphone application was developed to enable the subject to document events or activities that are time-synchronized to the EGG recording. Examples include meals, snacks, bowel movements, sleep, symptoms, etc.

Eight 24-hour ambulatory EGG recordings were carried out on a single healthy adult subject (age = 28, BMI = 22.6) over the course of a 6-month period. The electrodes were arranged in a radial array (5 cm inter-electrode spacing) positioned halfway between the umbilicus and xiphoid process. The reference electrode was placed in the middle of the array and the ground on the subjects left side (see Figure 4.2a). The subject was instructed to conduct routine daily activities and refrain from showering, while logging meals, exercise, bowel movements, and sleep using the smartphone application.

Informed consent was obtained from all subjects who participated in this study. The study protocols and consent documents were approved by the institutional review boards at both the University of California, San Diego and Rady Childrens Hospital, San Diego.
4.2 Results

4.2.1 Effect of Filtering of Artifacts on EGG Data

Motion artifacts are typically manifested in the signal as short bursts of high-amplitude activity. The time-scale of the EGG events are usually longer than the artifact duration (i.e. the period of stomach contractions are 20 seconds, while most artifacts are a few seconds or less). Therefore, instead of deleting windows of data with motion artifact, the artifacts can be suppressed with the LMMSE filter (Figure 4.3). Within these instances, the amplitude of the artifact is typically on the order of mV while the EGG signal lies between 50-200 µV. Consequently, the artifacts result in high broadband power which completely masks the EGG signal. The nature of the broadband effect of the artifacts does not allow for removal using band-pass filters alone, but our subtraction of artifacts from the data using the adaptive filter reveals a clear peak in the frequency domain around 0.05 Hz (red star in Figure 4.3c), which is the peak expected from the EGG signal. Time-series representations of the raw signal (Figure 4.3a) feature artifacts prominently, meeting our expectation from the literature that results are prohibitively noisy without proper processing. After removal of the artifacts, the signal around 0.05 Hz becomes clear in all recordings (Figure 4.3b), rendering further analysis possible.
Figure 4.3: (a) Time-series of raw EGG data with motion artifacts and (b) after artifacts have been removed using the adaptive LMMSE filter. (c) A FFT of both time-series with red star indicating the EGG frequency, which becomes apparent after artifact removal.

4.2.2 Validation of Artifact Filtering by Comparison to Manometry

The power of the signal in the 0.04-0.06 Hz frequency band is representative of the magnitude of the gastric electrical activity [Parkman et al., 2003]. The manometry motility index is a measure of the contractility of the stomach measured from the invasive catheter. In 10 subjects, both invasive manometry probes and non-invasive EGG were recorded simultaneously. Figure 4.4 is an example of the artifact rejection in one of the subjects. The vertical red lines in the spectrogram of the raw data (Figure 4.4a) are the broadband signals from the motion artifacts. After artifact removal, the EGG signal is clearly visible (Figure 4.4b). An overlay of the EGG power and manometry motility index illustrates the similarity in trends recorded by both modalities (Figure 4.4c).
A least-squares regression was computed between the EGG power and the manometry motility index for each channel to evaluate the relationship between the two recordings. We found significant agreement between manometry motility index and gastric electrical activity in all subjects ($r = 0.34 \pm 0.12$; Table 4.1). This correlation increased significantly in all subjects following artifact removal ($r = 0.55 \pm 0.13$, $p = 0.0007$ for comparison of $r$-values pre- and post-filtering; Figure 4.5, Table 4.1), suggesting the 0.05 Hz signal being enhanced by filtration corresponds to biological gastric activity.

![Figure 4.4](image)

**Figure 4.4**: Spectrograms (4 minute windows, 75% overlap) of the (a) raw EGG data and (b) data after removal of artifacts with adaptive LMMSE filter. (c) Overlay of the EGG power between 0.04-0.06Hz and the manometry motility index ($R = 0.64$).

### 4.2.3 Ambulatory EGG Recordings

The method for suppressing artifacts enables the robust recording of gastric electrical activity in an ambulatory setting with a wearable EGG system. We used
Table 4.1: Correlation coefficient between EGG power and manometry motility index for ten subjects before and after EGG artifact removal.

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>AGE (YEARS)</th>
<th>GENDER</th>
<th>RAW DATA R-VALUE</th>
<th>ARTIFACTS REMOVED R-VALUE</th>
<th>ADM CHANNEL</th>
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<td>F</td>
<td>0.53*</td>
<td>0.73*</td>
<td>Pylorus</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>F</td>
<td>0.17</td>
<td>0.66*</td>
<td>Antrum #4</td>
</tr>
<tr>
<td>3</td>
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<td>M</td>
<td>0.27*</td>
<td>0.42*</td>
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<td>0.37*</td>
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</tr>
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<td>0.60*</td>
<td>Pylorus</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>F</td>
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<td>0.71*</td>
<td>Pylorus</td>
</tr>
<tr>
<td>8</td>
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<td>M</td>
<td>0.26*</td>
<td>0.43*</td>
<td>Antrum #2</td>
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<tr>
<td>9</td>
<td>15</td>
<td>M</td>
<td>0.40*</td>
<td>0.57*</td>
<td>Pylorus</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>F</td>
<td>0.49*</td>
<td>0.61*</td>
<td>Pylorus</td>
</tr>
<tr>
<td>MEAN</td>
<td>12 ± 3</td>
<td></td>
<td>0.34 ± 0.12</td>
<td>0.55 ± 0.13</td>
<td></td>
</tr>
</tbody>
</table>

* p < 10\(^{-5}\)

such a system to record continuously for 8 separate 24-hour sessions in a free-living subject (Figure 4.6). Non-invasive recordings of gastric dynamics with this combination of resolution and duration have not previously been feasible. The dominant frequency and power, normalized to background noise, of each EGG throughout the 24 hours from the eight recordings were combined for analysis of average features across the day. We found significant relationships between time of day, time of sleep, and meal times, and extracted peak EGG power (Figure 4.7). Mean EGG frequency across all recordings was higher in the evening than the morning, with a peak around 14:00 (0.0486 Hz) and trough around 02:00 (0.0459 Hz) (p = 3E-5). There was also a different significant effect of time relative to sleep-onset (Figure 4.7b) on gastric frequency. Finally, we found a postprandial change in power of the EGG. We assessed only isolated meals (n = 6), defined as meals that occurred after at least 5 hours of fasting along with no other reported
postprandial events for at least 5 hours. The EGG power showed a significant
effect of time-from-meal-completion (Figure 4.7c, vertical gray line). The pattern
takes 3-4 hours from meal completion to return to baseline.

4.3 Discussion

Unlike the ECG, time-domain EGG waveforms are difficult to interpret
since the signals do not have a unique morphology similar to the QRS complex.
Therefore, spectral analysis is an important tool for analyzing EGG data, with
large windows of data required for adequate frequency resolution of the low fre-
quency signal. Even though the artifacts in the signal may be much shorter in
duration than the window used for spectral analysis, the amplitude is typically
Figure 4.6: (a) Spectrogram representation of EGG over a 24hr period after the removal of artifacts. (b) Extracted EGG power from the 0.04-0.06Hz frequency band with event markers. The accelerometer data is plotted in gray.

much larger than the EGG signal. This results in uninterpretable spectral estimates by completely masking the EGG signal within the window.

The approach described in this manuscript for removing artifacts from the EGG signal has several advantages. Small segments of the time-series are processed independently, enabling efficient computation and scalable parallel processing of the data. The adaptive LMSSE filter can be implemented to remove artifacts in real-time, which is useful for applications such as biofeedback. Unlike machine learning approaches, this method does not require vast amounts of labelled training data. Unlike ICA approaches, this method can remove non-stereotyped artifacts from the signal, which is the most common type of artifact in EGG recordings. Finally, segments of the time-series with artifacts are not deleted, which results in more accurate spectral decompositions within the window and preserves the time
Figure 4.7: Data extracted from multiple recordings (n = 8) on a single healthy subject. Mean of the (a) EGG frequency and (b) normalized EGG power from multiple continuous recordings from a single subject throughout a day (n = 8). Average time with the subject asleep in dark gray at top, plus or minus standard deviation (light gray), with average time in wake in white. (c) Pre- and postprandial EGG power response to isolated meals (n = 6). The time of meal completion is indicated by the vertical gray line.
of day necessary to associate with logged events. Although this approach may not
have the mathematical sophistication of other techniques, our experimental results
indicate that it is very effective and computationally efficient tool for removing
artifacts from the EGG.

We expected a correlation between manometry and the EGG because the
smooth muscle contractions in the stomach are initiated by the electrical activity
(i.e. a contraction cannot exist without coordinated electrical activity). Also,
it has been shown that stronger contractions of the stomach lead to increased
amplitude in the EGG [Smout et al., 1980]. Therefore, in a stomach that has
an intact enteric nervous system, the EGG amplitude (a measure of electrical
activity) and manometry pressure amplitude (a measure of contraction strength)
should be correlated. The subjects that were included in the analysis had at least
one migrating motor complex (MMC) during fasting, indicating a well-functioning
enteric nervous system.

Pediatric manometry was used in this case because UC San Diego only has
pediatric manometry at the research site. Motion artifacts appear indistinguishable
in pediatric and adult recordings, so this was not seen as a weakness, nor do we
believe it alters our interpretation of our application of the noise removal techniques
described here. However, it illustrates the point that manometry is sufficiently
rare and difficult to arrange that the scope of its application is severely limited,
demonstrating both a research and clinical need for easier-to-apply alternatives.

There are advantages to using multiple measurement electrodes. Additional
measurement electrodes can provide more spatial sensing coverage of the stomach. When the electrodes are placed further from the stomach, the EGG amplitude decreases due to the attenuation of the signal as it conducts through a longer distance in the body. Since there is a significant amount of anatomical variability between subjects, by adding more sensors to cover a larger surface area, the measurement electrodes at different locations can more accurately record the electrophysiology.

There is, however, a tradeoff with respect to the number of measurement electrodes in some applications. For example, an excess number of measurement electrodes is not desirable because too many electrodes can be obtrusive, cause a subject to feel uncomfortable, and trigger unwanted subject stress that may impact GI activity. For a given target monitoring area, increasing the number of measurement electrodes beyond a certain number may also limit the practical physical size of each electrode so that the size of each electrode should be reduced to provide sufficient spacing between different electrodes. Smaller electrodes have higher impedances relative to larger electrodes and this increased impedance due to reduction in electrode size can lead to an increase in the signal noise. Currently, there is no established standard electrode placement for the EGG, and this is still an active area of research.

Although manometry was used as the gold standard for comparison, the measurements had some limitations. The catheter has four sensors that are typically positioned in the antrum of the stomach, but it sometimes migrated prior to or during the measurement and had to be repositioned. The gastric accommo-
dation due to a meal may also change the location of the sensors relative to the stomach. Though there was a statistically significant correlation between the two modalities in all the subjects, the correlation coefficients would likely further improve with more accurate manometric measurements. There exist high-resolution manometry catheters that address these limitations, which we plan to utilize in future validation studies.

Our observation of a postprandial peak of gastric motility lasting 3-4 hours is consistent with this being a non-invasive observation related to gastric emptying. Gastric emptying is the process by which the stomach empties itself of food content following a meal. Gastric emptying typically takes 3-4 hours from the time of the meal, but at present it can only be measured invasively. Gastric emptying has variability (time of day, meal composition, size), and repeat measures on patients have been unreliable. Our ambulatory system enables us to look at multiple meals across the day without needing to administer repeated doses of radioactive marker to cover longer time spans of observation. Once the relationship between gastric emptying and our stereotyped postprandial arc of gastric mobility has been clearly established, use of the present technique will give us a better understanding of gastric responses to various meals at different times of day, across subjects. This will paint a better picture of the dynamics and produce more reliable results.

Risk for gastric pathologies is substantially increased by circadian disruptions, such as shift work, jet lag, and a lack of stable meal times (e.g. eating at night, or around the clock) [Konturek et al., 2011, Mattson et al., 2014]. Diabetes,
obesity, gastrointestinal cancers, ulcerations, and inflammation all increase under circadian disruptions [Harrington, 2001, Sephton and Spiegel, 2003, Buxton et al., 2012]. While many circadian rhythms are regulated by the brain to match the environmental light/dark cycle, metabolic cues from feeding are sometimes dominant cues to organs involved in digestion. This suggests that a misalignment of timing mechanisms across organs maybe a contributing factor to gastric disease following circadian disruptions. Here we demonstrate with high temporal resolution that time of day, sleep timing, and meal timing all contribute to gastric dynamics within a 24-hour period for a free-living subject. In this study, sleep and circadian rhythms were not systematically desynchronized from each other, but allowed to vary with the sleep habits of the subject. The influence of one cannot be wholly differentiated from the other. Nevertheless, our findings suggest that the approach described here could be used for identifying the component contributions of sleep, meal-timing, and circadian rhythms on healthy and disrupted gastric regulation. It may be possible in the future to detect such disruptions from an individuals profile in real time by non-invasive means. Future efforts in this direction could have substantial value for public health and the prevention of gastric and metabolic diseases associated with circadian disruption.
4.4 Acknowledgements

Chapter 4, in part, is currently being prepared for submission for publication of the material. Gharibans, Armen; Smarr, Benjamin; Kunkel, David; Mousa, Hayat; Coleman, Todd. The dissertation author was the primary investigator and author of this material. We would like to acknowledge Joanne Ly for making Figure 4.2 in this chapter.
Chapter 5

Clinical Studies

5.1 HR-EGG in Gastroparesis

Gastroparesis is an upper GI disorder characterized by delayed stomach emptying in addition to the symptoms presented in functional dyspepsia, and is estimated to effect 4% of the United States population [Abell et al., 2006]. Approximately 30% of its etiology is related to diabetes [Soykan et al., 1998, Rey et al., 2012], which is a costly and under-treated health epidemic with a doubling of its prevalence between 1990 and 2008 in the United States [Geiss et al., 2014]. Also, the overall prevalence of gastroparesis in Parkinsons disease is estimated to exceed 70% and is not routinely diagnosed [Heetun and Quigley, 2012]. In the past decade, hospital admissions for gastroparesis have increased by 150%, posing a substantial healthcare cost [Wang et al., 2008].

The interstitial cells of Cajal (ICCs) generate the gastric myoelectric slow
wave which provides the signal for antral peristalsis. Invasive electrical mapping has revealed that spatial abnormalities of the slow wave are present in subjects with gastroparesis [O’Grady et al., 2012]. Moreover, depletion of the ICC has been identified as the key cellular defect in gastroparesis [Bashashati and McCallum, 2015, Angeli et al., 2015]. The cutaneous high-resolution electrogastrogram (HR-EGG) has been shown to estimate the direction and speed of the gastric slow wave in healthy subjects (see Chapter 3). In this study, we assessed whether the cutaneous HR-EGG can detect spatial gastric dysrhythmias in subjects with well-phenotyped gastroparesis versus controls.

HR-EGG was performed on seven subjects with gastroparesis, who had 30±10% gastric retention at 4-hours on scintigraphy (range 18-49%). Two of the gastroparesis subjects had diabetes, three were idiopathic, one had connective tissue disease, and one was post-viral (age: 59±14 years; BMI: 27±4; 5M/2F). HR-EGG was also performed on ten asymptomatic controls (age: 43±24 years; BMI: 24±6; 7M/3F). All subjects completed the PAGI-SYM questionnaire to evaluate fore-gut symptoms [Rentz et al., 2004]. The HR-EGG was recorded with an array of 25 skin mounted electrodes arranged in a 5 by 5 array with 2cm spacing. Each subject was asked to fast prior to the start of the recording, and the duration of the recording was 30 minutes preprandial and 60 minutes postprandial. A volume reconstruction of the torso and stomach from CT images was performed in the gastroparesis subjects to ensure accurate placement of the electrode array (Figure 5.1a).
The subjects with gastroparesis had a mean Gastroparesis Cardinal Symptom Index (GCSI) score of 1.9±0.8, while the controls had a mean score of 0.1±0.2. The GCSI score is calculated from the PAGI-SYM questionnaire [Revicki et al., 2004]. All gastroparesis and control subjects had a normal single-channel EGG pattern, with 97±5% 2-4 cpm activity and a postprandial increase in amplitude. On the other hand, the HR-EGG analysis revealed spatial abnormalities in terms...
Figure 5.2: Results from healthy subject. (a) The signal-channel spectrogram and (b) power map of 3 cpm activity from the electrode array. Histograms of slow-wave (c) direction and (d) speed.

of direction and speed that discriminated gastroparesis from the controls. The controls had an average speed of 4.4±1.0 mm/s versus 3.3±0.5 mm/s in gastroparesis (p = 0.009). Also, three out of the seven gastroparesis subjects had slow-waves with irregular direction (i.e. not traveling in a consistent direction along the stomach axis) for greater than or equal to 20% of the recording, unlike the controls which were all less than or equal to 15% (5±5 %). An example of a subject with abnormal wave propagation is shown in Figure 5.1 while a representative healthy control is shown in Figure 5.2. The detailed results for the gastroparesis and healthy subjects are presented in Table 5.1 and Table 5.2, respectively.
Table 5.1: Gender, BMI, and age along with HR-EGG, questionnaire, and gastric emptying results for subjects with gastroparesis.

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>GENDER</th>
<th>BMI</th>
<th>AGE</th>
<th>% 2-4 CPM</th>
<th>% ABNORMAL WAVE DIR</th>
<th>SPEED (MM/S)</th>
<th>GCSI SCORE</th>
<th>GES % 4HR</th>
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<td>11</td>
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<td>3.3±0.5</td>
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Table 5.2: Gender, BMI, and age along with HR-EGG and questionnaire results for healthy controls. Gastric emptying results are not available.

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>GENDER</th>
<th>BMI</th>
<th>AGE</th>
<th>% 2-4 CPM</th>
<th>% ABNORMAL WAVE DIR</th>
<th>SPEED (MM/S)</th>
<th>GCSI SCORE</th>
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<td>5±5</td>
<td>4.4±1.0</td>
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</table>

The preliminary results presented here demonstrate that the cutaneous HR-EGG can identify slow-wave spatial abnormalities in gastroparesis. Further testing is necessary to determine if HR-EGG can be used for sub-categorization of gastro-
paresis patients, for example identifying patients who may benefit from targeted therapies on the pylorus or those who have ICC abnormalities.

5.2 Gastric Outlet Obstruction Case Study

Prolonged monitoring has the potential to increase the diagnostic yield of the EGG. Here we sought to characterize the 24-hour EGG findings in a subject with gastric outlet obstruction and compared this to data from asymptomatic controls.

A subject with active gastric outlet obstruction due to pyloric stricture (80% gastric retention at 4 hours measured by scintigraphy) and two asymptomatic controls were enrolled. Six measurement electrodes were placed in a radial circular array on each subject overlying the stomach, with reference electrode in the middle and the ground electrode on subject’s left side. The array was centered halfway between the xiphoid process and umbilicus, and the spacing between measurement electrodes was 5 cm. The EGG was recorded for a 24-hour period with a custom, battery-powered wearable system. Subjects were asked to maintain a log of their eating and sleeping patterns throughout the day and to restrict intense physical activity. A spectral analysis methodology was used that provides a robust estimate of the gastric slow wave frequency and power across time (see Chapter 4 for details).

The subject with gastric outlet obstruction had an abnormally high amplitude gastric slow wave occurring continuously throughout the recording period,
Figure 5.3: Spectrogram plots of the 24-hour EGG for two healthy controls and a subject with gastric outlet obstruction. The EGG signal is contained in the band between 0.04-0.06 Hz and the color represents power level, as indicated by the color bar.

which was a physiologically anticipated result. Figure 5.3 shows the EGG spectrograms for the three subjects and Figure 5.4 plots the extracted EGG power near the 3 cpm (0.05 Hz) frequency for the three subjects over a 24-hour period. The percentage of the recording where the dominant frequency was between 2-4 cpm was 59% for the first control, 59% for the second control, and 85% for the subject with gastric outlet obstruction. Figure 5.5 is a histogram representation of the data, demonstrating that the patient with obstruction exhibited significantly higher sustained EGG power throughout the recording compared to the healthy controls.

The 24-hour multichannel cutaneous EGG is able to clearly identify gas-
Figure 5.4: Extracted EGG power over 24-hour period for control subjects and a subject with gastric outlet obstruction.

tric outlet obstruction in this case study. We speculate that this patient-friendly technology can play a role in identifying non-structural or functional pyloric outlet obstruction subtypes of gastroparesis. The simplicity and noninvasive nature of the test can also enable monitoring post-treatment (e.g. pyloric balloon dilation) to guide treatment and quantify the resolution of the obstruction. Future large studies are necessary to validate our findings.
Figure 5.5: Distribution of EGG power for both controls compared to the subject with gastric outlet obstruction.

5.3 Acknowledgements

Chapters 5, in part, is currently being prepared for submission for publication of the material. Gharibans, Armen; Kunkel, David; Mousa, Hayat; Coleman, Todd. The dissertation author was the primary investigator and author of this material.
Chapter 6

Conclusion

Functional gastrointestinal motility disorders are prevalent in all age groups. Despite the significant personal and socioeconomic costs associated with GI disorders they remain poorly understood [Moayyedi and Mason, 2002], in part due to a lack of appropriate tools for the study of GI dynamics outside the clinic. Most existing tools to assess upper gastrointestinal function are invasive or require radiation. For example, gastric emptying tests measure how quickly the stomach empties by imaging the stomach for several hours after consumption of a radioactively labeled meal. Manometry involves inserting pressure sensors along a catheter to measure the physical contractions of the GI tract and the catheter is typically placed under general anesthesia and guided by a continuous x-ray (i.e. fluoroscopy). Due to the difficulty administering manometry and interpreting its results, it tends to be available through a limited number of skilled gastroenterologists. The invasive nature of these techniques, combined with the time and expertise required for their
application, creates a backlog of patients who sometimes must wait for months to see a GI specialist. In addition, to avoid excessive radiation exposure and to see as many patients as possible, gastroenterologists cannot repeat these procedures to guide therapies and track changes over time.

The EGG is a promising technology for monitoring the GI system noninvasively, but its limitations have hindered widespread clinical adoption. The current techniques do not account for anatomical variability between subjects, cannot detect spatial myoelectric abnormalities, and are difficult to interpret due to the inherently low signal-to-noise ratio and susceptibility to motion artifacts, making prolonged recordings challenging.

In Chapter 3, we outlined a methodology for noninvasive estimation of gastric slow-wave propagation called the HR-EGG. This approach builds on recent findings demonstrating that gastric slow-wave spatial abnormalities can go undetected by traditional single channel recordings. Our proposed technique does not depend on the placement of the reference electrode and is fully automated. For the first time, to our knowledge, we are able to generate estimates of slow-wave propagation direction and speed at each time point using surface electrodes. Improved spatially detailed analysis of propagating gastric myoelectrical events will facilitate better understanding of the pathophysiology of gastric dysrhythmias among patients with motility disorders. This in turn will create opportunities for interventions to reduce gastric dysrhythmic activity and improve symptoms.

In Chapter 4, we presented a system and method for robust ambulatory
monitoring of the EGG signal. There are many advantages and opportunities that noninvasive ambulatory monitoring of gastrointestinal function provides. Recording for longer periods increases the likelihood of recording abnormal myoelectrical events. The ambulatory EGG monitoring is a less expensive alternative to inpatient monitoring, which involves a nursing staff and room. Children can be monitored at home, which reduces stress on both children and parents. Since it is noninvasive, repeat recordings can be easily performed to objectively guide treatment. The wearable monitoring can be scaled to collect data from patients living in distant locations, allowing remote diagnosis and treatment of patients. Capturing many meals and symptomatic events enables assessment of intra-subject variability between days, meals, etc. Finally, the prolonged monitoring allows for research on the implications of circadian and sleep disruptions on GI disorders.

There appears to be a trend towards portable, noninvasive systems to quantify health outside the clinic. Synergistic with this theme, there have been recent developments in demonstrating thin, flexible, and stretchable skin-mounted electronics that can measure a multitude of electrophysiological signals [Kim et al., 2011], as well as developments in improving reliability, latency, and cost associated with the microfabrication procedures needed to build such systems at scale [Kang et al., 2015]. The maturation of these technologies, in parallel with developments in analytical methods such as the HR-EGG and artifact rejection techniques, will enable improved unobtrusive quantification of the state of the gastrointestinal system in health and disease.
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