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Techniques for Quantification and Interpretation of Gastric Slow Wave Activity

Niranchan Paskaranandavadivel
npas004@aucklanduni.ac.nz

Supervised by
Assoc. Prof. Leo K. Cheng
and
Prof. Andrew J. Pullan

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy
in
Engineering

Auckland Bioengineering Institute
The University of Auckland
Auckland, New Zealand
August 2013
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**Nature of contribution by PhD candidate:** Experiment design, collection, analysis and writing of manuscript

**Extent of contribution by PhD candidate (%):** 80%

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**Ch 5: Section 5.1 : The bioelectrical basis and validity of gastrointestinal extracellular slow wave recordings, The Journal of Physiology, 2013**

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<td>Prof. Samuel J. Asirvatham</td>
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The undersigned hereby certify that:

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- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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CO-AUTHORS

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---|---
Prof. John Windsor | Review of manuscript
Prof. Gianrico Farrugia | Review of manuscript
Prof. Andrew Pullan | Review of manuscript
Dr. Leo K. Cheng | Experiment design and review of manuscript

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Professor Andrew Pullan sadly passed away on March 2012.

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Abstract

Rhythmic bio-electrical events known as slow waves coordinate the muscular contractions of the stomach and are essential for physical propulsion and digestion of food. Dysrhythmic slow wave activity is associated with major gastrointestinal (GI) motility disorders, such as gastroparesis, and convey a substantial socio-economic health burden. Unlike the field of electrocardiology, where cardiac bio-electrical signals are routinely used for diagnostic purposes, the bio-electrical activity in the GI tract is not well understood and is not widely used in clinical practice.

In recent years, the advent of extracellular multi-electrode high-resolution (HR) mapping in the GI field has significantly improved experimental and clinical understanding of serosal gastric slow wave activity in normal and dysrhythmic states. One of the current limitations of HR mapping is the inordinate amount of data, making manual analysis a tedious and time-consuming task. More importantly, the use of manual analysis is prone to observer bias and error and could misconstrue experimental observations. Another traditional technique, that has been used since the discovery of bio-electrical events in the GI tract in the 1920s, is the use of extracellular body surface electrogastrograms (EGG). EGG signals are inherently noisy, leading to misleading quantitative estimates of the signal and are currently unable to reliably discriminate against different gastric motility disorders.

The thesis begins by providing a broad overview of the bio-electrical activity present in the stomach and the various cooperating mechanisms that influence gastric motility. Then, the focus is on developing a standardised set of filtering techniques and methods for detecting and visualising slow wave events using HR mapping in an efficient and accurate manner. It was found that inclusion of the
dominant frequency of the slow wave (3–5 cpm) and major harmonics up to 2 Hz are vital for morphological and time based analysis.

Reliable quantitative methods were developed for estimating the velocity and amplitude of the gastric slow wave propagation. The velocity method (FDSM) and amplitude method (derivative based) were compared to currently used methods (FD for velocity and ‘maximum-minimum’ for amplitude) with realistic synthetic propagation patterns and signals. The newly developed FDSM method resulted in half the error of the FD method (Speed error: 12% vs 6%, angle error: 7° vs 3°), while the new amplitude estimation method resulted in a third of the error of the current method (mean error: 44 µV vs 16 µV). These methods allowed for an improved understanding of the gastric slow wave propagation in normal and dysrhythmic states by prescribing a defined quantification for various types of propagation. One of the major findings was that dysrhythmic slow wave propagations were associated with rapid, high amplitude circumferential wavefronts.

The biophysical basis of the slow wave activity was explored with an investigation into normal and abnormal gastric slow wave propagation. In normal slow wave propagation, the activation-recovery interval of the slow wave interval was higher compared to dysrhythmic slow wave propagation (mean: 4.3 s vs 3.3 s), while the activation-activation interval was shorter in normal propagation compared to dysrhythmic slow wave propagation (mean: 16.4 s vs 32.1 s). Thus, with a reduced slow wave interval during dysrhythmic slow wave propagation, it was hypothesised that the potential for spike activity and muscular contraction was reduced, potentially causing gastric motility disorders.

With the framework of processing and quantifying HR mapping firmly established, an automated classification and identification tool was developed, capable of detecting and localising the pacemaker, colliding wavefronts and conduction block sites. The automated classification and classification was on average 96% accurate compared to manual classification and identification. While the manual method took an expert in the field 20–40 minutes to classify and identify the slow wave propagation patterns, the automated methods performed the task almost instantaneously. The inclusion of automated analysis, which can be implemented in
real-time, permits HR mapping to be employed as a routine clinical utility in the GI field.

Automated methods for analysing cutaneous EGG signals were developed that can discard sections of the signals that are corrupted by noise, thereby allowing reliable quantitative estimates of frequency and amplitude. This work was motivated due to the fact that in current clinical practice, the frequency and amplitude of the EGG traces are frequently manually estimated in an expedited manner, which introduces observer bias and error. The first step in the automated approach was to develop filtering techniques to suppress noise, after which, running estimates of frequency and amplitude of the EGG signal were calculated. Then the frequency and amplitude characteristics of the EGG signal were assessed as to whether the EGG signal was corrupted by noise to discard quantitative estimates. The manual versus automated frequency (mean: 3.3 cpm vs 3.4 cpm) and amplitude (mean: 0.143 mV vs 0.144 mV) estimates were in concordance with each other. The automation of estimating the frequency and amplitude of the EGG could validate the usefulness of EGG in routine clinical practice through large scale clinical trials performed in normal patients, and those with gastric motility disorders.

The work presented in this thesis presents a path forward in the GI field to utilise the bio-electrical slow wave signals in a quantitative manner for patient care to prescribe a diagnosis, prognosis and direct treatment strategies accordingly.
“Constant dripping hollows out a stone”

Lucretius
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First and foremost, I would like to thank my supervisors Assoc. Prof. Leo Cheng and the late Prof. Andrew Pullan for their endless dedication, guidance and discussions. Andrew was an instrumental force in setting up the Auckland Bioengineering Institute (ABI) and the gastrointestinal (GI) research group at the ABI, and I am indebted to him for introducing me to the joys and perils of research. I am privileged to be one of his students and his presence will be missed. Leo has been an outstanding supervisor, and I am immensely grateful for his support, patience, supervision and friendship. I have greatly benefited from his research insight, scientific rigour, and engagement of new ideas, which has contributed to a rewarding research experience for me, and I am sure for the whole Auckland GI group as well.

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<td>AAi</td>
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<td>ANalysis Of VAriance</td>
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<td>ARi</td>
<td>Activation-Recovery interval</td>
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<td>Activation Time</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>Direct Current (0 cycles per minute)</td>
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<td>Discreet Wavelet Transform</td>
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<td>EGG</td>
<td>Electrogastrography</td>
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<td>Finite Difference with SMoothing</td>
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<td>Falling Edge Variable Threshold</td>
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<td>Gastrointestinal Electrical Mapping Suite</td>
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<td>Gastrointestinal</td>
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<td>GORD</td>
<td>Gastroesophageal Reflux Disease</td>
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<td>Graphical User Interface</td>
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<td>HR</td>
<td>High-Resolution</td>
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<td>Interstitial Cells of Cajal</td>
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<td>Inositol trisphosphate</td>
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<td>Occurrence percentage</td>
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<td>POLY4x4</td>
<td>Polynomial based method of velocity estimation using a 4x4 array</td>
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<td>Recovery-Activation interval</td>
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<td>RRi</td>
<td>Recovery-Recovery interval</td>
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<td>SDR</td>
<td>Signal Distortion Ratio</td>
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<td>Savitzky-Golay</td>
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<td>SIV</td>
<td>Spatially Interpolated Visualisation</td>
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<td>Smooth Muscle Cell</td>
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<td>SNEO</td>
<td>Second-order Non-linear Energy Squared Operator</td>
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<td>SQUID</td>
<td>Superconducting QUantum Interference Device</td>
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<td>STFT</td>
<td>Short Term Fast Fourier Transform</td>
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Chapter 1

Background and objectives

The motility of the stomach is underpinned by a rhythmic bio-electrical event known as the slow wave [79]. Understanding the initiation, maintenance and termination of gastric slow wave activity is key to comprehending normal gastric function and gastric motility disorders. Sparse extracellular electrical recording techniques have been used to study gastric slow wave activity [10, 20, 76, 91], and in recent years an extension of this technique, known as extracellular multi-electrode high-resolution (HR) electrical mapping, has been used in many studies [45, 49, 111, 138, 139]. HR electrical mapping provides the ability to conclusively map the two dimensional propagation pattern of gastric slow wave activity. Thus, HR slow wave mapping allows for an improved and accurate spatiotemporal description of dysrhythmic propagation patterns of initiation, maintenance and termination. Most studies to date have used frequency as measure to detect abnormalities [18, 37, 38, 118]. However a recent study has found that spatial dysrhythmic patterns of propagations can also occur at the normal slow wave frequency range of 3 cycles per minute (cpm) [138], making frequency analysis alone an insufficient measure to detect abnormalities. Thus there is an imperative need to develop methods incorporating spatial characteristics of gastric slow wave propagation to understand dysrhythmic slow wave activity and how it relates to gastric motility disorders.
1. BACKGROUND AND OBJECTIVES

For an accurate description of the spatiotemporal nature of slow wave activity, HR mapping presents a large amount of data, making manual analysis of the data an ineffective approach to research and development. Manual analysis of gastrointestinal (GI) HR recordings is laborious and could lead to observer bias and error. In this thesis, novel automated methods were developed to analyse and quantitatively characterise the spatiotemporal nature of serosal extracellular gastric HR recordings and the temporal nature of sparse body surface electrogastrography (EGG) recordings. These methods were validated and applied to experimental recordings. These methods were used to develop an improved comprehension of gastric electrophysiology and presents novel ways for detecting, understanding, and visualising abnormalities of gastric slow wave activity. An overview of the gastrointestinal field is given, followed by the objectives for this thesis.

1.1 Background

Control of GI motility is exerted via co-operating myogenic, neural, hormonal and mechanosensitive mechanisms [79]. Slow wave activity is an intrinsic myogenic activity of the stomach, and is the focus in this thesis. Understanding the intrinsic electrical activity of the GI tract - slow wave activity - will allow for a better comprehension of how other mechanisms, such as neural and hormonal, will affect gastric motility during normal and abnormal states.

GI diseases are an economic and social burden on our society. Around 10–25% of the western population suffer from GI disorders, and this is not taking into account that only one third of the population suffering from GI disorders see a medical professional [50, 86, 151]. In Canada, 12% of hospital admissions are related to GI disorders (excluding cancer), in comparison to 9% for circulatory diseases and 13% for respiratory diseases, making it a significant burden on the healthcare system [173]. The economic impact of GI disorders is also severe with the United States spending around $142 billion per year in direct and indirect costs [158] to combat adverse health effects caused by GI disorders. Research and development is required to advance novel methods of diagnosing GI disorders, and
develop effective therapeutic and treatment strategies, so that the population will have a better quality of life and reduced costs for the patient and the healthcare system. Public and social awareness is also warranted to combat GI disorders.

The GI research field is continually growing and evolving with the discovery of mechanisms controlling normal and abnormal functions in the GI tract. As a result, novel treatment strategies are being proposed and validated. One example is the gastric motility disorder ‘gastroparesis’, where the ability to empty the food from the stomach is debilitated in the absence of any mechanical obstruction \[153\]. Gastroparesis is diagnosed in patients using a scintigraphy test, where the patient consumes a standard radio-labelled meal. The contents of the meal are scanned while in the stomach to measure the delay in gastric emptying, which is used as a marker for diagnosis. If more than 50% of the food the patient has ingested is retained in the stomach after 2 hours, or greater than 10% of the food is retained in the stomach after 4 hours, the patient is considered gastroparetic (See Figure 1.1) \[125\]. Recent advances have attributed one cause of the disease to dysrhythmic slow wave activity and disruption in the ICC networks \[69, 138, 188\]. Based on these findings novel treatment options (which are still experimental) are becoming available to patients \[126\].

### 1.2 The problem

With sparse serosal extracellular slow wave recordings (usually less than 8 electrodes), the primary approach of analysis was based on the frequency of the slow wave, whereby the researcher would manually count the number of slow wave events over a defined time period (Figure 1.2a). With the introduction of serosal HR mapping techniques by Lammers et al. \[109\] and Du et al. \[45\], a detailed spatiotemporal pattern of the gastric slow wave propagation can be mapped. Various experimental studies were undertaken, where the analysis performed was in a manual fashion. These studies provided vital information about slow wave propagation across the stomach, and across various animal species and humans \[49, 111, 139\]. The downside with HR mapping compared to sparse electrical mapping is that
1. BACKGROUND AND OBJECTIVES OF THE THESIS

Figure 1.1: Gastric emptying scintigraphy test used to diagnose gastroparesis. Scintigraphy images are obtained at 0, 30, 60, 120, 180, and 240 minutes after ingesting a meal which has been radioactively labelled. A region of interest is drawn at T=0 minutes and is set as the baseline. Over time, the geometric mean of gastric counts (fluoresced region) to the baseline is expressed as a percentage denoting gastric retention. The percentage of gastric retention for solids was 45% at 2 hours after meal ingestion and 31% at 4 hours after meal ingestion. Reproduced from [196].
there is a large number of electrode recordings to analyse. This approach is very inefficient and laborious when done manually and prone to bias (Figure 1.2(b)). Automated techniques and software frameworks are being developed as a result and have started to alleviate the time spent on analysis [25, 52, 53, 103, 198]. These software implementations have also allowed for automated analysis making HR mapping a pertinent tool in understanding gastric slow activity.

Figure 1.2: Comparison of sparse versus high-resolution electrical mapping on the serosal surface of the stomach. (a) shows the surface of the stomach with two electrodes placed on the serosal surface, and corresponding signals. Here the slow wave events can be visualised clearly and manual analysis can be done efficiently, without the need for noise removal such as baseline wander. (b) show a high-resolution electrode array placed on the serosal surface of the stomach with its corresponding signals. Here, with the increased number of signals, manual analysis is laborious, inefficient, and might potentially cause observer bias. In (b) the signals require to be analysed separately in an individual manner and would require specialised plotting to integrate the analysis.

The use of body surface EGG is an alternative technique to record gastric slow waves in an non-invasive manner. EGG signals are faint in comparison to the
1. BACKGROUND AND OBJECTIVES OF THE THESIS

serosal gastric recording due to the attenuating effects of the abdominal wall [100]. EGG recordings also represents the activity from multiple gastric wavefronts simultaneously present in the stomach [44, 187]. Currently in a clinical research setting, analysis of sparse cutaneous EGG analysis is performed manually, which is prone to observer bias and error [100]. As a result, methods of analysis are increasingly being automated, with frequency of the signal being the parameter of interest [28, 30, 119, 192]. The downfalls of most automated methods thus far is that they have been unable to deal with noisy signals without user intervention. Novel methods of analysing sparse EGG signals were developed in this thesis that are capable of disregarding noisy recording segments while performing reliable quantitative estimates of EGG frequency and amplitude. This development is key to realising HR cutaneous EGG mapping in a clinical setting, which has shown, in a mathematical modelling scenario, to provide vital spatial information about slow wave activity, not attained through sparse EGG recordings [94, 95].

1.3 Thesis objectives

The objective of the thesis was to record, quantify and interpret gastric slow wave activity using in vivo extracellular mapping techniques in normal and dysrhythmic conditions. The goal was to apply novel automated methods and techniques that were able to display and extract key measures that are able to succinctly characterise the nature of the gastric slow wave activity in a dynamic fashion. Due the large size of the recorded data, automation of analysis and quantification is important for practical management of the data sets and to limit the the bias of manual review. Automated methods of analysis and quantification were applied to two in vivo extracellular recordings modalities; (i) HR gastric serosal recordings (Chapters 3–6) and (ii) sparse cutaneous body surface EGG (Chapter 7).

The application of automated methods to HR extracellular serosal gastric slow wave propagation will allow descriptions of slow wave activity to be developed more accurately and efficiently, and will aid in the understanding of normal and abnormal slow wave propagation. Once methods were established to detect, track
slow wave propagations and calculate quantitative metrics, the aim was to automatically classify and identify gastric slow wave propagation patterns. The purpose of this methodology was to develop a clinical tool that can be readily used to provide intuitive quantitative and qualitative information about the nature of the gastric slow wave activity present in the patient or animal subject.

Reliable automated techniques to analyse sparse cutaneous body surface EGG recordings were developed, so that clinical information about the nature of slow wave activity can be gained using non-invasive recordings methods. Using novel methods to automatically discard noisy sections of the EGG signal will significantly improve the estimation of the EGG parameters of interest such as frequency and amplitude. This will aid in providing reliable EGG parameters, and can potentially allow body surface EGG to be used as a useful clinical utility for non-invasive diagnosis of gastric motility disorders in the future.
Chapter 2

Introduction

Gastric motility is key in acquiring sustenance for the human body, and is mediated by co-operating myogenic, neural and hormonal mechanisms. This chapter outlines the various mechanisms involved in coordinating gastric motility and highlights some of the key research in understanding and treating gastric motility disorders. Then methods used to record the bio-electric gastric slow wave activity are described along with a brief review of the recording modalities used in this thesis.

2.1 Gastric anatomy and musculature

Anatomically, the stomach is divided into five regions; cardia, fundus, body (or corpus), antrum, and pylorus (Figure 2.1). Cardia is the area just below the lower esophageal sphincter, while the fundus is located towards the greater curvature, and is defined as an imaginary horizontal line running from the lower esophageal sphincter across the stomach. The fundus acts as a reservoir for undigested food. The corpus is the central region of the stomach, while the antrum is at the caudal end of the stomach. The pylorus is inferior to the antrum, while the angularis is a notch in the lesser curvature in the caudal end of the stomach. An imaginary line running horizontally across from the angularis separates the corpus from the
antrum and the pylorus. The pylorus acts as a valve and regulates the transfer of chyme to the small intestine. These anatomical locations in the stomach can be used to determine the divisions in the stomach across patients and animal subjects in an experimental setting.

![Stomach anatomy](image)

**Figure 2.1:** Stomach anatomy. (A) shows a stylised view of the five different regions in the stomach; cardia, fundus, body, antrum and pylorus. The lower esophageal sphincter serves as a guide to separate the fundus from the body of the stomach and the angularis serves as a guide to separate the body of the stomach from the antrum. (B) shows an endoscopic view of the fundus emanating from the cardia. (C) shows the endoscopic view of the pylorus emanating from the antrum. Adapted from [2].

There are four tissue layers in the stomach from inside of the lumen to the exterior; (i) mucosa, (ii) submucosa, (iii) muscularis, and (iv) serosa (Figure 2.2). The mucosa layer is filled with gastric glands which secrete enzymes, hydrochloric acid and mucus for digestion. The submucosal layers have blood vessels that supply the mucosal layer. Proceeding it is the muscularis layer, which drives the phasic peristaltic contractions, and is composed of the oblique, circular and longitudinal muscle layers. The oblique muscle layer is present in the fundus and fuses into the circular muscle layer as it enters the corpus region of the stomach. The longitudinal and circular muscle is present throughout the stomach, and the circular muscle becomes increasingly thicker as it reaches the pylorus, to form the pyloric sphincter.

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2.1 Gastric anatomy and musculature

Figure 2.2: Schematic illustration of muscle layers in the stomach. There are four layers to the stomach musculature; (i) mucosa, (ii) submucosa, (iii) muscularis, and (iv) serosa. The mucosa is densely packed with gastric glands that produce the digestive juices. The muscularis is composed of the longitudinal, circular and oblique muscle layers, which drive phasic peristaltic contractions. Reproduced from [3].
2.2 Gastric electrophysiology

The motility of the stomach is governed by an underlying bio-electrical event known as “slow waves” in the stomach musculature, which is regulated via various physiological processes as seen in Figure 2.3. Each of the physiological processes is briefly described in this section. Under certain physiological circumstances bio-electric “spike potentials” accompany slow waves and play a key role in regulating GI motility. Smooth muscle cells (SMC) in the stomach were originally thought to initiate and perform contractions [183], but recent research shows that this hypothesis is only partially true [168]. Smooth muscles in the stomach are responsible for contractions, but are not able to establish this activity on their own. This activity is initiated by a specialised network of cells known as “interstitial cells of Cajal” (ICC) which are present throughout the GI musculature. A brief review of ICC is given in Section 2.2.1 followed by how they generate myogenic slow wave activity, along with neural and hormonal stimuli that regulate GI motility.

![Gastrointestinal motility diagram](image)

**Figure 2.3:** Factors mediating GI motility. Slow wave activity is an intrinsic myogenic event, but is also regulated by layers of control through neural and hormonal mediated mechanisms.
2.2.1 Interstitial cells of Cajal

In 1892 Santiago Ramón Cajal described a peculiar set of interstitial cells with nerve endings in the GI tract (Figure 2.4) [123]. Histological staining and electron microscopy suggested that these cells were of some importance, and it was hypothesised that ICC could act as pacemakers to initiate the electrical activity to govern motility in the gut [56, 98]. The experimental evidence to support the hypothesis was initiated by Madea et al. [122], where they administered a c-kit (tyrosine protein kinase) neutralising agent to newborn mice to find abnormalities in GI motility. This and other studies, such as in [80, 137, 193], found that c-kit is vital for the normal development of ICC. Hence the abolishment of c-kit leads to a degraded ICC network formation in the GI musculature, leading to an abnormal slow wave activity, thus causing aberrant GI motility. The myogenic nature of slow waves was confirmed after slow waves were recorded in the stomach of mice that lacked neural control of the gut [194].

From experimental studies, it has been confirmed that ICC generate and propagate slow wave activity through to SMC to coordinate motility in the gut [39, 43, 75, 96]. Slow waves are generated as cycles of depolarisation and repolarisations, which conduct from ICC to the SMC and are orchestrated by voltage-dependent ion channels present in SMC and ICC. Figure 2.5 shows a slow wave event in the ICC and its transduction to the SMC. There are two main phases in the generation of the slow wave in the ICC; (i) depolarisation and (ii) repolarisation. These two phases are both potentially regulated by regenerative inositol-trisphosphate (IP$_3$) dependent calcium release and uptake, and via calcium release generating inward currents such as calcium activated chloride channels [186, 202] (Figure 2.5(a)). When the slow wave has been conducted to the SMC, voltage gated sodium and calcium currents allows positive ions to flow into the cell depolarising the cell from roughly -70 to -30 mV (Figure 2.5(b)). After the depolarisation, the voltage gated sodium and calcium currents start to slowly deactivate, while at the same time, voltage dependent potassium currents are activated, allowing potassium ions to leave the SMC, making the SMC membrane potential negative. An equilibrium called the plateau period is formed, whereby the inward calcium and
2. INTRODUCTION

Figure 2.4: Sketch and light microscopy images of stained ICC. (a) Original drawings by Santiago Ramón Cajal of the interstitial cells of the gut. (b) and (c) are the same cells that can be found in the original slides that were left stained by Cajal, with silver dichromate impregnation in (b) and methylene blue in (c). Scale bar = 50 µm. Reproduced from [123].
sodium currents balance the outward potassium current. The outward potassium current begins to dominate and repolarises the SMC membrane potential (Figure 2.5(b)). The exact mechanisms and the precise ion channels involved in slow wave initiation and conduction are under deliberation, and are discussed in detail elsewhere [55, 114].

2.2.2 Non-ICC factors affecting GI motility

There are a number of non-ICC factors that affect GI motility, and three of those factors are briefly discussed; (i) spike activity, (ii) migrating motor complex and (iii) hormonal activity.

Spike potentials are bio-electrical events that have been recorded in the presence of the slow wave event, and are associated with contraction of the smooth muscles [108] (Figure 2.6). Experimental evidence has shown that spike activity occurs due to an influx of calcium ions in the SMC during depolarisation, the state of which is normally initiated by the slow wave event from ICC [197]. If the SMC have not been depolarised to a certain threshold (variable by region in the gut), spike activity does not occur [168]. Spike activity acts to increase the phasic contraction of the stomach muscle wall, particularly in the antrum [26, 91, 189].

The migrating motor complex (MMC) is a cyclic electrical activity occurring in the smooth muscle layer of the GI tract, in particular, the stomach, intestines and colon, and are associated with GI motility [178, 180]. The MMC is a slow moving motor activity, where the muscles are tonically excited, as well as the same time, rapid phasic propulsive contractions occurs [79]. The MCC was initially recorded in fasted states [180], but has also been recorded in fed states resembling a similar but variant on the typical MMC pattern of activity [195]. The MMC was usually seen in the presence of the slow wave activity, but recent intracellular studies have shown that MMC activity relies on the enteric nervous system rather than slow wave activity [178]. It has been hypothesised that MMC acts to induce hunger and also takes on a ‘housekeeping’ role to clean up ingesta and bacteria present in the gut [42].
2. INTRODUCTION

(a) Slow wave in ICC and SMC. Adapted from [78].

Figure 2.5: Intracellular recording of slow wave in ICC and SMC. (a) shows the slow wave event in both the ICC and SMC. In (a), A is the slow wave event recorded from an ICC while B is the slow wave event from the circular smooth muscle layer. C shows the two events overlaid and shows that the slow wave event from ICC conducts to the circular muscle layer. (b) shows the schematic representation of the spatial nature of ICC and SMC, along with the corresponding slow wave event.

(b) Schematic of the spatial nature of ICC and SMC. Adapted from [108].
2.2. Gastric electrophysiology

Hormones exert an additional and important regulation to GI motility and the hormonal mechanisms are briefly reviewed here [85]. In the stomach, hormones such as gastrin promotes gastric emptying, while hormones such as gastric inhibitory peptide, secretin, and cholecystokinin delay gastric emptying based on the type of ingesta present in the stomach [15, 85]. Recent studies have found the hormone ghrelin, which stimulates growth hormones, is found in the fundus of the stomach and is attributed to increasing motility and hunger [83]. Levels of ghrelin decreased after consuming a meal.

Figure 2.6: Force generation in SMC. When the SMC membrane potential is not above a certain voltage threshold, contraction of the SMC does not occur. When the SMC membrane voltage is over the threshold, mechanical contraction of the SMC occurs. Spike activity also occurs during this time due to the increased calcium influx into the SMC. Adapted from [89].

2.2.3 Contractile force regulation

In the stomach not all of the bio-electrical events lead to a mechanical contraction of the muscle wall. Myogenic slow waves are omnipresent and contraction of the muscular wall is only initiated when the slow wave event depolarises the SMC membrane voltage beyond a threshold – referred to as the ‘mechanical threshold’ (Figure 2.6). Once the SMC membrane potential is over the mechanical threshold,
2. INTRODUCTION

the contractile force is dependent on the SMC membrane voltage, which controls
the release of calcium via voltage gated ions and is crucial for muscular contraction [181]. A variety of physiological, myogenic, neurogenic and hormonal factors have the ability to push the SMC membrane voltage beyond the ‘mechanical threshold’, and thus regulate the contractile force in the stomach.

2.2.4 Abnormalities in ICC and slow wave leading to gastric disorders

Abnormalities in ICC have been implicated in major gastric functional and motility disorders such as gastroparesis and functional dyspepsia. A brief summary of the research into gastroparesis is presented below.

Gastroparesis is a chronic gastric motility disorder where there is a delayed or almost non-existent gastric emptying of the ingesta in the absence of any mechanical obstruction [153]. Gastroparetic symptoms occur in varying severities across patients, from mild to severe and includes; loss of hunger, vomiting, dehydration, nausea, bloating, pain and nutritional impairment [69, 87]. Gastroparetic patients are categorised into two major groups: diabetic or idiopathic [69]. Studies have shown that patients with gastroparesis have low numbers of ICC, damaged ICC networks, a degenerated enteric nervous system, and a remodelled ICC network [60, 69, 87, 146]. The remodelled ICC network has been a major research focus [64, 65], and a recent study has shown that during the presence of abnormal motility in the stomach, the gene anoctamin 1 which express calcium activated chlorine channels in ICC has been modified [127]. These studies along with extracellular slow wave mapping studies have revealed that loss of ICC lead to dysrhythmic slow wave activity that disrupt the normal motor functions of the stomach [69, 138]. Based on these findings about the pathways present for gastroparesis, novel treatments such as electrical stimulation are being developed and tested for their efficacy [126, 143, 199].
2.3 Gastric slow wave mapping

Other functional and motility GI disorders have also been related to abnormalities in slow waves, such as functional dyspepsia, gastro-oesophageal reflux disease (GORD), motion sickness, anorexia nervosa, unexplained nauseas and vomiting [113, 139]. Further research is required to reiterate the findings and propose mechanisms on how various symptoms are related to the type of abnormal slow wave activity.

2.3 Gastric slow wave mapping

This section will focus on the developments and importance of extracellular slow wave recordings. Electrical recordings in the mammalian GI tract were first attempted by Alvarez et al. [9, 10] where Alvarez probed the stomach and intestines using Einthoven’s and D’Arsonval’s galvanometers to record electrical activity on the body surface. Since then, and over the years, researchers have recorded the electrical activity in the GI tract intracellularly in *ex vivo* setups, and extracellularly using *in vivo* and *ex vivo* setups. Extracellular recordings in the GI tract were undertaken via placement of contact electrodes on the serosal surface of the GI organ and on the body surface to record the electrical activity of the GI tract across the abdominal wall. The technique of recording electrical activity of the stomach from the body surface using contact electrodes is referred to as ‘cutaneous electrogastrography’ (EGG). The collated experimental evidence has formed the basis of research and understanding about the mechanisms regulating digestion during normal and abnormal states.

The signal morphology of extracellular serosal slow wave recordings can be approximated by taking the second derivative of an intracellular slow wave recording [177]. Intracellular signals provide the most detailed identifiable current movements out of and into the cell, leading to the bio-electrical activity present in the GI tract. Serosal extracellular recordings provide a summed and distributed view of the intracellular recordings, while cutaneous EGG recordings provide a summed and smoothed representation of the electrical activity present in the GI tract from the body surface. The following sections provide a brief review of previously and
2. INTRODUCTION

currently used methods in gastric slow wave mapping, along with its significance, with an emphasis on extracellular recording techniques.

2.3.1 Review of slow wave recordings

Early electrical recordings on the surface of the GI tract were performed by Alvarez et al. [10] in the 1920s. He recorded the activity using calomel electrodes attached to a D’Arsonval string galvanometer, and used the term ‘action currents’ to describe the recorded slow wave activity. During the same era, Richter et al. [164] reinforced the findings by Alvarez et al. [10] about the existence of electrical activity in the stomach, and used suction disc electrodes for his study. Richter et al. [164] describe the various phases present in the ‘action current’ using the nomenclatures ‘q’ and ‘k’ to refer to the fast phase of the signal and ‘w’ to refer to the slow phase of the signal, as shown in Figure 2.7(a).

In 1945 Bozler et al. [20] used capillary calomel wick electrodes to record the electrical activity in the stomach, and used the nomenclature ‘R’, ‘S’, and ‘T’, from cardiac electrophysiology, to define the phases of the slow wave event which was termed ‘action potentials’ at the time (Figure 2.7(b)). These recordings by Bozler et al. [20] and Richter et al. [164] were similar in morphology but differed to those obtained by Alvarez et al. [10]. One reason for the variation in the morphology could be due to the electrode orientation, electrode contact size or inter-electrode spacing (which was not specified in the paper by Alvarez et al. [10]) [40].

As seen in Figure 2.7(b) and recordings from other GI experimental studies, there are two components to the slow wave event; (i) a fast component which relates to the R waves and (ii) a slow component which relates to the S and T wave. Suction and intracellular recordings were made to confirm the presence of the fast and slow components in the slow wave event and proposed mechanisms that underlie the slow wave activity [51] [82]. Papsova et al. [150] associated the first component to sodium channels and the second component to the calcium channels. They also observed that at high levels of calcium ions, muscular contractions were induced. Spike activity was first recorded by Bozler et al. [19] and it was shown that at
2.3 Gastric slow wave mapping

(a) Canine slow wave recordings by Richter et al. [164]. Adapted from [164].

(b) Canine gastric slow wave recordings by Bozler et al. [20]. Adapted from [20].

Figure 2.7: Early extracellular gastric slow wave recording traces (originally termed action potentials) with defined nomenclature at the time. (a) shows the recording by Richter et al. [164] who denoted ‘q’, ‘k’ and ‘w’ to represent the slow wave event. (b) shows the recording by Bozler et al. [20] who used the nomenclature ‘RST’ from cardiac electrophysiology.
2. INTRODUCTION

elevated levels of calcium, spike activity was observed on the second component of
the slow wave event \[150\]. Various researchers investigated the effects of drugs such
as ethyl alcohol \[167\] and pentagastrin \[134, 181\] on gastric slow wave activity to
elucidate excitatory and inhibitory pathways of gastric motility present in the GI
tract. Simultaneous pressure and electrical measurement were performed by Carlson
et al. \[26\] to confirm that electrical activity controls mechanical contraction
in the GI tract.

Experimental studies were also carried out to characterise the origin and propa-
gation of gastric slow wave activity. Kelly et al. \[90, 91\] showed that in a canine
stomach, slow waves originate in the corpus on the greater curvature of the stom-
ach and propagate towards the antrum. Slow waves are not present in the fundus
of the stomach (Figure 2.8). These findings were reiterated by Hinder et al. \[76\]
who performed gastric transection to identify the precise location of pacemaker in
humans as being in the mid-corpus region on the greater curvature. Intracellular
recordings by El-Sharwaky et al. \[51\] revealed that there is a gradient in the in-
trinsic frequency ranging from the corpus (3.66 cpm) to the antrum (0.66 cpm)
in the stomach, and that slow wave activity is able to entrain surrounding tissue
and propagate at the highest frequency. Mucosal experiments were first carried
out by Monges et al. \[132\] in 1970, who used suction based electrodes to latch
onto the mucosa to record the electrical activity, along with simultaneous pressure
recordings using a balloon. In a subsequent study, Monges et al. \[133\] used the
same technique to show that in the canine antrum, gastric slow waves were om-
nipresent, and when there was a muscular contraction, spike activity was observed
on the slow wave event. Since the slow wave recording by Monges et al. \[132, 133\]
in the 1970s and Hamilton et al. \[71\] in the 1980s, there was a quiescent period of
research into in vivo mucosal slow wave recordings. In 2004, Choleski et al. \[37\]
established endoscopic techniques for recording mucosal slow wave activity and
have applied these techniques to human patients.

Most of the studies described have had the focus on understanding the normal
physiology behind gastric slow wave activity, but based on the importance of slow
wave activity on GI motility, questions have been asked and experiments performed
on the role of slow waves in gastric disorders. Initial studies were performed in
2.3 Gastric slow wave mapping

Figure 2.8: Recording of canine gastric and duodenal electrical activity under resting conditions, which identifies the site of origin of gastric pacemaker potential between electrodes 3 and 4 in the upper-corpus region. The amplitude of the gastric slow wave event has a higher amplitude in the antrum, as shown in electrode 8. Reproduced from [91].
canines where gastric dysrhythmias were induced via drugs such as glucagon and atropine \[36, 70, 161\]. Subsequently, electrical recordings were taken in humans who had gastric motility disorders such as diabetic gastroparesis, and also patients who had undergone gastroenterostomies \[18, 162, 182\]. Gastric mucosal slow wave activity was also recorded in normal humans after administering drugs such as glucagon to induce dysrhythmia \[37, 38\]. In these studies, gastric dysrhythmias were classed in terms of frequency; as faster than normal (tachygastria 4–9 cpm), or slower than normal (bradygastria 1–2 cpm) \[37\]. It was seen that in canines, tachygastria normally occurred in the antrum and followed in a retrograde manner to override the main pacemaker from the corpus region, while bradygastrias were seen when the slow wave activity was pacing at a low frequency (1–2 cpm) \[161\]. The frequency of the slow wave event was used as discriminator for normal and dysrhythmic slow wave recordings, and was manually estimated by counting the slow wave events over a defined time period. Figure 2.9 shows five traces of canine gastric slow wave recordings, where two of traces were deemed normal, and the others dysrhythmic based on the frequency of the slow wave event \[70\]. The regularity of the slow wave was noted in a qualitative manner while classifying the slow wave recording as dysrhythmic \[70\].

All of the experimental gastric slow wave studies that have been described so far typically utilised less than 8 electrodes for extracellular or intracellular recording modalities, such as wick electrodes, micro-electrodes, needle electrodes, pressure and suction electrodes. These techniques are referred to as sparse electrical recording techniques. One of the major disadvantages of sparse electrical recordings is that a detailed spatial pattern of the slow wave activity cannot be ascertained. Also depending on the inter-electrode distance used, information about the slow wave propagation is interpolated or assumed, which may cause the results to be misinterpreted. This is particularly problematic during slow wave dysrhythmias as vital information on the slow wave propagation relating to the gastric disorder would be missed. Cardiac electrophysiology has shown that in cardiac dysrhythmias, complex wavefronts occur and they play a crucial role in the initiation and maintenance of the dysrhythmia. Similar roles may apply in the gastric slow wave activity and thus high-resolution (HR) electrical mapping techniques are imperative to understanding GI electrophysiology.
2.3 Gastric slow wave mapping

Figure 2.9: Five serosal gastric slow wave recordings from the antrum of a canine. Electrodes 1 and 2 show a typical normal slow wave recording at 4.8 and 4.27 cpm. Electrodes 3 – 5 show slow wave recordings that are classed as dysrhythmic. Note in electrode 3, the regularity of the ‘paired’ slow wave events. Electrode 4 shows a typical tachygastria slow wave signal, with electrode 5 called as ‘irregular clustering’ of slow wave events. Reproduced from [70].
2. INTRODUCTION

2.3.1.1 Review of extracellular gastrointestinal high-resolution mapping

The first extracellular HR electrical mapping study was performed by Lammers et al. [105] in 1993, where they recorded the slow wave activity from an *ex vivo* rabbit duodenum. Later in 1996, Lammers et al. [109] recorded slow wave activity from an *ex vivo* cat stomach and intestine. For GI HR mapping, Lammers et al. [109] utilised a modified data acquisition system from the cardiac field with various 240 electrode configuration, with inter-electrode spacing distance ranging from 2 to 5 mm [111]. The 240 electrode array was embedded in a rigid epoxy resin which was placed on the serosal surface of the GI organ. Lammers et al. have performed HR GI mapping experiments in the stomach and intestine *in vivo*, in rabbits, canines and felines, to identify normal and abnormal slow wave propagation patterns [105, 108, 109, 111, 112].

The second group to perform GI HR mapping was the Auckland group where Du et al. [45] designed a flexible printed circuit board (PCB) electrode array, with an inter-electrode distance spacing of 4 mm and 7.62 mm, capable of recording 256 electrodes [142]. The flexible PCB has the ability to conform to the curvature of the stomach surface and the materials can readily be sterilised, making it ideal for recording slow wave activity from humans undergoing surgical procedures. Egbuji et al. were the first to perform *in vivo* gastric HR mapping in pigs to reveal normal patterns of slow wave propagation [49]. At the same time, O’Grady et al. [139] performed the first *in vivo* gastric HR mapping study in humans to record normal slow wave activity. Further HR mapping studies were carried out by O’Grady et al. [138], in patients suffering from gastroparesis. In this study the patients had a lower ICC count and HR mapping revealed the presence of abnormal slow wave propagation patterns [138]. One of the critical findings that is beginning to emerge from HR electrical mapping of the stomach is the presence of abnormal slow wave propagation wavefront in the normal range of slow wave frequency [138]. Thus HR mapping adds a refined classification scheme for gastric dysrhythmia based on the frequency of the slow wave event and the spatiotemoral
2.3 Gastric slow wave mapping

pattern of the slow wave propagation, rather than slow wave frequency of sparse recordings (bradygastria, normal, tachygastria).

The critical advantage of HR mapping is that it provides the ability to visualise and characterise propagation pattern precisely without making assumptions about the pattern of slow wave activity. To illustrate, Figure 2.10 shows one column of slow wave recordings, where the electrodes in centre are shaded in grey, and the edge electrodes are shown in black. Without the electrode information in the center of the HR electrode array, the characteristics of the propagation cannot be defined accurately. Early significant studies such the ones carried out by Kelly et al. [91] calculated the velocity of the slow wave propagation by the closest time delay in sparse recordings (inter-electrode distance spacing of 3 cm), which may result in unreliable estimates. With information obtained from HR mapping, an improved understanding about slow wave activity is beginning to emerge. Studies by Lammers et al. [111, 112] and O’Grady et al. [139, 142, 144] are beginning to define normal and abnormal gastric slow wave propagation patterns, and more importantly define mechanisms for abnormal slow wave activity.

In this thesis, gastric serosal slow wave recordings were performed using high-resolution electrical mapping techniques as described in Appendix B. A software platform called Gastrointestinal Electrical Mapping Suite (GEMS) was developed and used during this thesis. Details of the software implementation and graphical user interface are described in Appendix C.

2.3.1.2 Non-invasive recording techniques

In the GI field two main modalities of non-invasive electrical recordings have been used; (i) cutaneous electrogastrogram (EGG) and (ii) magnetogastrogram (MGG). Due to the nature of these recording techniques, these signals are a far-field recording, whereby the electrical activity is recorded away from the organ of interest or underlying source. A brief review of the EGG and MGG recording methods are given below.

EGG was first used in 1920s, with Alvarez et al. [9] recording the electrical activity from a patient from whom the stomach could be seen contracting from the body
Figure 2.10: Misinterpretation of slow wave propagation using sparse electrical mapping techniques. The electrode array (on the right) has an inter-electrode distance of 4 mm and the recorded signals are shown on the left. This electrode is a typical electrode array for HR electrical mapping studies. The signals presented are from one column on the electrode array. If the top and bottom signal are only acquired (as occurs with a sparse recording setup) the propagation pattern and direction cannot be accurately defined. Information in between the top and bottom electrodes are required to define the direction and propagation characteristics accurately. The red arrow shows what slow wave direction might have been interpreted if the top and bottom electrodes were available, and the blue arrow shows the actual direction of travel of the slow wave event, as defined through HR mapping.
2.3 Gastric slow wave mapping

Figure 2.11 show the electrical event along with dots marked by Alvarez when he noticed a contraction. Two other researchers, Tumpeer et al. [185] in 1926 and Davis et al. [41] in 1957, also recorded the EGG independently without the knowledge of Alvarez’s work. Various researchers along the years have elucidated the nature of EGG recordings [33, 100, 174, 200]. Many studies have performed EGG analysis in normal patients and in patients with gastric motility disorders, and found that it could potentially detect abnormalities in slow wave activity [100]. The US Food and Drug Administration, has approved the EGG for recording gastric electrical activity as an aid for diagnosing gastric motility disorders [1], but EGG is not used widely in medical centres as a diagnostic tool, as the clinical utility of EGG is poor at present [5, 112]. Two of the main hindrances are the quality of the slow wave signals recorded from the body surface and the ability to reliably discriminate against various gastric motility disorders.

Figure 2.11: Cutaneous EGG recording by Alvarez in 1922. The signal trace is an EGG recording from a woman where these stomach contractions were visible on the stomach surface, where Alvarez marked a dot as a contraction passed through the electrode. The orientation of the electrode on the body surface is noted below. Adapted from [9].
2. INTRODUCTION

MGG records the magnetic fields generated by the gastric slow wave activity. Since the voltage generated from the stomach is low, weak magnetic fields are created, and thus a sensitive magnetometer is required. One such device is the SQUID (superconducting quantum interference device) which is based on bias currents to record the magnetic fields with the help of superconducting loops using Josephson junctions (Figure 2.12). As MGG recordings are magnetic field recordings, initial studies focused on decomposing the magnetic field recordings into an electrical projection \[22\]. Recent studies are beginning to show correlations between slow wave signals recorded simultaneously using serosal, mucosal, EGG and MGG recordings \[23, 176\]. The advantages of MGG compared to EGG is that magnetic fields are vector based and could potentially provide detailed information compared to scalar electrical mapping methods, but this would require advances in signal processing and analysis techniques. Another advantage of MGG over EGG is that MGG offers a non-contact approach to record the GI electrical activity. Magnetic fields are less affected by tissue layers or fat compared to electrical recordings, so in theory a high signal to noise ratio signal can be acquired \[95\]. This is particularly significant for intestinal slow wave recordings which are low in amplitude as recorded in the serosa, making body surface measurements of intestinal slow wave activity almost impossible, thus making magnetic electrical recordings a viable option for non-invasive electrical recordings \[163, 175\]. On the other hand, there are significant barriers to MGG recordings such as the high set-up and maintenance cost and the requirement of an isolated and noise free environment for adequate operation of the MGG machine. In comparison to the EGG recordings, MGG recordings are not performed routinely, and currently restricted to research studies.

2.4 Summary

In this chapter, an overview of the various physiological processes controlling the motility in the stomach were discussed. In particular, how ICC generate, propagate and conduct slow wave activity to the SMC to initiate muscular contraction of the GI tract. Following on was a brief review of recording extracellular slow wave
Figure 2.12: Schematic of a recording setup for MGG. (A) shows a schematic of the MGG hardware and the main components while (B) shows a subject lying under the MGG machine with the stomach aligned to the tail area. (C) shows nine electrical signal projections of the underlying electrical activity recorded via magnetic fields. (D) shows the corresponding frequency domain graph computed using fast Fourier transform. Adapted from [21].
2. INTRODUCTION

activity using *in vivo* sparse and high-resolution mapping techniques, along with non-invasive far-field mapping techniques.
Chapter 3

Signal processing framework for high resolution slow wave recordings

Experimental recordings of slow wave activity can provide us with essential information that can aid in understanding normal and abnormal gastric function. To acquire essential information from experimental recordings, signal processing is performed to present the raw experimental data in an intuitive form. In this chapter a signal processing framework was developed that is semi-automated and efficient. These methods mentioned have been incorporated into a graphical user interface for use in an experimental setting and for potential clinical translation.

3.1 Framework for processing signals

Signal processing plays a key role in the analysis of gastric slow wave activity, and its success depends primarily on four factors; (i) the quality of the raw recordings, followed by (ii) effective signal filtering, (iii) analysis methods, and (iv) appropriate visualisation techniques. Improper signal processing techniques could adversely bias the analysis and conclusions derived from the experimental recordings. Thus,
3. SIGNAL PROCESSING FRAMEWORK

thoroughly validated methods on synthetic and experimental recordings are necessary. A signal processing framework was developed for analysing HR serosal gastric slow wave signals (Figure 3.1). The signal processing framework was pertinent as it facilitated a workflow system for methods to be developed and implemented in tandem so that raw experimental recordings can be analysed in both a quantitative and qualitative fashion.

First, the raw recorded signals were downsampling to 30 Hz. Slow wave frequency is around 1–10 cpm and the frequency of spike activity is around 2–4 Hz, and the sampling frequency of 30 Hz is sufficient to capture these activities [99, 190]. Then baseline wander and high frequency noise in the recorded signal were removed using signal filters. The slow waves were then automatically detected with a fiducial marker using a variable threshold method [53]. These fiducial markers were then screened to assess if the markers represented a slow wave event. The slow wave fiducial markers were then clustered into their associated propagating wavefronts using a polynomial based region growing method [52]. Finally, the slow wave activity was visualised using static images and animated movies. Each of the steps in the signal processing framework is described in Sections 3.2–3.5.

3.2 Noise removal

Gastric slow wave recordings, like all bio-electrical recordings are contaminated by various sources of noise, and noise removal is, therefore, an essential first step in signal processing. Unlike the electrocardiology field, where there are established standards about the use of filter settings from professional societies [97], there are no standardised filter settings for use in serosal gastric electrical recordings. Thus a study was undertaken to determine appropriate filter settings for gastric HR mapping studies to understand slow wave activity. A brief overview of potential noise sources is given, followed by a brief review of the previously used filter settings in gastric serosal slow wave recordings. Synthetic signals were created to simulate experimental conditions and filters were applied to test for the effectiveness of noise removal. Appropriate filter settings were then recommended for use with gastric slow wave recordings.
Figure 3.1: Signal processing framework for extracellular high resolution gastric slow wave mapping. The first stage was to downsample the signals, after which noise was removed. Then slow wave events were detected and incorrect fiducial markers were removed, after which, the slow waves were clustered into their associated wavefronts. Finally, the properties of the slow wave events were visualised and quantified.
3. SIGNAL PROCESSING FRAMEWORK

3.2.1 Digital signal filtering

There are two key steps to effective signal filtering; (i) the identification of characteristics relating to the signal of interest (gastric slow wave event) and noise, and (ii) the application of filters to eliminate noise and maintain the integrity of the signal of interest. The noise sources during the experimental setup were identified, after which, the characteristics relating to the gastric slow wave were examined, along with currently and previously used filters. This is followed by a comparison of filters on the effectiveness of noise removal in synthetic and experimental extracellular slow wave recordings.

Noise is omnipresent and its sources include powerline interference (50 or 60 Hz), thermally generated (Johnson) noise, other nearby electrical devices and physiological artefact. The commonly observed physiological artefact comes in the form of respiration from the subject, and electrical and mechanical activity from the heart and other organs. Noise components in bio-electrical recordings can span the entire relevant frequency range, from essentially DC (0 cpm) to several cpm. The low frequency noise mainly manifests as baseline wander in the signals, which is due to the time varying electrode serosa impedance and body movement of the subject. Powerline interference and other noise artefacts (fundamental frequency above 15 cpm) are classed as high frequency noise. Respiration typically occurs about 9–15 cpm, which can be particularly problematic due the degree of spectral overlap with the harmonics of the gastric slow wave, which occupy the same frequency range (as seen in Figure 3.2).

To assess the characteristics of the slow wave signal, a frequency domain transformation of the time domain signal is undertaken via a fast Fourier transform (Figure 3.2). The large peak between 0–1 cpm represents the baseline wander in the raw slow wave signals. After the removal of the baseline wander, the slow wave signal content is visible in the frequency domain. The fundamental frequency is at 3.3 cpm (Figure 3.2), and its associated harmonics range to about 2 Hz. Previously used filters in GI HR mapping are listed below, after which, the filters used in this study are described.
3.2. Noise removal

**Figure 3.2:** Frequency domain transformation of the slow wave signal before and after baseline removal. (a) is the gastric slow wave signal in the time domain, while (b) is the corresponding frequency domain. The large spike in (b) at 0–1 cpm represents the baseline drift. (c) is the gastric slow wave signal in the time domain signal after baseline drift has been removed, while (d) is the corresponding frequency domain, where the frequency content of the slow wave and existing noise are visible. The sharp low amplitude oscillations that accompany the slow wave signal are caused by the electrical activity of the heart, in particular the ventricular activity (QRS complex). Adapted from [155].
3. SIGNAL PROCESSING FRAMEWORK

3.2.1.1 Previously used filters in GI HR mapping

Lammers et al. [105] were among the first to start recording and analysing slow waves using HR mapping techniques. Their recording hardware had a sampling frequency of 1 kHz and they applied a 20 point moving average filter to their data. Such a filter acts as a low pass filter and eliminates power line interference (at 50 Hz) and other higher frequency components without distorting the morphology of the signal. Baseline wander was not present in these signals as the recording hardware was band-limited from 2 to 400 Hz [105]. Following on, Du et al. [45] developed HR PCB electrode arrays to analyse electrical activity in the GI tract. The recording system used by Du et al. [45] allowed biological signals to be recorded from DC onwards and requires digital signal processing to eliminate unwanted noise for online visualisation and analysis. Different second order low pass Bessel filters with cutoff frequencies ranging from 2 to 10 Hz were applied in various studies to visualise online recordings of slow wave activity in the stomach recorded using flexible PCB arrays [45, 49, 139, 141]. Butterworth filters were used to analyse slow wave activity in the stomach, in an offline setting (passband 1–60 cpm) [52, 53], and in real time (passband 0.5–4 Hz) [25] using flexible PCB electrodes.

3.2.1.2 Filters under consideration

There are two types of noise that needs to be removed from raw HR gastric slow wave recordings, (i) baseline drift and (ii) high frequency noise. Six filter specifications are chosen to test the effectiveness of noise removal. Three of which are aimed as baseline removal and the other three are aimed at high frequency noise removal. The details of the chosen filters along with their specifications are listed in Table 3.1 and a brief description of the filter types are given below.

**Butterworth filters**

Butterworth filters are one of the most commonly used filters in signal processing. To compare against previously used filters, the same parameters of the Butterworth
3.2. Noise removal

<table>
<thead>
<tr>
<th>Noise removal</th>
<th>Filter</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
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<td>Baseline drift</td>
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<tr>
<td></td>
<td></td>
<td>Cutoff: 1 cpm</td>
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<tr>
<td></td>
<td>Moving median filter</td>
<td>Window width: 20 s</td>
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<td></td>
<td>Discrete Wavelet filter</td>
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<tr>
<td></td>
<td></td>
<td>Decomposition level: 11</td>
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<tr>
<td>Low Pass Butterworth filter</td>
<td>Filter Order: 2,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutoff: 60 cpm</td>
</tr>
<tr>
<td>High frequency</td>
<td>Savitzky Golay (SG) filter</td>
<td>Polynomial order: 9,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Window width - 1.7 s</td>
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<tr>
<td></td>
<td>Discrete Wavelet filter</td>
<td>Wavelet: Symlet,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soft threshold: BayesShrink</td>
</tr>
</tbody>
</table>

Table 3.1: Noise removal techniques, and specifications.

filter, as used by Erickson et al. [52, 53] was used for this study. This filter is often used in many applications because it has a maximally flat response in its passband and rolls off towards the zero in the stopband. Figure 3.3 shows the frequency response of the high and low pass Butterworth filters which illustrates the flat passband. The roll off rate of the Butterworth filter can be slow, and the steepness can be increased by increasing the filter order. The downside with increasing the order of a filter is that it could cause ripples in the passband which may distort the signal of interest during the filtering process.

Moving average filters

Moving average filters are relatively easy to implement and apply. Two types of filters are used here; (i) moving median filter and (ii) Savitzky-Golay (SG) filter.

To eliminate the baseline wander in the signal, a running estimate (window: 20 s) of the median of the signal was taken. A Gaussian filter was applied to the estimate of the baseline wander via the moving median filter to eliminate any sharp discontinuities [62]. Since baseline wander is usually composed of low frequency
3. SIGNAL PROCESSING FRAMEWORK

![Magnitude response plots](image)

(a) Frequency response for a second order low pass Butterworth filter (Cut-off: 60 cpm (1 Hz)).

(b) Frequency response for a second order high pass Butterworth filter (Cut-off: 1 cpm (0.017 Hz)).

**Figure 3.3:** Butterworth frequency filter response illustrating the flat band pass response. (a) shows the frequency response for a low pass Butterworth filter while (b) shows the frequency response for a high pass Butterworth filter.

components, the signals were downsampled for baseline estimation, and the resulting baseline estimation was upsampled for baseline subtraction from the signal.

\[ G_{\text{filt}} = e^{-x^2/\sigma^2} \] \hspace{1cm} (3.1)

The parameters for the Gaussian filter (Equation 3.1) were empirically chosen as, \(x\) to range from 0 to 500 sample points (0–16.67 s) and \(\sigma\) as 500.

SG filters employ a sliding smoothing technique to reveal the underlying signal under noisy conditions. In the sliding window, a polynomial is solved to a least squares fit [170]. The polynomial order and the length of the sliding window can be set accordingly to define necessary filter specifications. Either decreasing the polynomial order or increasing the sliding window will allow for increased smoothing of the signal. Conversely, either increasing the polynomial or decreasing the sliding window width will allow for reduced smoothing of the signal. Figure 3.4 shows the frequency response of the SG filter which has been designed to have a cutoff around 2 Hz (1.9894 Hz to be precise). Like the Butterworth filters it has a flat response in its passband. When SG filters are designed accordingly, it can eliminate noise and maintain the width and peaks of the signal of interest during the filtering process [171].
3.2 Noise removal

![Figure 3.4](image)

**Figure 3.4:** Frequency filter response of a low pass Savitzky-Golay filter with a cutoff at around 2 Hz. This figure illustrates the flat response in the pass band of the filter which rolls off smoothly after cutoff frequency of around 2 Hz.

Wavelet filters

Wavelet filters use wavelet decomposition to decompose the signal into various frequency sub-bands, perform correction, and then reconstruct the signals. Wavelet decomposition can be performed via continuous wavelet transform or via discreet wavelet transform (DWT). Here, the discussion of wavelet filters is limited to two DWT filter implementations; (i) baseline estimation via wavelets, and (ii) denoising via BayesShrink [29].

The framework for denoising a signal based on DWT is shown in Figure 3.5. The signals were first decomposed into approximations (low frequency) and details (high frequency) based on the use of quadrature mirror filters, after which thresholding takes place before reconstruction. Usually, the low frequency components relate to the baseline wander [201]. Using the sampling frequency as a guide, the target sub-band or level of decomposition can be identified. In our experimental case, the eleventh level of decomposition was chosen as it has frequencies in the band 0.88 cpm and below to represent baseline drift. The Symlet wavelet
of order 10 was chosen as it had a similar resemblance to the gastric slow wave event morphology. After decomposing the raw gastric slow wave signal to the 14th level, coefficients (details) that represented 0.88 cpm and above were zeroed before reconstruction of the underlying baseline wander.

To eliminate high frequency noise via DWT, the details of the DWT were thresholded before reconstruction via an inverse discrete wavelet transform (IDWT). A global threshold or a level depended threshold can be applied. A soft thresholding approach which employs a Bayesian (BayesShrink) based threshold was used for denoising high frequency noise in gastric slow wave signals [29]. The BayesShrink method finds the cutoff threshold for wavelets based on minimising the Bayesian risk. Assuming the profile of wavelet decomposition is a generalised Gaussian distribution, the minimum risk (or threshold for each sub-band under consideration) can be estimated as,

$$T = \frac{\sigma_n}{\sigma_x}, \quad \text{where} \quad \sigma_n = \frac{\text{median}(D_1)}{0.674},$$

$$\text{while} \quad \sigma_x = \sqrt{\max(\sigma_Y - \sigma_n^2)}, \quad \text{and} \quad \sigma_Y = \frac{1}{n^2} \sum_{i=1}^{n} A_i^2,$$

(3.2)

where $D_1$ is the first detail decomposition, $A$ is the sub-band under consideration and $n$ is its length.

### 3.2.1.3 Validation of gastric slow wave signal filtering

To validate signal filtering techniques on slow wave signals, realistic synthetic slow wave signals were created, as shown in Figure 3.6. The use of synthetic signals enabled control over the level of noise added to them to mimic experimental conditions. To create the synthetic signal, the morphology of slow waves from an experimental study was obtained. Gastric HR mapping was undertaken in three pigs for a duration of 10 minutes as described in Appendix A to include various morphologies of the slow wave event. For each pig experiment, five representative electrodes were chosen with a time period ranging from three to ten minutes. Figure 3.6(a) shows an example experimental gastric slow wave signal from a single
3.2 Noise removal

**Figure 3.5:** Framework for denoising signals using DWT. The gastric slow wave signals are first decomposed using the wavelet transform into details and approximations. Based on the type of filtering to be applied a threshold is applied to the details and approximations. To acquire the noise free slow wave signal, the thresholded approximations and details are reconstructed using the IDWT.

Electrode. For each of experimental signals, the slow waves were detected automatically (see Section 3.3), and were stacked according to the detected activation time of the slow wave event (Figure 3.6(b)). Average slow wave morphology for each electrode was then defined by the first principal component via a singular value decomposition of the stacked slow waves [7] (Figure 3.6(c)). The morphology was amplitude scaled and placed into its original position as seen in the experimental recordings, onto a uniform vector (Figure 3.6(d)). Artificial baseline and high frequency noise in sinusoidal form and random white noise were added to the synthetic signals to represent raw experimental recordings, as seen in Figure 3.7.
Figure 3.6: Creation of synthetic gastric slow wave signal from experimental gastric slow wave recording. (a) shows a raw gastric slow wave signal with the baseline wander eliminated. (b) shows each of the experimental gastric slow wave events from (a) stacked on top of each other using the detected activation times of the slow wave events. (c) shows the principal component of the stacked experimental slow wave events from (b). (d) is the creation of noise free realistic synthetic gastric slow wave signal using the principal component of the experimental slow wave event from (c). The timings and amplitude of the synthetic slow wave event were matched to the experimental slow wave recording.
Figure 3.7: Comparison of raw experimental gastric slow wave signal to synthetic gastric slow wave signal. (a) shows a raw experimental gastric slow wave recording, while (b) is the derived synthetic gastric slow wave signal with synthetic noise. (c) is a baseline removed experimental slow wave recording (with experimental high frequency noise), while (d) is the corresponding synthetic slow wave recordings with synthetic high frequency noise.
3. SIGNAL PROCESSING FRAMEWORK

3.2.1.4 Comparison of signal filters

To assess the filters, four performance metrics were used; (i) baseline correction ratio (Equation 3.3), (ii) Pearson cross correlation (Equation 3.4), (iii) noise correction ratio (Equation 3.5) and (iv) signal distortion ratio (Equation 3.6).

Baseline Correction Ratio (BCR) = \frac{\|b_o - b_e\|_2}{\|b_o\|_2} \tag{3.3}

Pearson Cross Correlation (PCC) = \frac{\sum (b_o - \mu_{b_o})(b_e - \mu_{b_e})}{\mu_{b_o}\mu_{b_e}} \tag{3.4}

Noise Correction Ratio (NCR) = \frac{\|n_o - n_e\|_2}{\|n_o\|_2} \tag{3.5}

Signal Distortion Ratio (SDR) = \frac{\|s_o - s_e\|_2}{\|s_o\|_2} \tag{3.6}

In Equations 3.3 and 3.4, \(b_o\) and \(b_e\) are the original and estimated synthetic baseline wander, while \(\mu_{b_o}\) and \(\mu_{b_e}\) are the mean estimates of the original and estimated synthetic baseline wander. While in Equation 3.5, \(n_o\) and \(n_e\) are the original and estimated synthetic noise signal and in Equation 3.6, \(s_o\) and \(s_e\) are the original and estimated synthetic signal of interest.

The use of the BCR and PCC metrics determined the effectiveness of the filters to eliminate the baseline wander. BCR takes a ratio of the L2 or Euclidean norm of the estimated baseline wander via filters and synthetic baseline wander. PCC assess the shape of the estimated baseline wander via filters to synthetic baseline wander. NCR and SDR quantify how well the filters perform during the high frequency noise removal and the signal integrity. Ideally, BCR, SDR and NCR would be zero, and PCC would be 1.

Figures 3.8 and 3.9 show the performance of the filters in 15 realistic synthetic slow wave signals under synthetic noise conditions. For baseline removal, the high pass Butterworth filter was not as effective as the Wavelet filter and the moving median filter. The BCR was similar for both the wavelet and the moving median filter.
but the PCC for the moving median filter was higher and had a low standard deviation than the wavelet filter. Based on this, the moving median filter was chosen to be the preferred filter for baseline removal in gastric HR mapping.

The low pass Butterworth filter performed poorly in SDR in comparison to the wavelet and SG filter. In terms of NCR, both the wavelet filter and the low pass Butterworth filter had similar performance, with the SG filter performing the best. Thus, the SG filter was chosen to be used for removal of high frequency noise in gastric HR mapping.

![Baseline correction ratio and Pearson cross correlation](image)

**Figure 3.8:** Comparison of three filters in 15 synthetic slow wave signals (as described in Section 3.2.1.3) to eliminate baseline wander using BCR in (a) and PCC of baseline estimates in (b). The high-pass Butterworth filter performed the worst in terms of BCR, with the wavelet filter and moving median filter performing equally well. However with PCC of the baseline estimates, the moving median filter works the best, followed by the wavelet filter and the high pass Butterworth filter.

### 3.3 Slow wave detection and clustering

The key feature in the gastric HR mapping is the slow wave event. The time at which the slow wave event has arrived at a particular electrode location defines the activation time of the slow wave event. The activation time also corresponds to the upstroke phase of the transmembrane potential in the underlying tissue.
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![Graphs showing Noise correction ratio and Signal distortion ratio for three filters: Low pass Butterworth, Wavelet, and SG filter.]

Figure 3.9: Comparison of three filters in 15 synthetic slow wave signals (as described in Section 3.2.1.3) to eliminate high frequency noise using the NCR in (a) and SDR in (b). With both metrics (a) and (b) the SG filter performed best, followed by the wavelet filter and the low pass Butterworth filter.

The slow wave event is typically manifested by a relatively large amplitude with a fast time scale (high frequency) and a negative deflection in the signal. This is followed by a relative slow recovery to baseline. The activation time in extracellular recordings is the point that relates to the fast initial large negative transient of the signal in the slow wave event.

When GI HR mapping was first used, the activation time of each slow wave event was manually assigned. Recently two automated algorithms have been developed to detect the point of interest. The first method was an amplitude sensitive differentiator that uses a fixed threshold based on the derivative of the signal to identify the point of interest [107]. The second method, known as the Falling Edge-Variable Threshold (FEVT) improves on the first method in two ways [53]. First, it exploits the nature of the sharp transient by taking a signal transform, and secondly, it uses a moving threshold to identify the points of interest. Figure 3.10(a) shows the detection of gastric slow wave using the FEVT algorithm, where the AT is marked as a cross. One of the risks of automated detection of activation times is that the signal or signal segment may not be representative of a true gastric slow wave activity and additional scrutiny through manual review or through an automated system (as described in Section 3.4) may be required. The automated detection
3.3 Slow wave detection and clustering

methods assume that the recorded slow wave activity is normal. They may have poorer performance in dysrhythmic scenarios, where the slow wave events can be irregular and may have varied signal morphology, such as double potentials which denote a potential collision site [112, 144].

![Graph showing slow wave activation and clustering](image)

(a) Slow wave activation events marked as red crosses.

(b) Clustering of slow wave events. Reproduced from [52].

**Figure 3.10:** Detection and clustering of gastric slow wave events. (a) show the results of the automatic detection of gastric slow wave events using the FEVT algorithm developed by Erickson et al. [53]. The red cross defines the activation time of the slow wave event. (b) shows the process of clustering a slow wave events into their associated slow wave propagation. Points in three dimensional space (x, y, time) represent a slow wave event and a polynomial surface is being estimated to group associated slow wave events to the propagating wavefronts. The filled circles represent fiducial markers that belong to the slow wave propagation, while the non-filled circles are not considered as part of the slow wave propagation.

Once the slow wave events have been marked using a fiducial marker in all the channels, isochronal maps depicting the spatiotemporal activity can be generated.
3. SIGNAL PROCESSING FRAMEWORK

by clustering individual wavefronts. This task used to be performed manually, but automated methods have since been developed to make it easier. Lammers et al. developed a wave mapping technique that groups waves based on the vicinity of fiducial markers in the surrounding electrode [106]. Erickson et al. further developed this technique to be more robust via the use of polynomial surface estimates to choose fiducial markers that belong to the propagating wavefront (Figure 3.10(b)) [52].

3.4 Data clean up

Automated techniques to detect and cluster slow wave events into cycles have been implemented and has been widely used in a number of GI HR mapping studies [142, 144]. This is a marked improvement from manual marking techniques which were previously employed. One of the time consuming tasks that remains is the manual correction of any automatically detected incorrect fiducial markers for slow waves. In this section, some of the potential noise sources are listed, along with an automated method to eliminate incorrect fiducial markers for slow wave events.

Signal filters enable the removal of noise, but as mentioned in Section 3.2.1 some of the noise overlaps in the spectral range of the slow wave signals. To prevent erosion of the signal of interest, filter parameters are set to allow the noise in the same spectral domain as the slow wave (such as respirator signals). Five such potential sources of noise that causes incorrect detection of slow wave events are as follows:

- Electrode contact on an electrically silent region of the stomach such as the fundus. This will yield a signal void of slow wave activity and will record primarily background noise.
- Non-contact or semi-contact of electrode with electrically active regions of the stomach, such as the corpus and antrum. This causes the signal morphology to be distorted, and as a result could also cause motion artefacts.
3.4 Data clean up

- Electrodes that are not recording with adequate signal to noise ratio. This could happen under conditions where the electrodes have been damaged.
- Motion and electrical artefacts. This could occur due to electrode reposition during an experiment, handling of the subject, subject ventilation or spurious artefacts from surrounding electrical devices.

These noise sources can manifest in a variety of morphologies as seen in Figure 3.11. Detection of noisy signal segment can be achieved through observing the recorded impedance values from the data acquisition system and setting a threshold on the recorded impedance values to delete low signal to noise ratio signals. The Biosemi data acquisition system used to record experimental data for this thesis allows the use of passive electrical recordings and the system outputs a variable called the “offset” and is designed to capture epochs or electrodes that are not recording properly. This “offset” is somewhat synonyms to the impedance value and is related to the saturation of the amplifiers in the recording system. In this case, there were no distinguishable limits that could be placed on the offset that could discriminate between slow wave signal content and noise. Thus, an automated algorithm was developed to remove spurious fiducial markers that did not resemble slow wave activity.

3.4.1 Algorithm to eliminate spurious slow wave markers

The algorithm uses a two stage process to eliminate incorrect fiducial markers representing the activation time for each slow wave event (Figure 3.12). The first step is based on a globalised approach which does not take into account the fiducial marker positions. This step is primarily aimed at eliminating channels that do not resemble any physiological gastric slow waves. The second step is a localised approach to assess whether the detected marker is a gastric slow wave event. Descriptions of each of the steps are detailed below.
Figure 3.11: Slow wave detection in channels with a range of noise levels. The red crosses represent the gastric slow wave events as determined by the FEVT automated detection algorithm [53]. The FEVT algorithm assumes the slow wave signal is noise free. The top two electrodes resemble gastric slow wave signal with high signal to noise ratio, while the remaining electrodes resemble noisy channels resembling low signal to noise ratio, with almost no slow wave events. High signal to noise ratio signals have slow wave events that are characterised by their regularly occurring pattern, and consistently defined morphology. Noisy signals are characterised by high amplitude (greater than 1000 µV), irregular timing, and inconsistent morphologies.
3.4 Data clean up

All signals filtered and slow waves detected

Compute average FFT frac (Short term fourier transform)

If FFT frac > 1

else

Good channel

Noisy channel

Acquire signal around slow wavemark

If sigV > sigThresh

else

Incorrect mark

Correct mark

Stack together for each channel

Compute Pearson correlation coefficients (PCC) against each signal

If average PCC < 0.4

else

Incorrect mark

Correct mark

Estimate the kurtosis (Kur) of the gradient of each signal

If Kur > 0

else

Incorrect mark

Correct mark

Figure 3.12: Algorithm to eliminate incorrect slow wave markers. A two-step process is used where the first step is a global check and uses frequency, while the second stage uses a local check which uses the signal amplitude, correlations, and kurtosis.
3. SIGNAL PROCESSING FRAMEWORK

The first stage is based on frequency analysis for each electrode. The time domain signals \( X(t) \) was transformed to the frequency domain via a fast Fourier Transform (FFT): \( Y = \text{FFT}(X(t)) \), where a fraction (\( \text{FFT}_{\text{frac}} \)) was calculated for each electrode signal, where the subscript of \( Y \) are the frequencies in cpm.

\[
\text{FFT}_{\text{frac}} = \frac{\max(Y_{f9-f20})}{\max(Y_{f1-f9})}
\]  

(3.7)

For robustness, a short term Fourier transform (STFT) was calculated with a moving window size of 2 minutes, and overlapped by 50%. STFT allows to capture the change in frequency over time and here it is primarily used to acquire multiple estimates of the frequency for a given signal. If the average of the \( \text{FFT}_{\text{frac}} \) for any of the electrode was greater than 1, it denotes that the dominant frequency of the signal lies in the frequency range of 9 to 20 cpm, which is not the dominant frequency range of slow wave signals. Thus, if \( \text{FFT}_{\text{frac}} \geq 1 \), the signal was not included for analysis. The \( \text{FFT}_{\text{frac}} \) measure was designed to eliminate the fiducial markers in channels which has dominant ventilator frequency (normally around 9–12 cpm), and maintain fiducial markers in channels which have a dominant slow wave frequency (normally around 3 cpm).

The second stage assesses the signal around the fiducial marker to quantify if the signal segment resembles a gastric slow wave event. Three metrics are quantified for each of the signal segments around a fiducial marker; (i) amplitude, (ii) cross correlation and (iii) kurtosis.

If maximum and minimum voltage limits of the signal segment did not fall within physiologically observed voltage limits for a gastric slow wave event, then that fiducial marker was removed. Secondly, cross correlations were computed to assess the shape of the signal segment. It is based on the fact that slow waves in a channel (or a particular segment) have similar morphologies. For each electrode signal, a window was placed around the fiducial marker, and stacked according to the activation time of the slow wave event (Figure 3.13). Pearson correlation coefficients (PCC) (Equation 3.8) were computed against each of the windows.

\[
PCC_{XY} = \frac{\text{cov}(X,Y)}{\sigma_X \sigma_Y}
\]  

(3.8)
In Equation 3.8, \( \text{cov}(X,Y) \) is the covariance of variables \( X \) and \( Y \), while \( \sigma_X \) and \( \sigma_Y \) are the standard deviation of variables \( X \) and \( Y \).

The PCC measure was chosen for morphological analysis because it is an amplitude insensitive measure, and variations in amplitude occur physiologically. For each fiducial marker, an average correlation coefficient value was obtained. If it was below a certain threshold (default was empirically set as 0.4) it was considered an incorrect slow wave fiducial marker. Figure 3.13 shows a set of pertinent and incorrect fiducial markers along with average cross correlation values. To take into account variations of slow wave morphologies in time, cross correlations were computed on a rolling time segment or for a defined number of slow waves.

Kurtosis was the third local metric used to assess whether the fiducial marker represents a slow wave event. This metric measured the peakedness of the histogram distribution and was estimated using Equation 3.9. The gradient of each signal segment was taken before the estimation of kurtosis. Thus, the estimation of kurtosis was used to assess the steepness of the negative deflection of the slow wave signal, which represents the activation time. As seen in Figure 3.13, a slow wave event with a high signal to noise ratio will yield a high kurtosis value (leptokurtic or platykurtic distribution), while a noisy signal would yield a low kurtosis value (mesokurtic distribution). One of the drawbacks of estimating kurtosis is that it can be sensitive to outliers making the kurtosis estimate misleading [81].

\[
\text{Kurtosis} = \frac{\sum_{i=1}^{n} (Y_i - \bar{Y})^4}{(N - 1)s^4} - 3
\]

The data clean up method was built into the GEMS software, where the user is able to adjust parameters as necessary during the analysis process. See Appendix C for further details on the GEMS software.

### 3.4.1.1 Validation and results

To assess the usefulness of the automated clean up algorithm, it was tested against the gold standard, which was manual deletion of fiducial markers. Two metrics,
3. SIGNAL PROCESSING FRAMEWORK

(a) Stacked pertinent gastric slow wave events.

(b) Stacked incorrect gastric slow wave events.

(c) Histogram of the gradient of the pertinent gastric slow wave events.

(d) Histogram of the gradient of the incorrect gastric slow wave events.

Figure 3.13: Stacking of pertinent and incorrect gastric slow wave events. (a) shows true detected slow wave events stacked on top of each other and are characterised by a consistent morphology. (b) shows incorrectly detected slow wave events stacked on top of each other and is characterised by varying amplitudes and an inconsistent morphology. (c) show the histogram of the gradient of the stacked slow wave events of (a) with the gradient signal shown in the inset. The true slow wave events have a sharp deflection which can be quantified via the histogram using kurtosis. (d) shows the histogram of the gradient of incorrectly detected slow wave events in (b) with the gradient signal shown in the inset. The incorrect slow wave signals do not have a sharp deflection and this can be quantified via the histogram using kurtosis.
sensitivity (Equation 3.10) and specificity (Equation 3.11) were measured for the effectiveness of the algorithm.

Six experimental gastric HR mapping datasets (3 pig and 3 human) ranging from 4.7–8.3 minutes were used. The experimental method used to acquire the datasets are described in Appendix A. First, noise removal was performed on the datasets, after which the FEVT algorithm was used to detect the signals of interest. Two experts in gastric slow wave mapping manually cleaned up the data sets. Two metrics, sensitivity and specificity were defined using true and false positives (TP and FP) and true and false negatives (TN and FN) as in Equations 3.10 and 3.11. Sensitivity and specificity were used to determine the effectiveness of the automated algorithm at eliminating incorrect fiducial markers for slow waves. TN is when authentic slow wave markers are correctly detected as authentic slow wave markers and TP is when erroneous slow wave markers are correctly detected as erroneous slow wave markers. FP is when authentic slow wave markers are incorrectly detected as erroneous slow wave markers and FN is when erroneous slow wave markers are detected as authentic slow wave markers. Sensitivity estimates the true positive rate of discarding erroneous slow wave markers, while specificity estimates the true negative rate of not discarding authentic slow wave markers. The results of the sensitivity and specificity of the algorithm are shown in a boxplot in Figure 3.14 with interquartile ranges, median and the outliers.

\[
\text{Sensitivity} = \frac{TP}{TP + FN} \tag{3.10}
\]

\[
\text{Specificity} = \frac{TN}{TN + FP} \tag{3.11}
\]

The algorithm results in an average of 91±3% (median: 91%) in sensitivity and 82±6% (median: 89%) in specificity to eliminate incorrect fiducial marker for gastric slow wave events. A default set of parameters has been used for testing of this algorithm. Varying the parameters based on a priori knowledge of the recorded data will increase the accuracy by removing incorrect slow wave events. For example, if the only noise present in the recorded data was the respiration artifact,
the FFT\textsubscript{frac} measure in the global check can be adjusted accordingly to increase the specificity of the algorithm. On the other hand, if the only noise present is from an externally applied pacing stimulus (World Precision Instruments, Sarasota, FL), then the local check can be applied alone with the signal threshold adjusted accordingly.

![Box plot showing sensitivity and specificity](image)

**Figure 3.14:** Quantification of the accuracy of the automated data clean up algorithm by comparison with the manual analysis. With the default parameters chosen for the algorithm to remove incorrect slow wave fiducial markers, the average sensitivity was 91\% and specificity was 82\%. Systematically determining the parameters for the algorithm, based on \textit{a priori} knowledge of the recording data set can increase the specificity and decrease the sensitivity and vice versa.

### 3.5 Visualisation

Once the slow waves have been clustered into their propagating wavefronts, the slow wave activity can be visualised to assess the spatiotemporal pattern and evaluate the stability over the recording. Before the use of these tools, it is sometimes necessary to perform interpolation to take into account missing data points.
One interpolation method used is the “spatially interpolated visualisation” (SIV), where an interpolation scheme is applied in two steps [52]. In the first step, any missing data points are interpolated around which there are three or more marked slow wave events. In the second step, any missing data points are interpolated around which there are four or more marked or interpolated slow wave events. The interpolation scheme used is an inverse distance squared method, as defined below in Equation 3.12

\[ Y = \frac{\sum_{i=1}^{n} \frac{X_i}{D_i^2}}{\sum_{i=1}^{n} \frac{1}{D_i^2}}, \]  

(3.12)

where, \( Y \) is the unknown value to be interpolated, \( X_i \) is the known value at point \( i \), \( D_i \) is distance between the known and unknown value, and \( n \) is the number of the known values in the grid.

One of the simplest ways to visualise slow wave propagation is via a square patch colour plot, where each electrode is denoted as patch and assigned a graded colour according to the activation time (Figure 3.15(a)). In this sequence of propagation, there is an ectopic pacemaker which excites circumferentially at the bottom of the array, and propagates upwards towards the bottom right of the array. Building up on the patch colour plot is the isochronal map, where each time block (i.e. 2 s intervals) is represented as a colour. This provides the same information as in the patch colour plot, but in a more visually intuitive manner (Figure 3.15(b)). Propagation direction can be assessed quickly along with a rough estimate of speed in linear propagating wavefronts.

Another intuitive approach to visualise the nature of the slow wave recording is to create an animated movie of the slow wave propagation. Here, an image frame is created for a certain time, with electrodes represented as square patches. As time progresses and if there is a slow wave fiducial marker in the electrode, it is ‘lit up’ to denote the activation phase of the slow wave and then fades away in time to represent the recovery phase of the slow wave (Figures 3.15(c) and 3.16). Figure 3.15(c) shows the sequence of frames from an animation of the propagation sequence from Figures 3.15(a) and 3.15(b).
3. SIGNAL PROCESSING FRAMEWORK

Figure 3.15: Spatiotemporal representation of slow wave propagation. (a) shows nine frames of a slow wave propagation illustrating the pathway of an ectopic pacemaker. Each white square represents an electrode that has activated which fades away in time into a black square representing an inactivation of the slow wave activity at the electrode at that particular time frame. The whole movie sequence is shown in [http://youtu.be/7HwDvBZ1540](http://youtu.be/7HwDvBZ1540). (b) is a patch color plot, where the activation time is marked as a coloured square. (c) show an isochronal time map where each colour band corresponds to the area activated in 2 s intervals.
3.5 Visualisation

With the knowledge of which fiducial marker belonging to which propagation, the propagating wavefront can be assigned a different colour. This is purely to denote the presence of separate wavefronts at any one time, which might not be intuitive during abnormal propagations. Figure 3.16 show an antegrade propagation colliding with an ectopic retrograde propagation. With only one colour to sequence the pattern of slow wave propagation, it is difficult to distinguish the wavefront (Figure 3.16(a)), but with the use of different colours to assign different wavefront, it can be visualised clearly (Figure 3.16(b)).

Figure 3.16: Visualisation of porcine gastric slow wave propagation via an animation. Four snapshots of gastric slow wave propagation are shown illustrating a clashing wavefront. In (a) the snapshots are in black and white, where the first snapshot shows the presence of two wavefronts, but in the other snapshots the clashing wavefront intersection is not discernible. The video in (a) is listed online on [http://youtu.be/PU8ce0ja8vQ](http://youtu.be/PU8ce0ja8vQ). In (b) the snapshots various wavefronts are assigned a different colour and the clashing wavefront is clearly visible. The video in (b) is listed online on [http://youtu.be/Pun--_E_jr0](http://youtu.be/Pun--_E_jr0).
3. SIGNAL PROCESSING FRAMEWORK

3.6 Summary

This chapter describes a signal processing framework for analysing HR spatio-temporal gastric slow wave signals, as recorded from the serosal surface of the stomach. The premise of this chapter was to describe the improvements and novel methods in developing a system for processing of gastric slow wave signals, which can provide an in-depth understanding of gastric slow wave propagation.

There are various noise sources during experimental conditions and the use of digital signal filters is an effective approach to eliminate most noise sources to reveal the underlying signal. To reduce the potential of the slow wave signal being degraded, optimal choice of recording techniques need to be employed and noise sources should be identified and minimised if possible during experimental recordings. The choice of recording system, electrode type and material, shielding of cables and wires, and experimental setup are important to acquire signals with a high signal to noise ratio [145].

Daniel and Chapman previously reported in 1963 that “Any system with a frequency response from DC to several hundred cycles per minute would appear to be adequate to record all of the slow waves ...” [40]. Based on analyses on serosal gastric slow wave recording, similar conclusions can be drawn. More specifically, the inclusion of the dominant frequency (3–5 cpm) and its major harmonics up to 2 Hz (120 cpm) allows a precise representation of extracellular gastric slow waves. In human gastric dysrhythmias, the slow wave activity is reported to be in the range of 0.5 to 10 cpm [99, 138]. This range of fundamental frequency does not change significantly from the normal case and the filter range of 2 Hz and below would still allow for a precise slow wave signal representation in gastric dysrhythmias [155].

Methods for automatically detecting slow wave events have already been developed, but one of the major hindrances was the presence of noisy segments of data or channels due to the inherent gastric electrophysiology, other physiological or non-physiological artefacts. An automated algorithm was developed to remove erroneously marked fiducial markers for the slow wave events in the signals. The automated algorithm achieved a sensitivity of 91% and a specificity of 82%.
3. Chapter summary

To summarise, a framework has been established for analysing HR gastric slow wave signals, under which appropriate filtering takes place, signals of interest are identified intelligently, and visualised in an intuitive manner. Although the framework has been designed with gastric slow wave signals as the primary focus, this framework can be adapted for other GI slow wave signals, such as for HR intestinal electrical recordings to analyse slow wave activity.
Chapter 4

Velocity and amplitude estimation

This chapter describes the quantitative methods for estimating the velocity and amplitude of the gastric slow wave propagation as defined by gastric HR mapping. Quantitative methods are imperative along with qualitative methods to reveal a deeper understanding of the gastric slow wave activity. Many of the quantitative and qualitative methods for gastric HR analysis have been derived from cardiac electrophysiology. However, due to differing physiological and signal characteristics, these methods have to be modified and new methods to be created specific for the use in GI electrophysiology [52, 53].

Accurate determination of slow wave propagation velocities and amplitude has become a central focus of gastric HR mapping analysis because substantial changes in velocity and amplitude have been associated with gastric dysrhythmias in the presence of abnormal circumferentially propagating wavefronts [142].

In this chapter, methods for estimating the velocity of the slow wave propagation were developed and applied in synthetic cases for validation, and then applied in experimental cases for verification. Methods of amplitude estimation were developed and compared to synthetic signals with artificial noise simulating experimental noise conditions. Velocity and amplitude of gastric slow wave propagation during dysrhythmic slow wave propagation pattern were then reviewed.
4. VELOCITY AND AMPLITUDE ESTIMATION

4.1 Velocity estimation

In the field of cardiac electrophysiology a number of studies have quantitatively validated different methods of velocity estimation and have guided appropriate usage \[14, 59\]. Some of the commonly used velocity estimation methods include the use of finite difference, polynomial fitting, and wavelets \[14, 59, 66\]. However, no validation studies have been conducted for gastric slow wave recordings. As the use of HR GI electrical recordings becomes more widespread, there is a pressing need to develop, validate and standardise methods to reliably and efficiently estimate and visualise velocities of slow wave propagations. This would also allow for a fair comparison of velocity outcomes between patient and studies.

Three different velocity estimation methods; (i) finite difference (FD), (ii) smoothed finite difference (FDSM) and (iii) polynomial based method (POLY4x4), were compared for their effectiveness for gastric HR mapping. The FD method is in current use in the GI HR mapping field \[110, 139\], with POLY4x4 and FDSM developed to address the shortcomings of the FD method. These three possible approaches of velocity estimation were validated using simulated and experimental data, and outcomes were quantitatively and qualitatively compared to identify the most suitable method for velocity analysis. Improved visualisation methods for velocity fields were also developed.

4.1.1 Methods

In simple terms, velocity describes the speed and direction of a moving object, which in this context is the slow wave propagation. This is computed by taking the gradient of the activation time at defined distances. In a two dimensional (2D) case, velocity is computed as follows \[14\],

\[
\begin{bmatrix}
V_x \\
V_y
\end{bmatrix} = \begin{bmatrix}
\frac{T_x}{T_x + T_y} \\
\frac{T_y}{T_x + T_y}
\end{bmatrix}
\]  \quad (4.1)

where \(T_x = \partial T / \partial x\) and \(T_y = \partial T / \partial y\) are the gradients of the activation time map with respect to the \(x\) and \(y\) directions of the recording array.
4.1 Velocity estimation

The simplest approach to estimate velocity on a 2D surface is to take a finite difference (one sided difference for the edges and central difference for the internal points) of the time array. This approach is implemented in the ‘SmoothMap’ software and has been used in several GI electrical mapping studies \[103, 110, 139\]. In practice, there are limitations with this method. Notably, any noise in the activation time map would be amplified after taking a difference in time values, leading to misleading estimates of velocity and would undermine the vector visualisation of the slow wave propagating wavefront. Also, if surrounding time values were not present in the time map, the velocity in the surrounding area was not estimated. This is particularly significant in clinical mapping studies when recordings are of reduced quality due to intra-operative recording restrictions, requiring some data interpolation \[52\].

To counter the disadvantages of the finite difference method, an interpolation and smoothing scheme was applied to generate a second method referred here as the smoothed finite difference approach, which has not been used in the GI HR mapping field before. Once \(\partial T/\partial y\) and \(\partial T/\partial x\) were found, any missing data points were interpolated using an inverse distance squared interpolation \[84\], which was defined as,

\[
Y = \frac{\sum_{i=1}^{N} X_i D_i^2}{\sum_{i=1}^{N} D_i^2}
\]

(4.2)

where \(Y\) is the unknown value to be interpolated, \(X_i\) is the known value at point \(i\), \(D_i\) is distance between the known and unknown value, and \(N\) is the number of the known values in the grid. The values of \(V_x\) and \(V_y\) were then smoothed using a Gaussian filter (Equation 4.3) using a 2D convolution in order to reduce any noise amplification by the finite difference approach. The Gaussian filter was defined as,

\[
G_{filt}(x,y) = e^{-\frac{x^2+y^2}{2\sigma^2}}
\]

(4.3)

where \(\hat{x}\) and \(\hat{y}\) define the size of the filter and \(\sigma\) is the standard deviation of the filter. The values for the Gaussian filter were empirically chosen to be \(\hat{x} = \hat{y} = 1, \ldots, 5\) in integer steps and \(\sigma\) as 0.75.
Bayly et al. [14] introduced a method of estimating velocities in cardiac electrical mapping, which eliminates the problem of noise amplification present in the finite difference approach. A second order polynomial of the form:

\[ T(x, y) = ax^2 + by^2 + cxy + dx + ey + f \]  

was fitted to the activation time map, where the coefficients (a–f) were found using a least squares fit, computed via singular value decomposition. The derivatives of the second order polynomial were then used to approximate the velocity. The polynomial fit of the activation time acts as an interpolant and a smoothing function. The criteria for selecting a window size for fitting the polynomial was suggested as being four times the sampling interval [14]. In this experimental setup, the sampling interval was 4 mm and thus a window size of 16 by 16 mm (or 5 by 5 electrodes in the flexible PCB setup) was used. In some previous GI electrical mapping studies, the polynomial based method was applied to the whole array of 60 by 60 mm, to visualise velocity fields [48, 49, 141], even though this application of the method effectively erodes spatial resolution for complex patterns.

### 4.1.1.1 Analytic test cases

Three synthetic test cases with known velocities were created to test the effectiveness and sensitivity of the velocity estimation methods. The electrode configuration for the analytic test cases was the same as experimental recordings. The first synthetic time map mimics orderly antegrade and retrograde slow wave propagation (Figure 4.1(a) [139, 144]). It was defined using the form:

\[ T(x, y) = ax + by \]  

where \( T(x, y) \) represents the time in a 2D activation time map at coordinate locations \( x \) and \( y \), while \( a \) and \( b \) are the coefficients in the equation \( (a = b = 0.1414 \text{ s mm}^{-1}) \).

The second synthetic time map was an elliptical wave with propagation emerging from the bottom left of the electrode array (Figure 4.1(b)), and mimics ectopic
focal activities\textsuperscript{[112, 144]}. The third synthetic time map has two elliptical waves propagating from opposing edges of the electrode array to clash in the center of the array (Figure 4.1(c)), and mimics interacting dysrhythmic activities and gastric pacing\textsuperscript{[139, 144]}. The second and third synthetic time maps were created from an elliptical wave of the form,

$$T(x, y) = K \sin \left( -k_r \sqrt{a(x - x_0)^2 + b(y - y_0)^2} \right)$$  \hspace{1cm} (4.6)

and approximated with known anisotropic propagation of gastric slow waves\textsuperscript{[141]}. The second synthetic time map was a single source propagation with coefficients, $K = -30$ s$^{-1}$, $k_r = -0.25$ s mm$^{-1}$, $a = b = 0.02$ s mm$^{-1}$, and $x_0 = y_0 = 10$ mm. The third synthetic time map represented two clashing wavefronts, where the coefficients were, $K = -30$ s$^{-1}$, $k_r = -0.25$ s mm$^{-1}$, $a = b = 0.02$ s mm$^{-1}$, and $x_0 = y_0 = 0$ mm for the one of the source, and $x_0 = y_0 = 60$ mm, for the other source. These synthetic time maps were perturbed with random noise (described in Section 4.1.1.2) to simulate experimental recordings.

**4.1.1.2 Experimental noise**

A potential limitation for velocity estimation comes in the form of noise in the data set. Two main potential sources of noise have been identified: (i) signal noise and (ii) electrode drop-out noise. These were simulated in the synthetic time maps to quantify the performance of the velocity estimation techniques.

**Signal noise**

Activation times are defined as the most negative deflections in the slow wave\textsuperscript{[53, 177]}, and signal noise arises from the judicious selection of the fiducial point for the slow wave. The process of selecting the fiducial point for the slow wave has recently been automated\textsuperscript{[53]}, but manual review is still required to eliminate and correct erroneous events. From experimental pig recordings, the width of a normal slow wave events were approximately 0.5 s in duration (Figure 4.2). Noise can be introduced either during manual marking, or when slow waves are ‘fractionated’
4. VELOCITY AND AMPLITUDE ESTIMATION

Figure 4.1: Three synthetic isochronal map (1 s interval) shown are; (a) a propagation of a linear plane wave, (b) elliptical wave with activity propagating from the center of the electrode array, mimicking ectopic focal slow wave activities, and (c) an elliptical wave with activity propagating from the opposing edges of the array to clash in the center, mimicking dysrhythmic slow wave propagation or propagation during gastric pacing. The red color represent the earliest time of activation and blue represents late activation at the site. Reproduced from [156].
(having multiple components) \[53\]. For comparison, the width of the QRS beat generated by the heart is around 0.04–0.12 s, such that the potential for error is markedly reduced \[169\].

\[\text{Figure 4.2: A typical extracellular gastric slow wave event. The dotted line shows the range along the negative deflection where the activation time could possibly be chosen via manual marking. Ideally the activation time would be the steepest negative deflection point in the signal, which is marked as a cross. Reproduced from \[156\].}\]

**Electrode drop-out noise**

Another potential source of problem from the electrode array is when the recorded signals become saturated. This can be due to insufficient electrode contact with the serosa, inadequate soldering, or if the electrode arrays are not connected properly. When this occurs, an incomplete view of the gastric slow wave propagation pattern may be obtained.

**Synthetic experimental noise**

Of the two potential noise sources described, signal noise was the most encountered noise in HR GI electrical mapping. Careful precautions were taken in order to
4. VELOCITY AND AMPLITUDE ESTIMATION

avoid electrode drop-out noise. These noise issues present significant problems not only for velocity estimation but also for isochronal contour mapping and analysis of slow wave activation wavefront [52]. Synthetic noise was added to test cases to replicate experimental recording conditions. To represent signal noise, errors in the activation times were added to the synthetic cases at each electrode position as uniform random perturbations ranging from 0 to 0.5 s. Electrode drop-out noise was simulated by random removal of between 0 to 40% of the electrodes from the synthetic data sets.

4.1.1.3 Validation and comparison methods

For synthetic test cases, the computed velocity using the three methods (FD, FDSM and POLY4x4) was compared to the analytic velocity vector. Speed error was expressed as a percentage, which was defined as:

\[
(1 - \frac{\text{Estimated speed}}{\text{True speed}}) \times 100
\]

and the angle error as a relative difference in degrees, as introduced by Fitzgerald et al. [59]. Once the difference between the estimated and the analytic map was found, the median difference of the map was taken. Since the noise introduced was of a random nature, multiple runs (n=100) at the same noise level were taken for statistical robustness. The data is reported as mean of the median difference and standard deviation of the median difference. To test if there are statistical difference between the velocity estimation methods, an analysis of variance (ANOVA) test was performed on the results of the simulated tests.

In the presence of the electrode drop-out noise, not all three methods were able to estimate the velocity at all electrode positions where there was an activation time. The percentage of electrodes estimated with velocity was calculated as:

\[
\% \text{ of electrode array} = \left( \frac{\text{Total no. of estimated velocity vectors in array}}{\text{Total no. of recorded activation time in array}} \right) \times 100
\]
For experimental data, the velocity values were estimated using the three different methods and the results presented as mean±standard deviation. As the experimental data was of normal organised gastric slow waves, a high standard deviation in the velocity estimation would confer that the methods did not perform reliably.

### 4.1.2 Results

#### Simulated Data

Velocity estimation error in synthetic test cases described in Section 4.1.1 with the presence of noise is presented in Figure 4.3 and Figure 4.4. The two figures are laid out in the same configuration, where the speed error is displayed in the first column, and the angle error in the second column. A table of p-values are also listed for each test case, with each of the specified noise types in Appendix D (Tables D.1–D.5).

As there was more uncertainty in the accuracy of the activation times, the FD method had a higher velocity error than the FDSM and POLY4x4 methods. When compared for all noise levels, in three synthetic cases, the FD method had an average speed error of 12% and an angle error of 7°, while the FDSM method and the POLY4x4 method both had a speed error of 6% and an angle error of 3°. There was a statistical difference in all levels of signal noise and FDSM had an overall better estimate of speed and angle (see Appendix D – Tables D.1 and D.2). Although FDSM and POLY4x4 both performed well, POLY4x4 had a slightly higher standard deviation than FDSM. The FD method had an error of approximately twice that of the FDSM method and the POLY4x4 method for its speed error and angle error.

With the presence of increasing electrode drop-out noise, the FD method had a modestly better estimate of velocity. The FD method had an average median speed error of 0.2% and angle error of 0.1°, while the FSM method and the POLY4x4 method had a speed error of 0.9% and 0.4% and an angle error of 0.8° and 0.2°. The FD was unable to estimate velocities in sections where there were missing
Figure 4.3: Error in estimating velocity using three velocity estimation methods on synthetic test cases with the presence of increasing signal noise. Each row represents a synthetic test case. The data for this graph along with the p values are shown in Appendix D. Reproduced from [156].
4.1 Velocity estimation

electrodes. An interpolation scheme is required for this, which is implemented in
the FDSM method. Figure 4.5 shows the percentage of velocity estimated of the
existing time map is recorded with increasing electrode drop-out noise. At 35% of
electrode drop-out noise, the FD method estimated velocity in 26% of the array
and the POLY4x4 method estimated 95% of the array and the FDSM method
estimated 100% of the array. Although the FDSM method performed the worst
in comparison to the FD and POLY4x4 method, the velocity error is very small
and practically negligible and also provides the benefit of estimating the velocity
at all electrode points where an activation time has been marked.

![Graphs showing error in estimating velocity using three velocity estimation methods](image)

**Figure 4.4:** Error in estimating velocity using three velocity estimation methods
on synthetic test cases with the presence of increasing electrode drop-out noise.
Each row represents a synthetic test case. The data for this graph along with the
p values are shown in Appendix D. Reproduced from [156].
Figure 4.5: Percentage of electrode array being estimated with velocity, in the presence of electrode drop-out noise. The percentage of electrodes estimated with velocity was calculated as in Equation 4.8. Reproduced from [156].
Experimental Data

Figure 4.6 (a) shows a typical example of dysrhythmic porcine gastric slow wave propagation pattern that is organised, while Figure 4.6(b)–(g) show the velocity map estimated using the FD, FDSM and POLY4x4 methods. This representative slow wave propagation pattern illustrates that the FD method has not estimated the entire recorded time map as was quantified for simulated data. In addition, the polynomial based method has “overshoots” at the edges, and its vector direction along the horizontal circumferential direction is lacking due to the intrinsic smoothing in the polynomial. The smoothed finite difference method shows the regions of interest in a readily appreciable manner and corroborates the qualitative face-value judgement taken from the activation time map.

Figure 4.7 shows the average velocity of gastric slow waves propagation from three pigs (10 waves each), derived from three velocity estimation methods, along with the standard deviation. All of the methods estimated similar mean speed estimates (FD: 7.3 mm s\(^{-1}\), FDSM: 6.3 mm s\(^{-1}\), POLY4x4: 6.3 mm s\(^{-1}\)) and similar angle estimates (FD: 113°, FDSM: 114°, POLY4x4: 102°) for velocity estimation. However the standard deviation of the FDSM was lowest for speed (FD: 7.2 mm s\(^{-1}\), FDSM: 1.5 mm s\(^{-1}\), POLY4x4: 2.7 mm s\(^{-1}\)) and angle (FD: 20°, FDSM: 13°, POLY4x4: 31°) for velocity estimation. Since all the slow wave propagation patterns are of normal organised activity, a lower standard deviation implies a better estimate of velocity.

4.1.3 Discussion

Three methods for velocity estimation in HR GI electrical mapping have been compared and their reliability and accuracy have been quantified. Various GI studies have utilised either one of these methods and comparison of velocity estimates across studies would need to take into account the variability and accuracy of the different methods. In the simulations performed, the FDSM method performed better than the FD method and the POLY4x4 method in the presence of activation time error. This finding was further reinforced in experimental data.
4. VELOCITY AND AMPLITUDE ESTIMATION

Figure 4.6: Comparison of velocity estimation methods in an experimental recording. (a) Isochronal activation time map (2 s intervals) of an organised dysrhythmic gastric slow wave propagation. (b)-(g) are the velocity estimates using the FD, FDSM and POLY4x4 methods. The left hand column and right hand column are the same maps shown with different scales. (b) and (e) are velocity estimates using the simple FD method, while (c) and (f) uses the FDSM method, and (d) and (g) uses a POLY4x4 method. In (a), the red dots are interpolated time values, while the black dots are recorded values of activation time, while in the velocity maps the color map represents speed (mm s\(^{-1}\)) and vectors show the direction. Reproduced from [156].
4.1 Velocity estimation

Figure 4.7: Velocity estimates of slow wave propagation from three experimental pig recordings (10 waves each) from the stomach serosa. Speed and angle of the velocity vectors were estimated using the FD, FDSM and POLY4x4 method. (a) shows the average speed estimate for the three method along with the standard deviation as error bars. (b) shows the average angle estimate along with the standard deviation as error bars. Adapted from [156].
analyses, where the FDSM method yielded a lower standard deviation in its velocity estimate than that of the FD method and the POLY4x4 method. Therefore the novel FDSM method was advocated for future applications in HR GI electrical slow wave mapping.

A psychometric analysis would need to be performed to define acceptable levels of velocity error, similar to the study conducted by Fitzgerald et al. [57], where isochronal contour maps and velocity maps were compared. The main barrier in performing psychometric studies in gastric electrical mapping is that the relationship between and within complex and normal slow wave activation wavefronts have not yet been well understood. Qualitative analysis of vector maps can be as important as quantitative analysis, because clinicians make treatment decisions based on visual interpretations of the maps denoting activation and velocity. Figure 4.6 shows the visualisation of an abnormal gastric slow wave propagation patterns as an isochronal activation map and velocity estimated using three methods. It shows that the FDSM method of velocity estimation allowed for better qualitative visualisation of the slow wave propagation pattern.

With the use of 2D HR electrical mapping one has to take into account any presence of transmural components when analysing velocity estimates [14]. In the field of cardiology it is common to analyse conduction velocity with respect to the fiber orientations. It was assumed that the ICC network in smooth muscles is a 2D plane along the electrode array as placed in the stomach, and the propagation velocity is defined with respect to the electrode grid. There are currently no HR transmural mapping studies of the GI tract, and if such studies were performed in future, these velocity estimation methods can used to inform a better understanding of the slow wave characteristics.

One of the assumptions of the described FD methodologies is that the electrode grid is regular. If the electrode grid is irregular or in a three dimensional topology, methods taking into account differing distances would need to be computed such as the use of divided differences, Lagrange, interpolation or Bessel’s central difference. In this context, the polynomial fitting method would not change significantly, other than introducing a third ‘z’ coordinate into the equation, and
4.2 Amplitude estimation

could offer an advantage. Other velocity estimation methods which have been used in cardiac electrophysiology could potentially be assessed for use in the GI field. Gaudette et al. [66] used wavelets to estimate velocities, but mentioned that it was unreliable with slow velocities. Since our velocities of interest are inherently slow, this method was not investigated further for our experimental set-up. Fitzgerald et al. [59] used a first order polynomial model to estimate velocities from catheter measurements. This method is an attractive option for use with a small electrode array. Another method which has recently been reported in cardiac electrophysiology is the fitting of activation times to radial basis functions, which is an extension to the polynomial fitting method [124]. This method might be better than the method proposed by Bayly et al. [14], but may be computationally more expensive.

4.2 Amplitude estimation

The strength of the slow wave event is represented by the amplitude of the slow wave deflection. There is a sudden increase in the amplitude of the slow wave event as it passes from the corpus to the antrum in the human stomach (mean: 0.27 mV to 0.52 mV), and similar patterns have been observed in animals [90, 111, 139]. Various types of ICCs have been discovered with regional spatial distribution across the stomach. For example, the ICC intramuscular network is the dominant network responsible for slow wave propagation in the corpus [73, 179], while the ICC Auerbach’s plexus network is the dominant network responsible for slow wave propagation in the antrum [75, 77]. One hypothesis for the change in serosal extracellular amplitude as recorded in vivo, is that the slow wave has traversed the different types of ICC network, across the stomach, to evoke unique spatial characteristics of slow wave activity [111]. A recent study has also indicated that high-amplitude slow wave activity may be linked to dysrhythmic slow wave activity [142]. Accurate amplitude estimation of extracellular slow wave activity is therefore pertinent to understanding the regional differences of slow wave amplitude in the stomach and the underlying GI electrophysiology.
4. VELOCITY AND AMPLITUDE ESTIMATION

In GI HR mapping, Lammers et al. [103] calculated the slow wave amplitude using a maximum-minimum method. In this section, a robust amplitude calculation method based on derivatives was developed and compared against the maximum-minimum method for its effectiveness in signals that have a low signal to noise ratio.

4.2.1 Methods

Lammers et al. [103] calculated the amplitude of the slow wave event by placing a 1 s window around the detected activation time and taking the difference between the maximum and minimum values – called the ‘maximum-minimum method’. This requires the signals to have a high signal to noise ratio, the maximum value of the signal as the peak of the slow wave deflection and the minimum value as the trough of the slow wave deflection.

The derivative of a signal provides information about the rate of the change of the signal. This information can be used to identify the peak and trough of the slow wave event so that the amplitude of the slow wave can be estimated. Figure 4.8 shows an idealised case of a slow wave event where the zero crossing of the first derivative of the signal identifies the peak and trough of the slow wave event.

However in experimental recordings, slow wave events do not always have a high signal to noise ratio, and an algorithm (Figure 4.9) was devised to estimate slow wave amplitude in experimental conditions. To prevent amplification of high frequency noise during differentiation of the slow wave signal, the slow wave differential signals were determined via Savitzky-Golay digital differentiators [121]. The parameters were empirically chosen to suppress noise amplification (1st derivative – polynomial order: 6, window size: 0.23 s, 2nd derivative – polynomial order: 6, window size: 0.63 s). The peak and trough positions were estimated from the zero crossing of the first derivative of the signal to find the slow wave peak and trough voltage value (‘peak and trough estimation’ in Figure 4.9). If the derivative information cannot ascertain a zero crossing for peak or trough, the algorithm reverts to the maximum and minimum method by Lammers et al. [103]. Also the computed
values undergo a check if the amplitudes were within the range of expected slow wave amplitudes (Figure 4.9). From experimental slow wave recordings and previously published studies, the range of acceptable amplitude values were systematically defined to range from 100 \( \mu \text{V} \) to 2 mV [49, 111, 139]. The wide variability in the amplitude range was to ensure slow wave recordings from various species can be analysed (maximum reported values; human: 0.8 mV, porcine: 1.4 mV, canine: 2 mV) [49, 111, 139].

### 4.2.2 Results

To evaluate the effectiveness of the derivative based method of slow wave amplitude estimation, experimental synthetic signals were used (as defined in Section 3.2.1.2). Normally distributed random noise was added to the 15 synthetic slow wave signals in increments of 10 \( \mu \text{V} \) up to 60 \( \mu \text{V} \). Prior to noise addition to the synthetic signals, the peak and trough positions were identified to compute the slow wave deflection width and amplitude. After noise was added, the slow wave deflection width and
VELOCITY AND AMPLITUDE ESTIMATION

\[ V = \text{Stacked SW events based on AT on electrodes} \]

\[ \text{Compute smooted SW derivates by convolving SG derivative coefficients} \]

\[ Z_{rC_1,2} = \text{Zero crossing of 1st and 2nd derivative of SW event} \]

Peak and trough estimation

- Find peak for each SW event
  - \[ \text{PeakPos} = Z_{rC_1,2} < \text{AT} \]
  - If PeakPos exists, Yes; No otherwise
  - \[ \text{Peak} = V \left[ \max (\text{PeakPos}) \right] \]

- Find trough for each SW event
  - \[ \text{TroughPos} = Z_{rC_1,2} < \text{AT} \]
  - If TroughPos exists, Yes; No otherwise
  - \[ \text{Trough} = \min (V) = V \left[ \max (\text{TroughPos}) \right] \]

\[ \text{Ampl}_{\text{comp}} = \text{Peak} - \text{Trough} \]

- If \[ \text{Amp}_{\text{min}} > \text{Ampl}_{\text{comp}} > \text{Amp}_{\text{max}} \] exists, Yes; No otherwise

- Assign NaN to SW amplitude
- Assign \[ \text{Ampl}_{\text{comp}} \] to SW amplitude

**Figure 4.9:** Flowchart to estimate the amplitude of a slow wave (SW) event. For computational efficiency, all of the slow wave events were stacked using the activation time (AT) of the slow wave. Then the derivatives of the slow waves were estimated using SG derivative coefficients, after which the zero crossings of the derivative signals were determined. Then zero crossing position prior to the activation time and past the activation time are the peak (PeakPos) and trough (TroughPos) of the slow wave event. Subtracting the signal value of the peak and the trough provides the slow wave amplitude (Ampl\text{\_comp}). If the peak and trough were not found or the calculated amplitude were not within physiological limits, it was discarded (set to not a number (NaN) in the array).
signal amplitude from the maximum-minimum method and the derivative based method were compared to the manually estimated values. Figure 4.10(a) shows the boxplot of the error in estimating the width of the slow wave deflection.

For estimation of the slow wave deflection width, the maximum-minimum methods had an average error of 0.45±0.75 s, while the derivative method had an average error of 0.07±0.1 s (Figure 4.10(a)). For amplitude estimation, the maximum-minimum method had an average error of 44±63 µV, while the derivative method had an average error of 16±15 µV (Figure 4.10(b)). Amplitude estimation errors were biased due to the fact that the manual estimates of the amplitude were done prior to the addition of noise. Nonetheless, the bias would only surmount to the level of random noise added (maximum mean noise: 30 µV). From the boxplots in Figure 4.10 it can be seen that the derivative based method consistently has errors in a narrow range, but the maximum-minimum method has a large error band. Thus, the derivative based method is more robust and reliable than the maximum-minimum method for slow wave amplitude estimation.

4.2.3 Discussion

Slow wave amplitude estimation is critical to understanding the underlying electrophysiology of gastric slow wave activity and motility. Two methods of amplitude estimation have been compared with realistic synthetic slow wave signals. The maximum-minimum method assumes the signal is of a defined morphology, and if regular, then this method is sufficient. Unfortunately slow wave signals recorded using PCB electrodes can be of a lower signal to noise ratio due to insufficient electrode-tissue contact, and this method may lead to misleading amplitude estimates. Figure 4.11 shows an example of slow wave recordings where the uppermost signal with a low signal to noise ratio has a distorted signal morphology with a lower amplitude, whereby amplitude estimates (either automated or manual) at this site would be physiologically misleading. Also it is known that double potentials occur with slow wave activity, making the maximum-minimum method unreliable to estimate slow wave amplitude [144]. The developed derivative based method was able to identify the peak and trough of the slow wave signal precisely, and thus estimate amplitude accurately.
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Figure 4.10: Error in estimating the amplitude and width of slow wave deflection. Two methods of amplitude estimation, maximum-minimum (Max-Min) and a derivative based method (Derivative), were compared to manually marked events of the peak and trough of the slow wave events prior to noise addition. (a) shows the absolute error in estimating the width of the slow wave deflection, while (b) is the absolute error in estimating the amplitude. For the slow wave interval, the Max-Min method has an average error of 0.45±0.75 s, while the Derivative method has an average error of 0.07±0.1 s. For amplitude estimation, the Max-Min method has an average error of 44±63 µV, while the Derivative method has an average error of 16±15 µV.
Figure 4.11: Illustration of slow wave recordings with high and low signal to noise ratio. The signals show are from a column of a PCB electrode array. The top signal has a low signal to noise ratio potentially due to insufficient contact, which can lead to a signal with a distorted signal morphology. The automated amplitude estimation algorithm would not work well for this signal. The seven slow wave recordings below have a high signal to noise ratio with well defined and consistent morphologies, where the automated amplitudes estimation techniques would work well.
4. VELOCITY AND AMPLITUDE ESTIMATION

4.3 Characterisation of porcine gastric slow wave propagations

With the use of HR mapping, spatial characteristics of the normal gastric slow wave propagation are being identified in humans and in animals [49, 111, 139].

In the normal human stomach, the pacemaker region (greater curvature in the upper to mid corpus) has a higher amplitude and velocity (0.57 mV, 8 mm s\(^{-1}\)), compared to the corpus region of the stomach, which has a mean amplitude of 0.25 mV and mean velocity of 3 mm s\(^{-1}\) [139]. At the corpus antrum border it was found the slow wave wavefront increased in amplitude (to 0.52 mV) and velocity (to 5.9 mm s\(^{-1}\)) [139].

With the ability to detect dysrhythmic patterns of slow wave propagation using HR mapping techniques, it is pertinent to understand the differences in the characteristics of a dysrhythmic slow wave propagation pattern. A method was developed to establish the presence of dysrhythmic propagation wavefronts, after which validated methods of velocity and amplitude were used to assess the characteristics of the wavefront.

4.3.1 Methods

Gastric HR mapping was performed on seven pigs for a duration ranging from 3–12 minutes using the experimental protocols as described in Appendix A. The signals were processed using the steps mentioned in Chapter 3 to create an activation time map. Velocity and amplitude of the gastric slow wave propagation were then calculated using the methods described in this chapter.

For the normal pacemaker region studies, the ‘area of interest’ for statistical evaluation was defined as being the area contained within the first 2 s of propagation. This determination was guided by previous HR mapping studies, in which high-amplitude, high-velocity normal pacemaker was empirically demonstrated by 2 s of propagation time in most subjects [111, 139].
4.3 Characterisation of porcine gastric slow wave propagations

For dysrhythmia studies, the presence and location of a circumferential propagation was determined by an algorithm (Figure 4.12). First, for a normal propagation wave in the data set, the angle of the propagation was determined from the velocity vectors (Equation 4.9),

$$\theta = \tan^{-1}\left(\frac{V_x}{V_y}\right),$$  \hspace{1cm} (4.9)

where $V_x$ and $V_y$ are the normalised velocity components in the $x$ and $y$ directions on the recording array.

The angles were then averaged for the normal waves (set as $\overline{\theta}$) and the standard deviation ($\theta_{std}$) was also calculated to account for deviations in the mean angle of propagation. Two assumptions are made about the velocity field; (i) the average angle of the normal slow wave propagation $\overline{\theta}$ was assumed to be the longitudinal axes, and (ii) the orientation of the circumferential axes of the slow wave propagation is tangential to the longitudinal axes.

Subsequent velocity fields of gastric slow wave propagation patterns in the same data sets were then compared to the normal $\overline{\theta}$. If the velocity vector was greater than the specified threshold, it is considered an abnormal velocity vector in the propagation field. The specified threshold was defined to be 10 degrees ± 95% of the standard-error-mean. The velocity components of these abnormal velocity vectors in the field are then decomposed into longitudinal ($V'_l$) and circumferential ($V'_c$) components (Equation 4.10). An ‘anisotropic’ ratio was calculated between $V'_l$ and $V'_c$, as $\frac{V'_c}{V'_l}$, and if that exceeded 2, it was called a circumferential velocity field. The threshold of 2 was chosen empirically based on previously recorded HR mapping data.

$$V'_l = V'cos(|\overline{\theta} - \theta|)$$
$$V'_c = V'sin(|\overline{\theta} - \theta|)$$  \hspace{1cm} (4.10)

Calculated amplitude and velocity values within the defined area of interest for each experiment were averaged. A paired Student’s $t$-test was then used to test statistical difference ($p<0.05$). Means were calculated and standard error of mean
4. VELOCITY AND AMPLITUDE ESTIMATION

(a) Flowchart to detect dysrhythmic slow wave identification.

(b) Representation of the dysrhythmic velocity vector decomposition.

Figure 4.12: Dysrhythmic slow wave identification. (a) Flowchart of the identification algorithm. The orientation of the velocity vector was used as the indicator of dysrhythmia. The angle of each velocity (θ) and the average angle of the normal activity (θ̄) was calculated. The standard error of mean was calculated from the standard deviation (δ), number of events (n), and the z-value at 95% confidence interval. The threshold value was calculated by adding an offset value (Δ) to the standard-error-mean. (b) An identified dysrhythmic velocity (V) was decomposed into a longitudinal component (V′_l) and a circumferential component (V′_c), with the longitudinal direction defined by the direction of the normal velocity (V). Adapted from [47].
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is reported. Confidence intervals within 95% are noted as CI with the lower and upper bounds in square brackets.

4.3.2 Results

Circumferential propagation during dysrhythmia

Experimental slow wave recording from eight datasets acquired from seven pigs were included for the analysis of circumferential propagation profiles during gastric dysrhythmia. These recordings comprised of five instances of spontaneous ectopic pacemaking from the distal corpus, and one case each of incomplete conduction block, complete conduction block with escape events, and slow wave re-entry. Circumferential propagation emerged in conjunction with the dysrhythmias in all eight recordings. Figure 4.13 demonstrates an example of an escape event arising in the gastric corpus and generating wavefronts propagating in all directions. In this example, the velocity in the area of interest during circumferential conduction (adjacent to the escape events; Figure 4.13B) was higher than the velocity in the same area during normal control cycles (Figure 4.13A; mean 10.8±3.4 mm s⁻¹ vs 6.5±1.4 mm s⁻¹; p<0.001). Recorded potentials within this area of interest also had higher amplitudes during dysrhythmic cycles (mean 823±296 µV vs 580±236 µV; p<0.001) than during normal cycles. The flexible PCB array recording in Figure 4.13 was placed in the greater curvature of the stomach near the upper corpus. The velocity difference, in the region of interest (denoted by red dots in Figure 4.13B (d)), in the escape pattern indicates that the activation characteristics of the ICC network generating the slow wave event has changed. It has been hypothesised that the myenteric ICC network acts as a primary potential to drive longitudinal propagation, while the intramuscular ICC network acts as a primary potential to drive circumferential propagation [142], and the interplay of the ICC networks determines the propagation pattern as seen in Figure 4.13.

Significant increases in velocities and signal amplitudes occurred with circumferential propagation in all other (n = 7) dysrhythmic recordings (p<0.01 in all cases).
4. VELOCITY AND AMPLITUDE ESTIMATION

Figure 4.13: Normal and ectopic pacemaking of slow wave propagations on the pig stomach. (A) Normal slow wave propagation recorded in the mid corpus region of the stomach, (B) Dysrhythmic slow wave propagation as the same position. An ectopic pacemaker is shown propagating and colliding with an antergrade slow wave wavefront. (a) Isochronal maps; Each black dot represents an electrode and each division (isochrone) corresponds to 1 s of propagation. (b) Velocity field map; Arrows shows the propagation direction, while the propagation speed is plotted by a colour spectrum (mm s\(^{-1}\)). (c) Amplitude maps; Slow wave amplitude is plotted according to a colour spectrum (\(\mu V\)). (d) Area of interest determination; Sites of circumferential propagation were calculated according to the algorithm described in Figure 4.12. Reproduced from [142].
4.3. Characterisation of porcine gastric slow wave propagations

Further examples are presented in Figure 4.14 (incomplete conduction block) and Figure 4.15 (distal ectopic pacemaking). Combined data across all eight experiments showed that the decomposed porcine gastric slow wave velocity values were on average around 30% higher during circumferential versus normal longitudinal conduction $[8.9 \pm 0.3 \text{ mm s}^{-1} \text{ vs } 6.9 \pm 0.5 \text{ mm s}^{-1}; \text{mean difference } 2.0 \text{ mm s}^{-1} \text{ (CI: 0.8, 3.1); } p = 0.004]$, and extracellular amplitudes were around 40% higher $[739 \pm 67 \mu \text{V vs } 528 \pm 99 \mu \text{V; mean difference } 211 \mu \text{V (CI: 76, 347); } p = 0.007]$. Figures 4.15 and 4.14 also show that the spatial velocity and amplitude mapping presents a useful method for reliably discriminating patches of high amplitude.

4.3.3 Discussion

The velocity and amplitude of the slow wave propagation was quantified for normal and circumferential propagations during dysrhythmias. Two of the main findings were that: (i) rapid high-amplitude circumferential slow wave propagation emerges during dysrhythmic slow wave propagations and (ii) rapid high-amplitude propagation profile of the pacemaker region is a consequence of localised circumferential propagation.

In the presence of a longitudinal incomplete conduction block, the slow wave propagation followed the longitudinal block, and when the block disappeared, it rapidly excited slow wave propagation in a circumferential manner, potentially colliding with the same wavefront. If excitable tissue were present either aborally or orally during dysrhythmia, diverging ring-like wavefront emerged travelling in both antegade and retrograde directions, potentially inducing organised retrograde wavefronts depending on the site of the excitable tissue. The clinical relevance of these slow wave dysrhythmias is yet to be related to gastric motility.

A potential explanation has been found for the high-velocity and high-amplitude slow wave activity, that has been observed in the presence of the normally dominant gastric pacemaker region in pigs, dogs and humans, but has not been previously understood $[49, 111, 139]$. The porcine gastric slow wave pacemaker profile turned to a corpus slow wave propagation profile when the pacemaker region was
4. VELOCITY AND AMPLITUDE ESTIMATION

Figure 4.14: Activation time map, velocity and amplitude profiles of gastric slow wave propagation during an incomplete conduction block. (A) Denotes the area where the PCB electrode array has been positioned on the serosal surface of the stomach (electrode spacing, 7.62 mm; area: 96 cm²). (B) Show the signal traces of slow wave activity where (c)-(e) correspond to activities and electrode positions in C-E. (C) Normal antegrade slow wave propagation with 1 s of isochrones used for the activation time map [mean velocity: 6.4±0.9 mm s⁻¹, mean amplitude: 440±170 μV]. (D-E) Cycles of slow wave propagation showing incomplete conduction block with circumferential propagation directed posteriorly (D) or anteriorly (E) beneath the conduction block. A region of high velocity and high amplitude is associated with the circumferential propagation (8.9±1.2 mm s⁻¹ for the area of interest, p<0.001 vs normal cycles: 640±135 μV, p<0.001). Rapid circumferential propagation below the conduction block gives rise to half-elliptical wavefronts, with the propagating antergrade or retrograde develops slower, low amplitude propagation profiles. Reproduced from [142].

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4.3 Characterisation of porcine gastric slow wave propagations

Figure 4.15: Activation time map, velocity and amplitude profile during ectopic pacemaking activity. (A) denotes the area where the PCB electrode has been positioned on the serosal surface of the stomach (electrode spacing: 4 mm², area: 36 cm²). The tissue area closer to the lesser curvature in the stomach was electrically silent. (B) shows the signal traces of slow wave activity where (c)-(f) correspond to activities and electrode positions in C-F. (C-D) Normal antegrade slow wave propagation with the activation map showing 1 s of isochrone (mean velocity: 5.6±0.8 mm s⁻¹, mean amplitude: 490±230 µV) (E-F) Ectopic slow wave pacemaking from the distal corpus. A region of high velocity and high amplitude is seen when there is circumferential slow wave propagation arising from an ectopic foci (8.80±1.4 mm s⁻¹ for the area of interest, p<0.01 vs normal cycles; mean amplitude: 710±270 µV p<0.001). Ectopic retrograde slow wave propagation organises to the transverse axis of the stomach, traversing orally with a slower, lower amplitude profile. Reproduced from [142].
dominated by organised retrograde propagation that lacks circumferential propagation. Thus, the rapid high-amplitude profile in the pacemaker region was likely due to a functional consequence of circumferential conduction occurring at the pacemaker site. This reinforces the findings that the normally dominant pacemaker region exhibits anisotropic propagation.

4.4 Summary

In this chapter, quantitative methods were developed to estimate the velocity and amplitude of gastric slow wave propagation. Two new methods for estimating velocity of the slow wave propagation and one new method for estimating the amplitude of the slow wave event in the HR GI mapping field were introduced. These new methods were compared to existing methods in the GI HR mapping field, validated using realistic synthetic slow wave propagation profiles and verified with experimental recordings.

Under realistic test scenarios, the newly developed FDSM method and the POLY4x4 method for velocity estimation had an average error of 6% in estimating the speed and an average absolute angle error of 3°, while the existing method (FDSM) resulted in a speed error of 12% and an absolute angle error of 7°. Under experimental recordings, with the presence of noise, the FDSM method performed better than the POLY4x4 method being able to estimate the velocity of the whole recording array with a lower standard deviation in velocity estimate in normal propagating patterns. Thus, the FDSM method is advocated for velocity estimation in gastric HR mapping studies.

In GI HR mapping, the slow wave events was estimated using the maximum-minimum method and it worked adequately for signals that have a high signal to noise ratio. If the recorded signals had a low signal to noise ratio, the methods would lead to misleading estimates. Thus, a new method based on derivatives was developed for estimating the amplitude of the slow wave event. Noise was simulated on realistic synthetic slow wave signals, and the ‘maximum-minimum’ method resulted in an average error of 44 µV while the derivative based method
4. Chapter summary

resulted in an average error of 16 µV, more than 2.5 times less than that of the ‘maximum-minimum’ method.

The methods of velocity and amplitude estimation were applied to experimental gastric recordings to ascertain an understanding of the slow wave propagation patterns. It was found that rapid, high-amplitude propagation was attributed to circumferential propagation, and that rapid, high amplitude propagation patterns were present in dysrhythmic wavefronts.

The use of improved quantitative estimates for the velocity and amplitude estimation can allow for a refined understanding of normal and abnormal slow wave wave propagation patterns, which may be able to assist in clinical understanding of gastric motility disorders.
Chapter 5

Analysis of the slow wave recovery time

Extracellular studies in cardiac electrophysiology have shown that changes to the interval of cardiac electrical events can increase the vulnerability and induce cardiac arrhythmias [63, 137]. Thus it is prudent to investigate the slow wave intervals in gastric HR recordings during gastric dysrhythmias and normal activity. Identifying slow wave features reliably using quantitative metrics may therefore allow a better understanding of the initiation and maintenance of dysrhythmic slow wave activity, and contribute to an improved foundation for clinically diagnosing gastric dysrhythmias using HR mapping.

In this chapter, an electrophysiological study of the slow wave event was undertaken, followed by an investigation into normal and dysrhythmic slow wave propagation. Novel methods of detection, analysis and visualisation were developed. First, an experimental study was performed using two recording modalities to showcase the validity of gastric slow wave activity. Second, changes in the slow wave interval were compared across normal and dysrhythmic slow wave propagation events as defined by HR mapping techniques.
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

5.1 Monophasic versus biphasic recordings

Extracellular in vivo monophasic and biphasic electrical recordings in the stomach are pertinent to understand gastric slow wave activity. The term biphasic recordings used here refer to slow wave activity recorded using surface contact electrodes, such as the flexible PCB electrodes. Monophasic recordings refer to electrical recordings made on the serosal surface of the stomach, but with pressure applied on the contact area of the tissue. Monophasic electrical recordings have their roots in cardiac electrophysiology, with the duration of the signal representing the time course of an action potential over many cells.

Early GI studies have used monophasic and biphasic recordings to understand slow wave activity. In particular Ichikawa et al. [82] in 1955 recorded monophasic and biphasic extracellular slow wave signals from the stomach and tested the effects of drugs such as adrenaline on the recorded potential. Later in 1967, Bortoff et al. [16] recorded intestinal extracellular signals and proposed a basic mathematical model for the observed monophasic and biphasic morphologies. In recent years, Bortolli et al. [18] used suction electrode recording in gastroparetic patients to understand the underlying mechanisms of dysrhythmic slow wave activity. However, a recent publication by Bayguinov et al. [13] brings into the question the validity of the slow wave activity, attributing in vivo slow wave recordings to motion artefacts. In this study, monophasic and biphasic slow wave signals were recorded simultaneously and quantified to address the validity of the bio-electrical nature of gastric slow wave recordings.

5.1.1 Methods

5.1.1.1 Experimental recordings

Gastric slow wave activity was recorded on three pigs in the greater curvature of the mid-corpus region of the stomach using two extracellular recordings methods: suction electrodes and flexible PCB electrodes. The experimental protocol and method of PCB recording were followed as described in Appendix A. The suction
5.1. Monophasic versus biphasic recordings

electrode was a silver-wire encased in a glass pipette construction (#573000, A-M Systems, WA, USA). The capillary tube (diameter: 1.2 mm) was filled with saline solution after which the electrode was lowered onto the serosal surface of the stomach and gentle suction pressure was applied until a portion of the serosa invaginated into the capillary (Figure 5.1).

The suction electrode was held in position using a test-tube clamp to minimise motion artefacts. Flexible PCBs were placed on the serosal stomach surface and gently held in place with the aid of warm saline-soaked gauze packs. Both electrode types were applied simultaneously in vivo on directly adjacent regions of the anterior procine gastric serosa, near the mid-corpus of the greater curvature (Figure 5.1). Experimental manipulations were performed with minimal gastric handling and the laparotomy wound was approximated and covered with warm saline-soaked gauze to help maintain intra-abdominal temperature and moisture. Ventilation was paused for monitored 30 s intervals during recordings to eliminate potential respiratory artefacts.

Figure 5.1: Recording setup for monophasic and biphasic gastric slow waves. (a) shows the experiment setup with the PCB contact electrode, shown in (b), and the suction electrode, shown in (c), placed side by side on the serosal surface of the stomach. (c) shows the biphasic slow wave signal morphology acquired via the PCB contact electrode and (d) shows the monophasic slow wave signal morphology acquired via the suction electrode. Adapted from [12].
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

5.1.1.2 Signal processing and detection

The HR flexible PCB signals were processed as described in Chapter 3 and the slow wave interval was detected using the method described in Section 5.2. The same method could not be applied to the monophasic signals acquired via the suction electrodes due to the different signal morphology and characteristics. Thus, the automated FEVT method [53] was adapted and incorporated into a new method to detect and analyse monophasic slow wave signals. Details of the method are described along with a graphical user interface (GUI) platform to analyse signals.

Firstly, the monophasic signals were filtered using a moving median filter to eliminate the baseline wander, and a Savitzky-Golay filter to eliminate high-frequency noise (parameters were the same as described in Chapter 3). After the signals were filtered the fiducial points of interest were found, as illustrated in Figure 5.2. Similar to the FEVT detection algorithm, a second-order non-linear energy squared operator (SNEO) was applied, followed by a moving median of the standard deviation to attain the point of interest, which denotes the presence of a monophasic slow wave event.

To detect the point of activation and recovery in the monophasic signal, the derivative of the signal was taken via a Savitzky-Golay derivative (polynomial order: 9 and window width: 2 s) to suppress noise amplification. A search was performed for the maximum derivative value 4 s prior to the fiducial marker for the monophasic slow wave event to identify the point of activation of the monophasic slow wave event. To detect the recovery time of the slow wave event on the monophasic signal, the most negative derivative value was chosen in the search window of 8 s preceding the fiducial marker for the slow wave event. The parameter for the search for the activation time (4 s) and the recovery time (8 s) was systematically determined based on reported experimental ICC half-width of the slow wave as 5.6 s by Hirst et al. [78].
5.1. Monophasic versus biphasic recordings

Signal transform
\[ \text{SNEO}(V) = V_n V_n - V_{n-1} V_{n+1} \]

Moving median of STD of SNEO(V) to find slow wave event

Compute SG based derivative of V

Activation time = maximum derivative in window

Recovery time = minimum derivative in window

---

**Figure 5.2:** Detection of fiducial markers for the monophasic slow wave event. (a) is the algorithm for detection of activation and recovery time in the monophasic slow wave recordings (V). First a second order nonlinear transform of the signal was taken as shown in (b) after which a moving median estimate was computed to identify the potential site of the slow wave event as shown in (c). (d) shows the use of SG derivative of the signal to find the point of maximum upstroke for the activation time of the slow wave event and the point of maximum downstroke of the signal to denote the recovery time for the slow wave event.
Figure 5.3: Graphical user interface for analysing monophasic slow wave signals. The monophasic signal can be loaded and the points of interest can be automatically detected using the algorithm described in Figure 5.2. Users can modify the activation or recovery points on the signal if the algorithm has failed to detect the points of interest accurately. Controls are available to show the signals in a defined time period and users can save the analysis and load previously analysed recordings.
5.1 Monophasic versus biphasic recordings

One of the risks of identifying the recovery phase of the slow wave accurately is the fact that it occurs over a larger time course than the activation phase, increasing the potential for error in detection. To enable careful scrutiny of the monophasic slow wave signals, a GUI was developed which incorporated the automated methods of analysis and also allowed for incorrect fiducial markers to be manually updated (Figure 5.3). Nonetheless, due to the large time constant in the recovery phase, estimates of the slow wave interval will have detection bias.

5.1.2 Results

Figure 5.4 shows a biphasic slow wave signal along with a monophasic slow wave signal to illustrate the validity of the gastric slow wave signals. A time lag exists between the monophasic and biphasic signal due to the fact that the two recording modalities were not recording from the same position. This shows that the gastric slow wave event propagated from one recording site to the other recording site and maintained its signal characteristics such as the slow wave interval, frequency and the morphology of the signal.

To compare the PCB signals and the monophasic signals, two signal measures were used: (i) frequency and (ii) activation-recovery interval (ARi) (Table 5.1). A Student’s t-test was performed between the ARi and frequency of the biphasic PCB slow wave signals and the monophasic suction electrode signal and they showed no significant difference. The frequency values for the both the monophasic and biphasic signal were identical for each of the experiments (mean: 3.6 cpm). The ARi showed variability across experiments as shown in the boxplot in Figure 5.5, but showed no significant in difference across each experiment (mean: 6.2 s) and across all experiments as shown on Table 5.1.

If extracellular gastric slow wave recording were motion artefacts as suggested by Bayguinov et al. [13], then the frequency and ARi in the signal of the suction electrode (monophasic signal) and the PCB electrode (biphasic signal) would have differed, as the suction electrode is less susceptible to movement artefacts than the PCB electrode.
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

![Graph showing biphasic and monophasic slow wave recordings]

**Figure 5.4:** Comparison of simultaneous biphasic and monophasic gastric slow wave signals. The black fiducial cross denotes the point of activation of the slow wave event, while the green fiducial plus sign denotes the point of recovery in the slow wave event. The two signals were recorded at neighbouring positions and the time lag between the fiducial markers in the biphasic and monophasic signals reflects this aspect.

<table>
<thead>
<tr>
<th>Frequency (cpm)</th>
<th>Monophasic</th>
<th>Biphasic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.6 ± 0.6</td>
<td>3.6 ± 0.5</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ARi (s)</td>
<td>6.2 ± 0.4</td>
<td>6.2 ± 0.5</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

**Table 5.1:** Results comparing the ARi and frequency of simultaneous gastric slow wave recording using suction electrode to obtain the monophasic signals, and PCB electrodes to obtain the biphasic signals. There was no significant difference in the ARi and frequency of gastric slow wave activity between the monophasic and biphasic recordings.
5.1. Monophasic versus biphasic recordings

Figure 5.5: Boxplot of the ARi of biphasic and monophasic gastric slow wave activity in three experiments. There were variations in the slow wave interval across the experiments, but there was no significant difference in the slow wave interval in both the monophasic and biphasic signal in each of the experiments.
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

5.1.3 Discussion

Extracellular slow wave mapping has elucidated key mechanisms as to how GI motility is coordinated [29]. Recent studies by Bayguinov et al. [13] have suggested that in an in vitro setup that slow wave activity cannot be recorded using surface contact electrodes and the deflections acquired are largely due to motion artefacts. They further stipulate that motion suppression needs to be an ‘obligatory control’ for extracellular in vivo slow wave mapping studies. The results from this study suggest that this is not necessary, and this is further elucidated below along with the significance of these findings.

Gastric slow wave signals have been quantified and compared across two extracellular recording modalities: (i) suction electrode acquiring a monophasic signal and (ii) surface PCB contact electrode recording a biphasic signal. The mean frequency and slow wave interval between the monophasic and biphasic signals were the same, as illustrated in Table 5.1. In fact, for each data set, the frequency values for the monophasic and biphasic signals were identical, while there were very slight variations in the slow wave interval in the data sets. In cardiac electrophysiology, movement artifacts have been shown to slightly affect the signal morphology of monophasic cardiac potentials but not degrade them, when recorded properly [61]. Similar variations in signal morphology have been seen in the slow wave monophasic slow wave signal, and these artifacts have been attributed to the slight variation in slow wave interval across the monophasic and biphasic signals. A further finding from this investigation is that the points of maximum downstroke and upstroke of the PCB slow wave signal correlate to the activation and recovery phase of the slow wave, allowing for quantification of the recovery time of slow waves using in vivo techniques.

The finding from this study forms a part of a larger study by Angeli et al. [12] which showed conclusively that slow wave activity was of a biophysical basis and can be reliably recorded in vivo without motion suppression as a control. The three main findings from the study by Angeli et al. [12] are as follows. First, intestinal slow waves were able to be recorded in vivo after the application of nifedipine, which blocked muscular contractions. Second, as illustrated here, the
interval and frequency of the gastric slow wave using two recording methods (suction and contact electrode) were congruent. Third, a modelling study based on a core conductor model, initially developed by Spach et al. [177], elucidated the nature of monophasic and biphasic signal morphologies acquired via experimental recordings.

5.2 Slow wave intervals in dysrhythmic propagation

Recent studies of high-resolution mapping of gastric slow waves have revealed complex dysrhythmic spatiotemporal propagation patterns which have been linked to motility disorders such as gastroparesis [12, 13, 14]. As the role of gastric slow waves is becoming clear in health and disease, the details in the morphology of extracellular recordings obtained \textit{in vivo} are one of the important issues that need to be addressed. In particular the factors that initiate, maintain and terminate gastric dysrhythmias need to be determined in order to understand and treat gastric motility disorders in an effective manner.

The activation time of extracellular events, which relates to the depolarisation of the underlying membrane potential, and its frequency are commonly used for assessing temporal and spatial propagation of slow wave wavefront [111, 139]. Here the recovery time in the extracellular gastric slow wave event was detected, which relates to the repolarisation phase of the membrane potential of the underlying tissue directly underneath the recording electrode. This provides an additional new utility to GI HR mapping to understand normal and dysrhythmic slow wave propagation.

5.2.1 Methods

Gastric HR mapping was undertaken in the upper corpus of the greater curvature as described in Appendix A (n=8 from 4 pigs, recording duration: 5–12 minutes).
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

The recordings were filtered and activation time maps were formed as described in Chapter 3. Gastric slow wave propagation patterns for each of the data sets were classed as normal and dysrhythmic in a manual fashion for this study (four normal and four dysrhythmic).

A two-step algorithm was developed to automatically detect the fiducial point for the recovery time (Figure 5.6). In the first step, the derivative of the signal was computed using a low pass digital differentiator using the SG derivative algorithm (window size: 2 s, polynomial order: 6) [121]. This step reduced the high frequency noise components from the derivative of the signal. In the second step, a linear search was performed from 1.5 to 6 s (times based on gastric intracellular recordings [51]) after each activation event to identify the point of maximum upstroke, which represents the recovery time in the slow wave event. This was a similar approach to what has been undertaken in cardiac electrophysiology, where the maximum upstroke is taken as the point of recovery in extracellular signals [74].

Four interval measures were computed from a priori knowledge of the fiducial markers for activation and recovery from the slow waves, as illustrated in Figure 5.7:

- ‘Activation-recovery interval’ (ARi) or slow wave duration
- ‘Recovery-activation interval’ (RAi) or the refractory period
- ‘Activation-activation interval’ (AAi) or the period of slow waves based on the activation time
- ‘Recovery-recovery interval’ (RRi) or the period of slow waves based on the recovery time

5.2.2 Results

The average slow wave intervals for normal and dysrhythmic data sets were computed and displayed as a box plot in Figure 5.8. The mean intervals (ARi, RAi,
5.2 Slow wave intervals in dysrhythmic propagation

Figure 5.6: Flowchart illustrating the stages involved in detecting the recovery point of slow waves in gastric extracellular recordings. The first three stages were pre-processing steps, which included downsampling of the data, removing noise, and detecting the activation time of slow wave event using the automated FEVT algorithm. The final two stages belong to the recovery point estimation algorithm, which begins by differentiating the signal using the SG algorithm. This is followed by a search for the maximum derivative in a specified time interval after the activation time.
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

![Graph showing recovery time and activation time with fiducial markers for ARi, RRi, RAi, and AAi]

**Figure 5.7:** An illustration of interval estimation from extracellular serosal gastric slow wave recording acquired from a porcine subject. Four interval measures (ARi, RRi, RAi and AAi) were computed which were based on the recovery time and the activation time of the gastric slow wave. The fiducial marker for the recovery time was chosen as the point that defined the largest upstroke in the slow wave signal past the activation time.
AAi and RRi) of normal and dysrhythmic data sets were compared for statistical significance. All normal cases had low SD compared to dysrhythmic activity. The only interval that showed a statistical difference was the ARi. The ARi of slow wave in dysrhythmic data sets had a lower mean and higher standard deviation compared to that of normal data sets (3.3±0.5 s vs 4.3±0.1 s). For all the other intervals (RAi, RRi, AAi) the mean interval of the dysrhythmic propagating waves was twice that of normal slow wave propagation with a large standard deviation (Figure 5.8), but were not statistically significant (but were close to the threshold for significance).

In Section 5.1.2 it was noted that the mean ARi was 6.2 s (mid-corpus) while the mean normal ARi here was 4.3 s (upper-corpus). This is in line with expected regional variations of the underlying electrophysiology of the stomach tissue. El-Sharkawy et al. has previously shown that there is an increase in the ARi from the corpus to the antrum, and the same phenomenon was observed here [51].

With high resolution mapping, a detailed spatiotemporal map can be created for the activation time as previously described in Chapter 3. An equivalent map can be constructed for the recovery points for the slow wave propagation (Figure 5.9).

5.2.3 Discussion

This study quantifies the recovery aspect of the gastric slow wave extracellular potentials. For the first time, changes in the recovery component of extracellular potentials have been related to dysrhythmic slow wave activity. Potential findings and associated problems with the current methodology are discussed.

Detecting the point of recovery in extracellular signals is important because it allows for an improved understanding of normal and dysrhythmic slow wave activity. With dysrhythmic activity, the detection of the point of recovery is significant, because dysrhythmias tend to occur when the electrical event is prolonged or shortened, as seen in cardiac electrophysiology [63]. Similar patterns of cardiac electrical activity are being found in GI electrophysiology [99], thus bringing in the following questions; (i) what are the characteristics of dysrhythmic slow wave...
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

Slow wave interval | Normal | Dysrhythmic
--- | --- | ---
Activation-recovery interval (ARi) | 3.3±0.5 s | 4.3±0.1 s
Recovery-activation interval (RAi) | 12.2±0.7 s | 28.8±15.88 s
Activation-activation interval (AAi) | 16.5±0.9 s | 32.1±15.36 s
Recovery-recovery interval (RRi) | 16.3±0.9 s | 32.0±15.39 s

Figure 5.8: Boxplot and table of slow wave intervals (ARi, RAi, AAi and RRi) in normal and dysrhythmic gastric slow wave propagations. There was a significant difference in the activation-recovery interval between normal and dysrhythmic data sets as indicated by a * (p < 0.05). The rest of the slow wave intervals (RAi, AAi and RRi) did not reveal a significant difference, but were close to the threshold for significance. The average values for the box plot data are also listed as a mean ± standard deviation to signify the change in slow wave interval between normal and dysrhythmic slow wave propagation.
5.2 Slow wave intervals in dysrhythmic propagation

Figure 5.9: Propagation of a slow wave event. (a) shows the spatiotemporal activation time map while (b) shows the recovery time map of the propagating wavefront. The slow wave activity starts from the top left corner of the electrode array and curves down towards the bottom right of the electrode array. The colours (red to blue) are associated from earliest to latest time for each propagating slow wave wavefront. The black dots are recorded activation and recovery times, while the white dots with the red circles are interpolated points.

activity, and (ii) whether similar hypothesis from the cardiac field would apply in the GI field.

Two significant findings arise from this study. First, the recovery phase of the extracellular slow wave can be quantified in a reliable manner using a derivative based algorithm. Second, there was a significant difference in the mean ARi between normal and dysrhythmic slow wave activity. Compared to normal activity, the dysrhythmic activity has a lower ARi interval (4.3±0.1 s vs 3.3±0.5 s). Based on the analyses performed, the RAi, AAi and RRi were approximately double in dysrhythmic data sets compared to the normal case, but were not statistically significant. One plausible explanation for the changes in intervals is that the reduction in ARi and increase in AAi lead to a longer refractory period, during which, there could be an increased opportunity for an ectopic pacemaker to initiate an entrained propagation in the surrounding tissue. The presence of spike activity which is related to muscular contraction occurs during the ARi. Thus, if the ARi is shortened as a consequence of dysrhythmic slow wave propagation, then it is less likely for spike potentials and contraction to be initiated, leading to gas-
5. ANALYSIS OF THE SLOW WAVE RECOVERY TIME

Tric dysmotility. Further experiments need to be performed and similar analyses performed to explore the validity of this explanation and observed findings.

Although the method mentioned in this study allows for precise detection of the recovery points of the underlying slow wave activity, there are some difficulties and issues that need to be resolved. When the slow wave signal has a reduced signal to noise ratio, due to noise artefacts such as respiration or due to insufficient tissue contact, the point of recovery would be detected incorrectly and could bias the results. If the signals have a low signal to noise ratio, modification of the SG derivative algorithm parameters can assist to accurately detect the recovery point. A potential improvement in the experiment design is to make the set-up less invasive. With the introduction of laproscopic recording modalities for gastric slow wave activity, these techniques of analysis can be applied to those recordings in normal patients and patients suffering from dysmotility to inform a better understanding of GI electrophysiology [141].

5.3 Summary

In this chapter, novel methods and platforms were developed for assessing the recovery phase of the slow wave event in both monophasic and biphasic signals.

Furthermore, in this chapter, recent claims by Bayguinov et al. [13] have been addressed by comparing slow wave signals acquired via two different recording modalities (suction electrode, and contact PCB electrode). One of the findings from the study by Bayguinov et al. [13] was that a motion control was required for recording extracellular slow wave recordings. To test these findings, the ARi and frequency of the slow wave was calculated for contact PCB electrode recordings and suction electrode recordings, which are less susceptible to motion artefacts. The average slow wave ARi was 6.2 s and the frequency was 3.6 cpm for both extracellular modalities, which illustrated that slow wave recordings can be mapped reliably using PCB contact electrodes without the need for motion suppression.

Gastric HR mapping studies to date have concentrated on analysing the activation time of the slow wave interval. For the first time, the interval of extracellular
5. Chapter summary

slow wave has been analysed and linked to normal and dysrhythmic slow wave propagation patterns. Preliminary studies suggest that abnormalities in slow wave propagation can be linked to changes in the slow wave interval. In particular there was a significant difference in the ARi between normal and dysrhythmic slow wave propagation (normal $4.3 \pm 0.1$ s vs dysrhythmic $3.3 \pm 0.5$ s). It was also seen that the dysrhythmic slow wave activity presented with a larger variation in interval estimates compared to normal slow wave propagation patterns. These results suggest that during dysrhythmic slow wave propagation, the potential to initiate muscular contractions is reduced, due to the reduced ARi, potentially inducing gastric motility disorders. Further experimental and mathematical modelling studies are warranted to investigate and confirm these findings.
Chapter 6

Classification and identification of slow wave propagations

The advent of HR mapping of gastric slow waves has afforded comprehensive spatiotemporal descriptions of gastric dysrhythmias [105]. It has been shown that in addition to the frequency characteristics, the spatial organisation of slow waves exhibited significant deviations from the normal activity [112, 144], which may routinely occur even at normal frequencies [138].

To date, all HR mapping studies of gastric dysrhythmia have used manual methods for classification and visual analyses of spatial slow wave propagation patterns [104, 138]. Manual approaches introduce the possibility of missing certain critical features that are pertinent to gastric slow wave dysrhythmia, prone to observer bias and inefficient. The introduction of guided tools, and real-time analysis (e.g., [25]), would be a major step toward successful clinical translation of GI HR mapping, by enabling its routine use by clinicians untrained in signal processing, as has been the case in cardiac HR mapping [172].

In this chapter, two novel automated methods have been developed to quantitatively classify and identify gastric slow wave propagations [154]. First, an automated classification method to characterise slow wave propagation was developed based on the similarity of wavefront patterns. Second, based on the characteristics
of the slow wave propagation, patterns of interest in the slow wave propagation were identified and localised regionally. These tools will allow for normal and abnormal slow wave propagations to be classified in a consistent manner, and enable the automated detection and visualisation of key regions of normal and dysrhythmic slow wave propagation.

6.1 Classification of slow wave propagations

The goal of the automated classification algorithm was to efficiently quantify the degree of similarity between heterogeneous AT maps. Similar slow wave propagation patterns were categorised into a single class. The representative propagation pattern for each class was computed as an average of the individual AT maps within the class, and these representative propagation patterns were denoted as ‘templates’.

A schematic of the automated classification algorithm is shown in Figure 6.1. The algorithm assigned the first candidate AT map from the HR recording sequence as a template, and subsequent candidate AT maps were compared to all existing templates using a Pearson correlation coefficient (PCC) similarity metric:

$$PCC = \frac{\sum[(X \cdot \mu_X) (Y_i \cdot \mu_{Y_i})]}{\sigma_X \sigma_{Y_i}}$$  \hspace{2cm} (6.1)

where X is a two-dimensional matrix of times in the candidate AT map, Y_i is a two-dimensional matrix of times in the i\textsuperscript{th} AT template, \( \mu_X \) and \( \mu_{Y_i} \) are the associated means, and \( \sigma_X \) and \( \sigma_{Y_i} \) are the associated standard deviations of X and Y_i respectively. If there was no corresponding time value for either the candidate AT map or AT templates, those time values were discarded prior to estimation of the PCC. If the candidate AT map does not cover at least 20% of the electrode array, the AT map was discarded from the classification algorithm.

A PCC threshold (PCC\textsubscript{th}) of 0.9 was selected by systematically varying this parameter when applied to synthetic data and experimental recordings (see Section 6.3.1) to group similar wave events. That is, if a candidate AT map had PCC greater
than 0.9, it was considered to be similar to an existing template. If the candidate AT map had PCC greater than 0.9 for multiple templates, the template with the highest PCC was selected. The candidate AT map was then assigned to the matching template, and the template was updated by averaging the candidate AT map with the template itself at each electrode position. If a candidate AT map had PCC below the threshold of 0.9 across all existing templates, it was considered dissimilar to any existing templates, and it was assigned as a new AT template.

**Figure 6.1:** Flowchart for the automated classification algorithm. A PCC was used as a similarity metric to categorise activation time (AT) maps into the matching AT templates depending on a threshold (PCC$_{th}$).
After all the AT maps were assessed by the above classification algorithm, the total number of resultant templates represented the number of propagation pattern modes present in a particular experimental recording. If the recorded data had consistently stable propagation patterns, then the result would only be a single AT template. On the other hand, if the recorded data had unstable propagation patterns, then a larger number of AT templates would result. To assess the stability of the slow wave propagation in an experimental recording, the occurrence (Occ) of each AT template was calculated as percentage:

\[ \text{Occurrence (\%)} = \frac{I}{N} \times 100 \]  

(6.2)

where \( I \) is the number of AT maps that were used to construct the template, and \( N \) is the total number of AT maps in the experimental recording.

### 6.2 Identification of slow wave propagation patterns

Once the gastric slow wave propagation pattern modes were acquired as AT templates, regions of interest with key slow wave propagation features were identified in the AT templates. A 2D Gaussian low pass filter (size: 2 x 2 electrodes, \( \sigma \): 0.25) was applied to the AT templates to filter any noise accumulated as part of the averaging process from the automated classification method. Mathematical operations on the velocity vector of the slow wave propagation were used along with image processing techniques to detect the regions of interest, as illustrated in the flowchart in Figure 6.2.

The three spatial propagation patterns of interest were: (i) pacemaker (normal or ectopic) activity, (ii) colliding wavefronts and (iii) conduction block. An explanation of these patterns and justification for their selection as priority patterns is provided.
6.2. Identification of slow wave propagation patterns

Figure 6.2: Flowchart illustrating the steps taken to identify key regions of interest in the slow wave propagation. Three patterns of interest were (i) pacemaker (in green boxes), (ii) colliding wavefront (in blue boxes) and (iii) circular propagation or re-entry (in orange boxes). Note that a single activation time map (ATmap) may possess more than one key propagation pattern, and the propagation pattern identification algorithm flowchart illustrates this using dotted arrows. The divergence of the activation time map (DivATmap) is used to identify the pacemaker and colliding wavefront, while the mean curvature of the activation time map (MeanCurvATmap) is used to identify circular propagation or re-entry.
6. AUTOMATED CLASSIFICATION AND IDENTIFICATION

6.2.1 Pacemaker region (normal and ectopic)

The pacemaker region is a site where slow wave activity originates. Normally, the pacemaker originates from the greater curvature of the mid- to upper-corpus region of the stomach [111] [139], but ectopic initiations also occur, causing abnormal slow wave activation patterns [49]. Ectopic pacemakers have been found to underlie dysrhythmic propagation at bradygastric, normal and tachygastric frequencies in animal and human models, causing ‘retrograde’ or aboral propagations [112] [138] [132] [144]. To detect pacemaker regions from the AT template map, the divergence of the velocity field of the AT templates was computed. The divergence denotes whether the velocity vectors are diverging from a point, or are converging from all directions to a point. To illustrate this case, a synthetic function of the exponential form was created,

\[ T(x, y) = a (X - X_0) e^{-(X - X_0)^2 - a(Y - Y_0)^2}, \]  

(6.3)

where \( a = 0.25 \), \( X_0 = Y_0 = 2 \) and \( X \) and \( Y \) are the x and y coordinate positions in 2D. This function represents a time map where there is a source of activation, and another point, which is a source of collision or sink (Figure 6.3(a)). Figure 6.3(b) shows the corresponding divergence map to illustrate the source of activation and sink locations.

A divergence threshold of greater than 1 (based on synthetic and experimental data) was used to mark regions that denote the site of diverging velocity vectors from a point, and hence a pacemaker region in the AT template (Figure 6.2). If there is more than one separate region identified, it indicates the presence of multiple pacemakers. The largest divergence value in each of the separate thresholded regions were chosen as the pacemaker locations. For ease of visualisation and localisation, the pacemaker origin was dilated using a radius of 10 pixels (4 mm) in a separate field map, as shown in Figure 6.3(c).
6.2. Identification of slow wave propagation patterns

(a) Activation time map with velocity vectors
(b) Divergence time map.

(c) Detection of source location.

Figure 6.3: Test case showing (a) an AT map with an origin where velocity vectors are diverging and a point where all the velocity vectors are converging. (b) shows the corresponding divergence map of (a). The synthetic test case AT map was defined using Equation 6.3. In the divergence map, a positive value (red) indicated a source location and a negative value (blue) indicated a sink location. In (c) the largest divergence value in the map was used to detect a pacemaker site, and for visualisation it has been dilated by 10 pixels (4 mm).
6. AUTOMATED CLASSIFICATION AND IDENTIFICATION

6.2.2 Colliding wavefronts

A colliding wavefront occurs when two or more slow wave propagation wavefronts propagate into one another. The presence of colliding wavefronts is a key indicator of disorganised conduction sequences [112, 138, 142, 144], and can be attributed to one of two scenarios. In the first scenario, there is more than one slow wave pacemaker active, and these sources may ‘compete’ for entrainment of the surrounding tissue, leading to wavefront collisions in a stable or unstable manner. In the second scenario, a slow wave wavefront encounters a region of incomplete conduction block, causing a wavelet to arise, that travels around the block that subsequently collides with the same wavefront.

At a region of a colliding wavefront, velocity vectors of different directions would converge onto a point, and hence would be reflected as a ‘sink’ in the divergence map. A threshold of -0.4 for the divergence map was determined by systematically varying this parameter when applied to synthetic and experimental data, and was found satisfactory for identifying colliding wavefront regions in most cases (see Figure 6.4), but with false positives being detected in some cases. Therefore, to further increase the specificity of identification, an inter-pixel watershed algorithm was applied to the AT template [129]. Here the watershed algorithm finds the ridges on the AT map (synonymous to a hilltop of a mountain range), which represent two or more slow wave wavefronts intersecting at a point or a plane from opposing directions denoting a colliding wavefront (see Figure 6.4(c)). To avoid detecting false positives, only ridges with a height (time difference) of greater than 0.15 s were retained with certainty. The intersection of areas between the watershed and the thresholded divergence map (Figure 6.4(e)) was identified as the region where two or more wavefronts collided (Figure 6.4(f)). Both the divergence and the inter-pixel watershed algorithm were used as this combination provided corroborative detection of a colliding wavefront (Figure 6.4(e)–(f)). Finally, for ease of visualising the colliding wavefront, the colliding wavefront region was dilated and morphologically closed (see Figure 6.4(g)). If the resultant detected colliding site was less than 200 pixels (corresponding to roughly 30 mm²), it was considered as a false positive and discarded.
6.2. Identification of slow wave propagation patterns

Figure 6.4: Steps used to denote areas of colliding slow wave wavefronts. (a) shows the isochronal activation map with 1 s intervals. (b) shows the divergence map of (a). (c) shows the result of the watershed of the AT map in (a). (d) shows the overlap of the thresholded area in the divergence map. (e) is the overlap between (c) and (d). (f) shows the resultant intersection of (c) and (d). (g) is the dilation of (f) to clearly illustrate the area of collision.
6. AUTOMATED CLASSIFICATION AND IDENTIFICATION

6.2.3 Conduction block

A conduction block is a premature termination of the propagating wavefront, which can arise due to either a functional or anatomical consequence. A key characteristic of a re-entrant propagation sequence is a conduction block. It has been well established in cardiac electrophysiology that re-entry and functional and anatomical blocks are the basis for many cardiac arrhythmias, some of which may lead to fatal disorganization of cardiac contractions [8, 160]. Kay et al. have used the curvature of the wavefront to understand the drivers and perpetuators of disorganized cardiac arrhythmia patterns, such as spiral activity, wave breakup and colliding activity, in a modelling scenario to be extended for use in optical mapping experiments [88]. In the GI field, re-entrant and conduction block patterns of slow wave activity have recently been discovered [11, 112, 144], but its clinical significance is yet to be studied in detail [104].

The presence of a conduction block was detected in the gastric AT template by calculating the mean curvature ($C_m$) of the AT template.

$$C_m = \frac{eG - 2fF + gE}{2(EG - F^2)}, \quad(6.4)$$

Equation 6.4 is an analytical equation for a regular surface in 3D space (x, y, activation time) defining its mean curvature, where E, F, G are the coefficients of the first fundamental form of the AT map, while e, f, g are the coefficients of the second fundamental form of the AT map [67]. A parametric representation of a point and its differentials on a surface are defined as:

$$S(x, y) = [X(x, y), Y(x, y), T(x, y)]$$

$$S_x = \frac{\partial S}{\partial x}, \quad S_y = \frac{\partial S}{\partial y}$$

$$S_{xx} = \frac{\partial^2 S}{\partial x^2}, \quad S_{xy} = \frac{\partial^2 S}{\partial x \partial y}, \quad S_{yy} = \frac{\partial^2 S}{\partial y^2}, \quad(6.5)$$

where X and Y are the variables for electrode array coordinate positions for the activation time $T$, at $x$ and $y$ are the coordinate positions. The coefficients in
Equation 6.4 are found as follows:

\[ E = S_x \cdot S_x, \quad F = S_x \cdot S_y, \quad G = S_y \cdot S_y, \quad m = S_x \times S_y \]

\[ e = S_{xx} \cdot m, \quad f = S_{xy} \cdot m, \quad g = S_{yy} \cdot m \]

During the conduction block, the slow wave does not spread homogeneously due to the tissue being in a refractory state, tissue damage, or loss of ICC. Thus, the slow wave revolves around a functional or anatomical obstacle. In the case of re-entry, it would revolve around the functional obstacle, as well as re-exciting the same circuit of tissue, to initiate continuous slow wave propagation. The pathway around a conduction block can be seen as a large change in curvature at the sites of the AT template (Figure 6.5(b)).

In the mean curvature map, the area of conduction on either side of a block can be identified, but the region of interest is actually the region located between the large curvature values, denoting the block [154]. To identify the site of the conduction block, first, areas were identified in the mean curvature map that had values greater than a specified threshold (chosen as 0.015 based on synthetic and experimental data). If there was a conduction block present in the AT map, the identified areas would be on either side of the conduction block (see Figure 6.5(b),(c)).

Two separate operations were then performed on the remaining areas. First, a topological skeleton was identified outside of the detected area via the mean curvature threshold (Figure 6.5(e)). The topological skeleton is a line that is equidistant to its boundaries and identifies the shape outside of the detected areas. Second, a morphological dilation was performed so that the boundaries of the areas merged (see Figure 6.5(d)). The intersection between the merged area and the skeleton formed the site of the conduction block (Figure 6.5(f,g)). Again for ease of visualisation, the identified site was dilated and morphologically closed (see Figure 6.5(h)). As the conduction block sites routinely span several millimetres [112, 144], areas of identified potential conduction block with less than 100 pixels (corresponding to an area of 16 mm²) were considered false-positives, and were discarded (see Figure 6.5(i)).
Figure 6.5: Steps used to identify a site of a conduction block. (a) shows an isochronal activation map (1 s interval) which has a pacemaker, as well as a conduction block, as illustrated by the stacked isochrones. (b) shows the mean curvature map of (a). (c) shows the thresholded map of the mean curvature map. (d) is the where the objects in (c) have been dilated so that the objects merge together, while (e) is the results of the skeleton algorithm of (c). (f) shows the intersection of the of the two images (d) and (e) overlaid, and (g) shows the intersection. In (h) the objects are dilated for clarity. To eliminate erroneous detection and to place physiological limits on the area of the conduction block, any identified objects less than 16 $mm^2$ or 100 pixels was eliminated, as shown in (i).
6.3 Validation of automated classification and identification algorithm

6.3.1 Synthetic cases

Synthetic AT maps were developed to test the effectiveness of the classification and identification algorithm. Four scenarios of propagations were created: (i) normal propagation, (ii) pacemaker, (iii) colliding wavefronts, and (iv) a linear conduction block.

Normal propagation was created using a linear planar function, while the pacemaker was created using an elliptical function (reflecting the anisotropic nature of gastric conduction, being more rapid circumferentially than longitudinally [142]). Parameters for the function were chosen to represent gastric slow wave propagation [139, 144, 156] (see Section 4.1.1.1). Colliding wavefronts were created using two elliptical functions with the source of propagation of two opposing corners of the electrode array with the collision path placed diagonally in the electrode array. To represent a conduction block, a linear forward propagating sequence was created for one half of the array, while the other half was constructed using a linear backward propagating sequence. To simulate realistic AT maps, normally distributed random perturbations of 0.5 s were added to each electrode position of the AT map during the creation of synthetic of slow wave propagation [156].

These four synthetic scenarios were applied to generate five synthetic sequences of AT maps (10 minutes long, i.e., the approximate duration of the experimental recordings). Two of the five sequences of synthetic slow wave propagation had one sequence of propagation representing normal slow wave propagation, while the rest of the 3 test sequences had 2, 3 and 4 different scenarios placed in systematically determined locations to depict dysrhythmic slow wave activity.
6. AUTOMATED CLASSIFICATION AND IDENTIFICATION

6.3.2 Experimental data

Experimental HR gastric slow wave recordings comprised 10 data sets from six pigs. The experimental method used to acquire the datasets are described in Appendix A. Five of the data sets exhibited exclusively normal propagation, while the other five data sets included dysrhythmic events encompassing the typical range of dysrhythmic propagation patterns [112, 138, 144]. To further define important spatial characteristics of the slow wave propagation patterns in each data set, the velocity and amplitude distributions were defined for each class of propagation as identified by the templating system, and these were tested by ANOVA for statistical difference in patterns (threshold p < 0.05).

Two expert investigators worked independently to manually classify the 10 experimental recordings as a benchmark for validation of the automated classification algorithm. After the application of the classification algorithm to the experimental data sets, the output templates were visually assessed by the expert investigators independently to identify the type of propagation pattern as, either: (i) pacemaker, (iii) colliding wavefronts and (ii) conduction block, and to localise the dysrhythmic features regionally.

To assess the accuracy of the automated classification methods, the results were compared against manual assessment of the maps. The same approach was performed to compute the accuracy of the localisation algorithm to define the pattern present. To define the error in localising the pattern of interest in the AT template, the root mean squared distance between the manually marked region and the automatically marked region was calculated.

6.4 Results

6.4.1 Synthetic cases

The automated classification algorithm was applied to synthetic gastric slow wave propagation and the algorithm classified all synthetic sequences correctly into their according classes (see Table 6.1).
6.4. Results

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</tr>
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Table 6.1: Validation of the automated classification algorithm using synthetic slow wave propagations. Five synthetic data sets were created where two of the cases has only one class of slow wave propagation representing normal activity, while the rest has two or more classes and represents abnormal activity. The automated classification algorithm classified all the synthetic slow wave propagations into the correct class.

The automated identification was applied to the four scenarios of synthetic slow wave propagation and were able to identify the type of propagation and localise it regionally in the AT map, as shown in Figure 6.6.

6.4.2 Experimental recordings

6.4.2.1 Automated classification algorithm

Table 6.2 presents the results of applying the automated classification algorithm across all experimental slow wave HR recording datasets, including number of waves analysed, number of template classes identified in each experiment, and the statistical outcomes of comparing amplitude and velocity profiles between templates. Compared to manual analysis the automated methods classified the AT maps with 96% accuracy. It took between 20–40 minutes to manually review, compare and classify AT maps, whereas the automated algorithm was almost instantaneous, taking less than 1 s.

The algorithm applied to an example dysrhythmic slow wave sequence (Experiment No. 10 in Table 6.2) is presented in Figure 6.7. Figure 6.7 shows a mode graph, which demonstrates the stability of slow wave propagation through time, and indicates AT templates identified throughout the sequence. The example also shows how the frequency of the slow wave propagation can be interpreted from
6. AUTOMATED CLASSIFICATION AND IDENTIFICATION

Figure 6.6: Automated identification of synthetic slow wave propagation. The first column shows the synthetic slow wave propagation plotted as an isochronal activation time map (1 s interval). The second column shows the automated identification of the regional characteristics of the gastric slow wave propagation. (a) is a synthetic pacemaker activity. (b) shows two wavefronts colliding across the diagonal in the electrode array. (c) is a zoomed in version of a linear conduction block.
### Results

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<th>Experiment No.</th>
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<td>–</td>
<td>–</td>
<td>*</td>
<td>*</td>
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**Table 6.2:** ANOVA analysis of amplitude and velocity estimates between different propagation pattern classes in five normal and five dysrhythmic data sets. If there was more than one AT template class, an ANOVA was performed between the calculated velocity and amplitude of the different classes identified. There was a difference in amplitude and velocity across patterns in all the data sets (* = p < 0.05).

the mode graph. For approximately the first 250 s of this recording, the slow wave propagation was 3.8 cpm, and then for the remainder of the recording, the frequency dropped to an average of 1.6 cpm. When the frequency was at 3.8 cpm, the AT maps switched classes twice. The switch was from an ectopic pacemaker propagation to a similar pacemaker pattern, but with a conduction block to half the field, for one wave, which then reverted back to the ectopic pacemaker propagation. With the drop in frequency, the AT maps switched classes seven times and the patterns of propagation were varied, indicating highly unstable activation.

A further sequence of typical porcine gastric dysrhythmia is demonstrated in Figure 6.8(a). In this example, the slow wave propagation reversed its direction from normal antegrade propagation to retrograde propagation, due to the occurrence of an ectopic pacemaker (Figure 6.8(b)). The mode graphs show that these two distinct propagation patterns have the same frequency of 3.3 cpm; this dysrhythmia would therefore have gone undetected by frequency-domain analysis alone. To further characterise the spatial properties of the sequence, the velocity and amplitude distribution for the AT maps belonging to the template propagation pattern were plotted as a histogram (Figure 6.8(c)). A clear separation in the distributions of the velocity and amplitude characteristics can be seen across the two patterns of slow wave propagation (refer Table 6.2 for further data and statistical comparisons - Experiment No. 2).
Figure 6.7: Mode graph and the AT templates with the key propagation patterns identified and marked. (a) shows that there are six AT templates that alternated throughout the recording. (b)–(g) shows the AT templates as an isochronal activation time map (1 s interval), their percentage of occurrence, and key features identified, along with a legend at the bottom to intuitively assess the propagation patterns.
Figure 6.8: Mode graph and histogram illustrating two classes of propagation present i.e., antegrade and retrograde slow wave propagation. In (a) the mode graph provides information on the order and percentage of propagation pattern occurrence, and frequency of the slow waves. Four of the AT maps are shown in the mode graph. (b) shows the final two templates generated by the automated classification method, with the arrows overlaid to show the dominant propagation direction. The antegrade propagation direction is the longitudinal propagation direction, while the retrograde template shows elements of circumferential propagation. (c) shows the amplitude and the velocity variation across the two classes along with the corresponding histograms.
6. AUTOMATED CLASSIFICATION AND IDENTIFICATION

6.4.2.2 Automated identification algorithm

The automated identification algorithm identified the patterns of propagation in the AT maps with an average accuracy of 95% with a mean localising error of 3 pixels (~1.5 mm) in comparison to manual identification. The identification algorithm marked all of the pacemaker sites (5/5) and colliding wavefronts (9/9) and one less conduction block site (6/7). The mean error in localising the pacemaker site was 3 pixels (~1.5 mm), colliding wavefront site was 2 pixels (~1 mm) and circular propagation and re-entry site was 4 pixels (~2 mm).

Figure 6.7 shows an example identification of the pacemaker activity and conduction block, while Figure 6.9 shows an example identification of colliding wavefronts. The automated pattern identification algorithm was also applied on individual AT maps in an experimental recording to track the pacemaker site over time to observe and analyse its spatiotemporal dynamics (see http://youtu.be/If7PlGs4Gk0).

6.5 Limitations and discussion

6.5.1 Limitations

One of the major limitations of the classification method is that it requires the slow wave event to be identified accurately and the AT map to be correctly clustered into propagating wavefronts. Lowering the PCC threshold for the classification algorithm will allow the method to work for imprecisely detected activation times (due to experimental noise). The downside to lowering the PCC threshold is that the method becomes less sensitive at differentiating propagation patterns. An imposed limitation of the classification algorithm was that if less than 20% of the electrode array was mapped, the method was instructed to ignore that map. Thus, it is imperative to have a priori knowledge about the existence of the area mapped before utilisation of this algorithm (e.g., fundus is known to be electrically silent).

Like the classification algorithm, the identification algorithm has parameters that can potentially be calibrated based on the level of experimental noise present in
6.5 Limitations and discussion

Figure 6.9: Mode graph and the AT templates with the key propagating patterns identified and marked. (a) shows that there are four AT templates and they progressively changed without reverting back to the same pattern. (b)–(e) shows the AT templates as an isochronal activation time map (1 s interval) and the corresponding key features identified. The slow wave activity within the mapped field changed from an antegrade activity to an ectopic pacemaker (with the characteristics of a pacemaker and a colliding wavefront), then to a colliding wavefront pattern alone, before retrograde activity entrained the whole mapped field.
6. AUTOMATED CLASSIFICATION AND IDENTIFICATION

the AT map. The parameters that can be adjusted for pacemaker detection is the divergence threshold; for colliding wavefront are the divergence threshold and time difference of the watershed algorithm for detection; and for the conduction block site it is the mean curvature threshold. One of the limitations of the automated identification method is that the accuracy of the localisation is based on the inter-electrode distance spacing used in the experimental setup. Also, the identification algorithm is unable to differentiate between a functional or anatomical block, or re-entry; and for colliding wavefronts, the potential resultant of merging wavefronts were not identified. Nonetheless, these specific patterns of propagation can be readily interpreted by the end user when presented with the summary of the recording via a mode graph and identified patterns.

6.5.2 Discussion

In this chapter, two novel automated methods to analyse and characterise spatiotemporal patterns of normal and dysrhythmic gastric slow wave propagation were developed. The first method was an automated classification algorithm to classify slow wave AT maps into similar propagation patterns. The second automated method identified specific slow wave propagation patterns and located their key features within the mapped fields. Utilisation of these two methods in tandem allows for an accurate quantitative analysis of gastric slow wave activation patterns in an efficient, specific, intuitive and unbiased manner. Existing methods that have provided inspiration to the methods are briefly discussed, with the potential advantages and uses in clinical development.

Other automated techniques have been used to analyse HR cardiac mapping studies [58] [88] [165] [166]. However these methods could not be directly applied to the GI field due to the significantly different characteristics in the spatiotemporal patterns, time course and signals between cardiac and GI electrophysiology [52] [53]. The automated classification techniques developed here were motivated, in part, by the work of Rogers et al. [165], where correlation was used to cluster cardiac wavefronts, and the multiplicity index used to account for the fraction of activation patterns in the cluster. Identification of specific slow wave propagation
patterns and regional localisation of patterns in the AT map was partly inspired by the work performed by Fitzgerald et al. \cite{58}, where curl and divergence operators were performed on spatiotemporal cardiac mapping data to identify cardiac rhythm. In the GI field, a method has been used to study slow wave dysrhythmias via the use of velocity vectors of the slow wave propagation (see Section \textsection 4.3.1) \cite{47}. Although this method is semi-automated, it still heavily relies on the clinician or researcher to manually define the normal slow wave propagation patterns, and can only ascertain if the AT map is normal or abnormal, and does not provide the information in an intuitive format.

The use of automated analysis for GI HR mapping eliminates the manual bias that might be present during analysis and provides a succinct summary of the slow wave activity present in the stomach \cite{154}. There are significant advantages of the automated classification and identification methods. The first is that it allows for a large number of experiments to be performed of which vital information about the nature of the slow wave activity can be assessed in an intuitive manner. This will lead to a better understanding of normal and abnormal slow wave activity and its specific mechanisms in gastric motility disorders. In human gastric HR mapping studies, it has been revealed that during the circumferential propagation that arises in dysrhythmia, local slow wave velocity increases by more than two-fold due to the inherent anisotropy in the stomach \cite{138}. A concurrent increase in extracellular amplitude also occurs, due to increased transmembrane current entering the extracellular space \cite{142}. Although the effect is less in pigs \cite{142}, these properties may still be appreciated in Figure 6.8 of the current study, where circumferential propagation arises during ectopic initiation. The higher velocity is indicated by the larger spacing of isochrones, and the zone of high velocity corresponded with the zone of higher amplitudes. The ability to accurately detect and identify these important spatial characteristics provides an essential additional level of clinical reliability for the correct detection and interpretation of dysrhythmic activation.

The second significant advantage is that these methods have the potential to allow GI HR mapping to be used for the clinical assessment of gastric slow wave activity. The automated methods could also be used to assess the efficacy of drug therapies.
for GI dysrhythmias, such as prostaglandin synthesis inhibitors and natural remedies on slow wave activity \[117, 149\]. With the emergence of gastric stimulation as a potential treatment option \[128, 141\], these automated methods will allow for immediate assessment of the gastric slow wave activity and can help guide the stimulation protocols. As occurs in clinical cardiology \[172\], the new methods described here could be applied in an online setting to allow clinicians to make an immediate assessment on the efficacy of the treatments such as pacing, and make alterations to the treatment as necessary. This is feasible because the methods are computationally efficient. The rapid processing time is advantageous because the computational overhead is a significant factor for implementation of visualisation and analysis of online HR data \[25\].

One of the downsides of the automated methods is that it is reliant on the accuracy of the pre-processed signals. For example, the classification method could potentially become over-sensitive in the presence of excessive noise, which may distort the activation maps \[52, 53\], resulting in a spuriously large number of classes. However, if templates of ectopic pacemaking, circular propagation and re-entry were not accompanied by these anticipated (and statistically verifiable) physiological velocity and amplitude changes, then such templates can be safely identified as false positive patterns and discarded. In future human and animal trials, a library of normal and abnormal slow wave propagation templates could also be developed for the various regions of the stomach, enabling automatic correct discrimination of key dysrhythmic patterns and their sources for clinicians. This step could also stimulate the development of more advanced algorithms for pattern analysis and identification via the use of neural networks or support vector machines.

6.6 Summary

One of the current limitations of GI HR mapping is that it generates a vast amount of data, making manual analysis a tedious task for research and clinical development. In this chapter two novel automated methods of analysing GI HR mapping recordings are presented. The first method classifies the slow wave activity into
similar propagation patterns that are present in the HR recordings, while the second method identifies the presence of key features and localises them spatially. The classification method uses a similarity metric to classify slow wave propagations, while the identification algorithm uses the divergence and mean curvature of the slow wave propagation to identify and regionalise patterns of interest. These two methods allow automated analysis of GI HR recordings in an efficient manner without bias.

The methods were applied to synthetic and experimental data sets and were also compared to manual analysis. The methods classified and identified patterns of slow wave propagation in less than 1 s, compared to manual analysis which took up to 40 minutes. The automated classification algorithm achieved 96% accuracy, while the automated identification method achieved 95% accuracy with a mean spatial error of 1.5 mm. These new automated methods will facilitate the efficient translation of GI HR mapping techniques to clinical practice, providing clinicians with vital information about the patterns of slow wave activity in patients.
Chapter 7

Automated quantification of electrogastrograms

The work performed in this chapter was in collaboration with, and financially supported by, the University of Mississippi Medical Center and University of Louisville.

Cutaneous electrogastrogram (EGG) provides information about gastric slow wave activity in a non-invasive manner. Walter Alvarez was the first to record EGG recordings which was then taken up by several researchers over the years [9]. The current status of cutaneous EGG will be reviewed, after which automated methods of analysis for sparse EGG are described, validated and verified. This is followed by a brief summary of the clinical relevance of EGG and the use of automated analysis to assist EGG in becoming a clinical utility.

7.1 Background

EGG recordings are undertaken with electrodes placed on the body surface to record the slow wave activity generated by the stomach (Figure 7.1). This approach to recording and characterising gastric slow wave activity is attractive because it is non-invasive. Presently however, EGG is not widely used for clinical diagnosis and is primarily used as a research tool. EGG has not had the successes
its counterpart, the 12-lead electrocardiogram (ECG), has achieved. The ECG is used widely in a clinical and ambulatory setting, and plays a vital role in the medical care of patients with cardiac electrophysiological disorders [184].

There are three key barriers that impede the use of EGG as a clinical utility; (i) low signal to noise ratio, (ii) inadequate hardware and software processing techniques and (iii) lack of physiological understanding of gastric electrical activity. Extracellular recording obtained from the serosa of the stomach possess a lower amplitude in comparison to cardiac electrical activity recorded on the heart surface (approximately 1 mV in the stomach compared to 20 mV on the epicardium of the heart) [68]. The fact that gastric slow waves have to travel through the tissues and fat layers in the abdominal wall results in a significant decrease in the amplitude of gastric slow wave activity as recorded on the body surface. Thus, it leads to a reduced signal to noise ratio of the EGG signal. Other than the slow wave signal itself, EGG recordings are also sensitive to noise in the form of body movements, respiration, patient speaking, other physiological artefacts such cardiac and intestinal electrical activity, and powerline interference [100 120 152].
These factors will also significantly reduce the signal to noise ratio of EGG recordings. Traditional signal filters, such as Butterworth filters, can eliminate the noise artefacts whose frequency range is outside the frequency range of the signals of interest. But for other noise artefacts whose frequency is in vicinity of the fundamental slow wave frequency, more complex signal processing and filtering would be required, such as the use of an adaptive filtering scheme [92, 93]. For example, one potential noise source is respiration, which occurs around 9–15 cpm and this overlaps with the harmonics of the slow wave frequencies, which can range up to 2 Hz [155]. Neural networks and the use of independent component analysis have been used to identify signals of interest using multi-channel EGG, but is unreliable if the signals recorded are corrupted by noise, or if the signals do not resemble physiological gastric slow waves [191, 192]. Thus, there is need for an approach to discard artefacts from EGG traces for analysis in an intuitive and automated manner.

With reduced signal to noise ratio, adequate signal acquisition systems are required, along with signal processing techniques to perform accurate and efficient analysis. In recent years, data acquisition systems have increased bandwidth, and as a result, this has allowed EGG data acquisition systems to capture gastric slow wave signals with a high signal fidelity. Also advances in computational efficiency have allowed for efficient real-time and off-line analysis of long segments of data which could span hours or days [28, 120]. Modern signal processing techniques from other research fields are also being used to analyse EGG signal traces, such as the use of empirical mode decomposition, which was originally used for space signal processing, but requires significantly more validation and verification [115].

With EGG recordings it is important to have an accurate understanding of the underlying anatomy and physiology of the stomach. It has been shown that the signal amplitude of the EGG signal increases from the pre-prandial to the post-prandial state (see Figure 7.2), and has been attributed to the increase in amplitude of the slow wave activity in the stomach and presents information about stomach contractions [32, 101, 159, 174]. The increase in amplitude of the EGG has also been thought to be due to the position of electrodes resting close to the stomach, due to the enlarged stomach [32, 130]. A recent modelling study by Du et al. [44]...
also confirmed that the increase in amplitude may be partly due the relative position of the electrode to the stomach. A further result from this study was that the EGG trace is visualised as a combination of multiple wavefront propagation and assigning a phase to the EGG recordings can be complex and is primarily dependent on the location and orientation of the stomach [44]. Another potential explanation for the increase in amplitude of the EGG signal has been attributed to the increase in propagation velocity profile of the slow wave activity [54]. It has been observed experimentally that normal slow wave activity has a higher amplitude with a rapid propagation velocity in the pacemaker region and when the slow wave activity reaches the pylorus [139]. Using mathematical models to simulate the EGG recordings it was shown that electrodes placed closer to the pacemaker site (greater curvature on the mid to upper corpus region of the stomach) and towards the pylorus would yield an EGG signal with a higher amplitude [44, 54].

Conflicting evidence exits in literature as to whether EGG can denote gastric contractions, possibly via the representation of spike or MMC activity. One study has shown that using EGG and fluoroscopic imaging, the phases of the EGG signal relate to gastric contractions [101], while another study utilising EGG and ultrasonogram could not find a significant correlation between the EGG signal phases and gastric contractions [159]. Due the presence of conflicting evidence, further controlled research into this topic is required, and the analysis of the changes in EGG amplitude needs careful review and assessment.

Since its inception, the use of EGG as a clinical utility has eluded industry, clinicians and researchers alike. The US Food and Drug Administration have approved the use of EGG, and companies have developed EGG machines with the main target for clinical use [11]. However, many of the companies have since disbanded their product and have relegated EGG to research purposes. In the research domain, EGG has had much success with its reported ability to detect stomach abnormalities from pseudo-obstruction, gastroparesis, diabetic nausea, functional dyspepsia, peptic ulcer and post-operative stress [152]. The slow wave traces are typically classified as normal (2–4 cpm) or dysrhythmic, as tachygastria (4–10 cpm) or bradygastric (1–2 cpm), based on frequency analysis [37]. Various research groups
Figure 7.2: Typical pre-prandial and post-prandial EGG recordings. The top trace is an EGG recording from a human in a pre-prandial state, while the second trace is after ingestion of water. The third EGG trace was taken right after a meal. The amplitude of EGG traces increase after ingesting water or food (post-prandial). Adapted from [32].
have used different frequency limits to assign the EGG traces as normal or dysrhythmic making comparison across studies difficult [152]. Also, the use of appropriate signal filtering techniques are imperative for EGG analysis, as it has been shown that if inappropriate filtering is used, the signal may be misinterpreted as dysrhythmic [131].

The understanding of serosal gastric slow wave activity using HR mapping techniques will serve as a vital tool to formulate an analytic understanding of cutaneous EGG recordings. For instance, the use of the velocity and amplitude profiles (Chapter 4), along with the use of intervals of slow wave signals (Chapter 5) and typical propagation patterns (Chapter 6) from experimental HR mapping can be modelled as the initial conditions for the forward problem to determine signal morphology and spatial profiles of slow wave activity as mapped on the body surface. Normal and dysrhythmic patterns of slow wave propagation can be mathematically modelled, which will then be able to guide development of techniques to understand cutaneous EGG recordings [35, 44, 94].

In this chapter, an improved methodology for sparse EGG analysis is presented along with validation and verification of the methods. All of the methods developed here were deployed in an easy to use GUI that can be used by a clinician to verify or use the results of the EGG traces for potential diagnosis or treatment strategies. See Appendix C.2 for a summary of the GUI and example output results.

### 7.2 Methods

Currently, the main parameter that most researchers identify is the dominant frequency of EGG signals. Other parameters of interest are primarily derived from the frequency domain of the EGG signal, such as percentage distribution of EGG power in the frequency bands of interest, power ratio and stability of the dominant frequency [100]. Figure 7.3(a) shows an example of the analysis currently performed on EGG signals where the frequency information over time is displayed as a waterfall plot. Typically the frequency bands of interest are also
monitored over time as a percentage (Figure 7.3(b)). We have developed methods to reliably estimate the frequency and signal amplitude of the EGG signal using similar approaches.

(a) Running spectral analysis of cutaneous EGG displayed as a waterfall plot.

(b) Percentage distribution of EGG power over time.

**Figure 7.3:** Typical EGG signal analysis over time. (a) shows the running spectral analysis of an EGG signal shown in (A) and (B) where the frequency information is displayed as a waterfall plot in (A1) and (B1). (A) is a baseline EGG strip while (B) shows the change in the signal amplitude after ingestion of water. (b) shows the distribution of percentage distribution of EGG power in the frequency bands 1–15 cpm. Signals with frequencies in 1–2.5 cpm were considered as bradygastric activity, while 2.5–3.75 cpm were considered as normal activity, 3.75–10 cpm as tachygastric activity and 10–15 cpm as noise representing duodenal or respiration (Resp) activity. Adapted from [100].

**Figure 7.4** shows a flowchart illustrating the framework for processing, analysing
and reporting the frequency and amplitude of the EGG slow wave recording. There are five main stages in the framework:

1. Data pre-processing (Section 7.2.1)
2. Frequency estimation (Section 7.2.2)
3. Amplitude estimation (Section 7.2.2)
4. Artefact detection (Section 7.2.3)
5. Reporting (Appendix B)

### 7.2.1 Data pre-processing

The EGG data on human patients were recorded using an EGG recording system (Sandhill Scientific, Highlands Ranch, Colorado). EGG electrodes were placed on the body surface roughly over the corpus and antrum regions of the stomach, and the data was recorded for 5–15 minutes. Details of the file formats and the extraction of data for analysis are listed in Appendix C.2. Once the EGG trace was extracted, signal filtering was performed. Three sources of noise were present in the signal, baseline wander, high frequency noise, and random signal fluctuation which are not of slow wave origin. Digital signal filters were applied to eliminate the baseline wander and high frequency noise, while random signal fluctuation were accounted for in the artefact detection stage.

To eliminate the baseline wander in the signals, a moving median estimate with a window width of 20 s was applied to the EGG signal trace to estimate the baseline wander. A second order low pass Butterworth filter with a cutoff at 3 cpm was applied to eliminate any sharp discontinuities in the baseline estimate via the moving median filter. The estimated baseline wander was subsequently subtracted from the EGG trace. To eliminate high frequency noise, a fifth order low pass Butterworth filter with a cutoff at 1.5 Hz was applied to the EGG signal trace after baseline removal using the median filter.
7.2 Methods

**Data pre-processing**
- Import and convert raw data and configuration files
- Eliminate baseline wander
- Eliminate high-frequency noise
- Overlapped windowing of signals

**Signal analysis**
- Frequency estimation
- Amplitude estimation
- Artefact detection

**Reporting**

**Figure 7.4:** Flowchart illustrating the framework for the analysis of cutaneous electrogastrography. There are five main stages to the framework; (i) Data pre-processing which include data import and signal filtering (baseline wander and high frequency noise), (ii) frequency estimation, (iii) amplitude estimation, (iv) artefact detection and (v) reporting.
7.2.2 Frequency and amplitude estimation

The dominant frequency was calculated by taking the Fourier transform of the signal and choosing the frequency component with the highest power. The implementation of the Fourier transform does not provide temporal resolution. If there are two peaks in Fourier transform, it could either mean that; (i) somewhere along the recordings the dominant frequency of slow wave changes from one frequency component to another, or (ii) for the duration of the recording there are two frequency components co-existing, or (iii) a combination of (i) and (ii) (see Figures 7.5(b) and 7.6(b)). In Figure 7.5, the frequency of the signal changes from 5 cpm to 3 cpm at 15 minutes of the 19 minute recording, while in Figure 7.6, the signal has both the 5 cpm and 3 cpm frequency components co-existing for the duration of the recording.

An improvement on the Fourier transform approach is to use a short term Fourier transform (STFT), whereby the signal is divided into smaller overlapping windows and the dominant frequency is computed for each window. This allows for changes in frequency of the signal to be localised temporally (see Figures 7.5(c) and 7.6(c)). In Figures 7.5 and 7.6, the time frequency is shown as an image, with the white bands representing the frequencies in time illustrating the presence of multiple frequencies at any one time (Figure 7.6) or the change in frequencies (Figure 7.5). The STFT approach is widely used in EGG recordings and in research and commercial EGG systems [100].

For frequency analysis, STFT was used with a moving window of two minutes, with an overlap of 83% (110 s of overlap). One of the problems with the STFT method is that it has a trade-off between the time resolution and frequency resolution, similar to the Heisenberg principle which showed that to localise the velocity of an object, the positional information becomes less certain and vice versa. In the STFT case, smaller window size for FFT calculation provides for a higher temporal resolution and a lower frequency resolution and vice versa (Equation 7.1).

\[
\text{Frequency} = \frac{1}{\text{Time}} \quad (7.1)
\]
7.2. Methods

Figure 7.5: Time-frequency resolution of Fourier transform of signal with two separate frequencies in time. (a) shows a sine wave at 3 and 5 cpm in the time domain. (b) shows the frequency domain of the entire signal in the frequency domain via a Fourier transform. (c) shows a time-frequency domain representation of the signal where the dominant frequency changes from 5 to 3 cpm around 15 minutes.
Figure 7.6: Time-frequency resolution of Fourier transform of signal with two separate frequencies in time. (a) shows a sine wave at 3 and 5 cpm in the time domain. (b) shows the frequency domain of the entire signal in the frequency domain via a Fourier transform. (c) shows a time-frequency domain representation of the signal where the dominant frequency of 5 and 3 cpm are co-existing.
A window of 2 minutes with an overlap of 110 s was chosen systematically as it allowed frequency to be tracked in time with a frequency resolution of 0.5 cpm (Figure 7.9). To acquire an accurate estimate of the frequency, prior to performing the Fourier transform on the signal of 2 minutes, the signal was zero-padded and a Hanning window was applied. The zero-padding and windowing of the signal was performed to reduced the spectral leakage inherent to FFT calculations [135].

For automated amplitude estimation, the same signal windowed approach (2 minute window with an overlap of 110 s) was used to extract a corresponding amplitude value to the frequency value. The amplitude was calculated by taking the difference between the maximum and minimum values. To decrease the sensitivity of the methods to outliers, a windowing method within the 2 minute window was used, with a window of 20 s and an overlap of 17 s as shown in Figure 7.7. It is assumed that within the 20 s, there is no baseline drift in the signals. The amplitude was calculated for each of the subwindows and the median values of these were taken as the amplitude for the main 2 minute window. This was primarily used to discard any transient large variations in the EGG signal trace while reporting the signal amplitude. Figure 7.9 shows the application of the frequency and amplitude estimation of a normal EGG trace, where the signal is corrupted by a sharp artefact and this has not affected the automated amplitude estimate.

7.2.3 Artefact detection

One of the barriers for automated analysis has been the presence of noise which corrupts the recordings and subsequently the analysis. To detect erroneous segments in the EGG recordings, four levels of scrutiny were undertaken in the frequency and time domain (Figure 7.9).

The first level of scrutiny was based on the amplitude estimate of the signal. If the estimated amplitude of the EGG signal was not within the acceptable physiological limits (less than 0.25 mV), then that particular signal segment was not included for analysis. The second and third levels of scrutiny are based on the frequency domain of the signal segment. If the maximum dominant frequency was
7. ELECTROGASTROGRAPHY

Figure 7.7: Illustration of automated amplitude estimation of an EGG trace. The first trace show a 5 minute window of a sine wave. A 2 minute window of the signal is taken, which is used for frequency estimation at that time point. The amplitude estimation further subdivides the 2 minute window into a 20 s window with 17 s of overlap. The amplitude for each of the sub-windows was calculated using the difference between the maximum and minimum values in the subwindow. The amplitude estimated for each 2 minute period was given by the median amplitude of the n sub-windows.
7.2 Methods

Figure 7.8: Frequency and amplitude estimation of an EGG signal. (a) shows a filtered EGG signal with a green line with star marker indicating the amplitude estimate over time. A large artefact is seen around 4.5 min which is not affected by the automated amplitude estimation algorithm. (b) shows the EGG signal corresponding frequency estimate.
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Determines the number of dominant frequencies in 1-10 cpm range

Amplitude estimate < 0.25 mV

Yes

Dominant frequency in the band of 1-10 cpm

Yes

Square the frequency domain and normalise the frequency spectra

No

Detect the no. of peaks greater than 0.75 as dominant frequency

No

No. of dominant frequency peaks = 1

Yes

Signal segment chosen for analysis

No

Noisy signal segment

Eliminate single good marker in a section of noisy markers

Figure 7.9: Flowchart illustrating the steps in artefact detection in EGG signals. Four levels of scrutiny are undertaken; (i) amplitude limit, (ii) frequency limit, (iii) number of dominant frequencies in the frequency limit of 1–10 cpm over 0.75 in a normalised spectrum, and (iv) elimination of false markers. Two EGG signals along with frequency domain are shown illustrating the computation of the dominant frequencies. The clean signal has two frequency peaks (in 1–10 cpm range), with the dominant peak almost twice the size of the first harmonic component. The noisy signal segment has multiple frequency components and has more than one dominant frequency peak.
7.3 Validation of methods

below 1 cpm or above 10 cpm, then that signal segment was not considered for analysis. The third level of scrutiny was to quantify the number of dominant frequency components in the EGG signal segment. This was done by first squaring the normalised frequency amplitude components and normalising them. All of the peaks with the 1-10 cpm are found, and the number of peaks above a threshold (empirically determined as 0.75) was defined as the number of dominant frequencies in the EGG signal segment. This scrutiny was synonymous to quantifying the regularity of the signal and in the future could be used as a discriminator against various motility disorders. In this case, it was assumed that if there was more than one dominant frequency in the signal then the EGG signal segment was not chosen for analysis.

Once the noisy and good signals segments were identified for the EGG signal trace, it was termed the signal integrity metric and represented as a ‘good signal’ or a ‘noisy signal’. A fourth level of scrutiny was performed on the signal integrity metric to detect if there was any single good signal segment in between sections of ‘noisy signal’ segments. More than likely that ‘good signal’ in between sections of ‘noisy signal’ is a false detection and was remarked as a ‘noisy signal’. More importantly for clinical relevance, a continuous segment of good quality data is required to reliably estimate parameters of interest. Figure 7.10 shows the results of the artefact detection in an EGG signal which was initially noisy, potentially due to movement artefacts, and then the EGG signal quality improved after 3 minutes.

7.3 Validation

7.3.1 Synthetic test cases

The frequency and amplitude estimation methods were applied to 5 synthetic slow wave EGG traces to test its effectiveness. A signal of 15 minutes duration was created with the EGG slow wave morphology represented as a sine wave. To mimic experimental conditions, Gaussian random noise was added to the signal
Figure 7.10: Artefact detection in an EGG signal. The signal starts off fluctuating randomly with large amplitude with the presence of multiple frequencies. This section has been automatically picked by the algorithm as being a ‘noisy signal’ segments. The signal then stabilises into a period of good slow wave recordings, which has been automatically detected by the artefact detection algorithm and marked the signals as a ‘good signal’ section.
7.4 Results

to represent high-frequency noise (mean: 0, standard deviation: 2) and movement artefacts (mean: 0, standard deviation: 20).

The first EGG test case had a stable 3 cpm frequency (Figure 7.11(a)), while the second EGG test case had a change in frequency from 3 to 5 cpm (Figure 7.11(b)). The third EGG test case had a stable 3 cpm for the first half of the recording, which was then corrupted by non-physiological signals (Figure 7.11(c)). The fourth and fifth EGG test cases were similar to the first two cases, except random fluctuations were introduced for 1 s interval(s) (Figure 7.11(d,e)). The first two test cases validated the automated estimation of frequency and amplitude under artefact free condition. The remaining cases validated the estimation of frequency and amplitude of the EGG signal trace in the presence of signals that contain artefacts.

7.3.2 Experimental cases

To validate the effectiveness of the frequency and amplitude estimation methods in experimental signals, the results were compared to the estimates acquired via manual analysis, which is currently the gold standard. EGG recordings from eight patients (one experiment per patient) lasting 8–16 minutes were assessed by two expert researchers in the field of EGG. Of the eight patients, four were male and four were female, and all of them were diagnosed with gastroparesis. The patients age ranged from 34 to 71 years old (mean age: 49 years old).

The manual estimates of EGG frequency and amplitude were then compared to the automated estimates of EGG frequency and amplitude for each experiment.

7.4 Results

7.4.1 Synthetic EGG traces

Figure 7.13 shows the the frequency and amplitude absolute error estimates for synthetic EGG traces. On average there was an error of 0.032±0.026 cpm for estimating the frequency of the EGG slow wave signal, with an error of 0.030±0.027 mV
Figure 7.11: Test cases to assess automated frequency and amplitude estimates of the electrogastrogram. (a) is a stable EGG trace at 3 cpm while (b) shows a stable EGG trace at 3 cpm changing to 5 cpm with an increase in amplitude. The signals in the presence of non-physiological EGG slow wave signals are shown in (c–e), with (c) showing half of the signal trace corrupted by random noise, while (d) and (e) has one second random noise deflections added to mimic movement artefacts.
for estimating the amplitude of the EGG slow wave signal. The amplitude errors were overly estimated due to the fact that the true amplitude was pre-determined before the addition of noise to the signal trace. The introduction of noise elevates the signal amplitude, and thus sets an upper bound for the amplitude error by the automated amplitude estimation algorithm. The absolute introduced noise error was random in nature and reached a maximum of 0.08 mV.

Figure 7.12: Boxplot illustrating the absolute error in estimating the frequency and amplitude in five synthetic EGG traces using automated methods of estimation. The mean absolute frequency error was 0.032±0.026 cpm, while the mean amplitude error was 0.030±0.027 mV. The boxplot shows the error range with interquartile ranges, median and outliers.

7.4.2 Experimental signals

Figure 7.13 shows four EGG signal traces which illustrates the method employed for manual frequency analysis, along with results of the automated approach. In Figure 7.13 (a), the potential bias in manually assessing the signal traces can be seen, whereby the manual estimates was given as 3.2 cpm, but on closer inspection this reading could potentially be disputed. Manual amplitude analysis is usually
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taken whereby the researcher would read the values from the peak to the trough of the signal to estimate EGG amplitude. Also, while the manual marker took around 30 minutes to estimate the frequency and amplitude of the EGG traces, the automated method was almost instantaneous.

Figures 7.14(a) and 7.14(b) show the comparison of the average frequency and amplitude estimates of the EGG trace for each patient between the expert marker and the automated methods. There was an absolute error of 0.33±0.29 cpm in frequency estimation and 0.03±0.03 mV for amplitude estimation between the automated and manual estimate from an expert marker.

7.5 Discussion

EGG recordings offer a non-invasive approach to detect and characterise gastric slow wave recordings. At present, however, EGG has limited use in routine clinical care, and is best summarised by Bortolotti et al. [17] as “a seductive promise, only partially kept”. Improvements in recording reliable slow wave signals has allowed for the development of automated analysis methods. Along with a renewed understanding of gastric motility disorders, it will allow EGG to become a clinical utility. Here, an approach to reliably and automatically estimate the frequency and amplitude of the slow wave in the EGG traces has been presented. Potential future work is also discussed.

Standardised methods for recording and analysis are imperative for EGG so that results can be compared between studies and between different labs or centres. A guideline has been specified by the American Motility Society Taskforce [152], but not all studies adhere to them. Also, with the advent of new technologies leading to an improved understanding of slow wave activity in normal gastric function and in gastric motility disorders, an international effort is required with the inclusion of the European and Asian GI motility societies to provide an up to date guideline. More research and development is required around utilising EGG as a clinical utility for directing treatment strategies and prescribing a diagnosis, as well as a prognosis. This will allow for a concerted effort for the field of EGG to improve
Figure 7.13: Four EGG signal traces with manual annotations to estimate frequency. The manual and automated estimates for frequency are shown above the signal trace. Red arc curves are representative of manual analysis employed at the current status for EGG frequency. Results are denoted as manual frequency estimate vs mean automated frequency estimate. In (a) the results are 3.2 cpm vs 4.1 cpm, in (b) 3.0 cpm vs 3.27 cpm, in (c) 4.0 cpm vs 4.1 cpm and in (d) 4.0 cpm vs 3.84 cpm. Although the manual analysis in (a) denotes 3.2 cpm, on closer inspection this could be disputed, and therein lies potential bias. Manual analysis from (b), (c) and (d) closely match the automated frequency analysis.
Figure 7.14: Comparison of manual and automated estimates of frequency and amplitude of the EGG trace for 8 patients. (a) shows the manual and automated estimates of frequency of the EGG trace. The average absolute difference between the manual and automated estimates was 0.32±0.27 cpm. (b) shows the manual and automated estimates of frequency of the EGG trace. The average absolute difference between the manual and automated estimates was 0.03±0.05 mV.
technologically and clinically and can allow EGG to be used as a clinical utility for patient care.

Automated frameworks are essential for the analysis of EGG recordings. With the use of manual analysis, especially with signals that have a low signal to noise ratio, information may not be analysed or over-analysed which may lead to misleading results. Methods to reliably estimate the frequency and amplitude of the slow wave signal have been developed. The method for estimating frequency used here was adapted from traditional methods used by Chen et al. [31]. The method for computing the amplitude of the slow wave signal in the EGG trace is novel as it is the first method that suppresses the inclusion of large amplitude variations in the signal that are infrequent and transient in time. The use of artefact detection is applied to the EGG signal in the time and frequency domain to allow for average EGG metrics (frequency and amplitude) to be identified reliably. The use of the described methods will allow reliable assessment of the underlying physiology of slow wave in normal humans and those with gastric motility disorders. With the application of this method in a large number of patients, further metrics may be developed to discriminate various gastric motility disorders. This will allow the use of EGG as a clinical utility and can be used in routine clinical care. With further controlled test cases of potential noise cases, an automated identification system similar to that developed by Liang et al. [116] can be developed and validated.

Another potential area to explore is to quantify the relationship of the frequency and amplitude of the EGG slow wave trace in a mathematical modelling scenario. Here, the parameters for normal and dysrhythmic slow wave propagation can be controlled and varied according to physiological specifications [44]. The use of forward modelling of gastric slow waves from the serosal surface to the body surface and the understanding of the results will be significant in advancing the knowledge of the EGG signals recorded in a clinical scenario. The use of multi-channel EGG recordings may be able to provide significantly more information using sparse recording [94]. In clinical cardiology, it is well known that multi-channel ECG can potentially provide a more comprehensive view of the bio-electrical events in the heart compared to the 12-lead ECG in certain cardiac dysrhythmias, such as the Brugada syndrome [24]. However, due to the complexity of recording and
analysing large number of ECG channels, the 12-lead ECG is used in clinical practice [6]. However in the GI field, at present, EGG is unable to resolve meaningful clinical information using sparse recordings. Thus, there is a strong proposition for multi-channel EGG recordings to be adopted in medical centres and research institutions to understand gastric motility disorders. This would require automated methods to provide useful information, as manual analysis of multi-channel EGG would be highly ineffective and prone to bias [94, 95]. Crucial to the success and widespread use of multi-channel EGG in a clinical setting is the inference of information from serosal HR slow wave mapping and mathematical models (forward and inverse models), to guide development of clinical tools [46, 94, 138].

7.6 Summary

In this chapter, novel methods to reliably estimate the frequency and amplitude of the cutaneous electrogastrogram were developed. These methods have been validated with synthetic signals and verified with experimental EGG signals via the use of manual analysis. With synthetic test EGG signals, the developed automated method resulted in an average error of 0.03 cpm in estimating the frequency of the EGG trace and 0.03 mV in estimating the amplitude of the EGG trace. With experimental recordings, manual analysis was defined as the gold standard, and the automated methods resulted in an average error of 0.33 cpm in estimating the frequency of the EGG trace and 0.03 mV in estimating the amplitude of the EGG trace.

The developed automated analysis is capable of reliably estimating the frequency and amplitude of the EGG trace almost instantaneously. These methods are anticipated to be used in a clinical setting to validate the use of EGG as a clinical utility.
Chapter 8

Conclusions and future directions

Bio-electrical slow wave activity coordinates motility in the stomach [79]. It is now known that dysrhythmic slow wave activity is associated with major GI motility disorders such as gastroparesis and functional dyspepsia [113, 118, 138]. Despite this, slow wave information has limited utility in clinical practice. Some of the major limitations hindering the use of slow wave information in clinical practice are the low specificity and sensitivity of detecting motility disorders, and a lack of understanding about the underlying electrophysiology of normal gastric function and gastric dysrhythmias.

Recent work in GI HR mapping has provided an improved understanding of spatiotemporal dynamics of slow wave activity and have started to define possible mechanisms for gastric motility disorders [112, 138]. It is expected that with a renewed understanding of slow wave activity, and with the development of novel methods of recording and analysis, that slow wave activity can be incorporated into clinical practice for diagnosis, prognosis, and for development and assessment of treatment strategies.

The work performed in this thesis presents a way forward for clinical translation of HR electrical mapping techniques for use in the GI field in clinical practice. A summary of the findings of this thesis are presented before concluding.
8. CONCLUSIONS AND FUTURE DIRECTIONS

8.1 Summary of findings & future directions

Signal processing and filtering

One of the main current barriers in the GI field is the lack of a specification for appropriate and standardised filtering techniques for in vivo extracellular gastric slow wave signals. Here, with use of frequency domain transformation of raw experimental signals and various filtering techniques, it was found that the inclusion of the dominant frequency of the slow wave (around 3 cpm in normal humans) and its major harmonic frequencies up to 2 Hz were pertinent for precise morphological and time based analysis [155].

Synthetic signals were created with realistic experimental noise to evaluate the effectiveness of filters. Six filters were chosen of which some have been used in prior experimental studies. It was found that the moving median filter (window size: 20 s) was most effective at eliminating baseline wander while the Savitzky-Golay filter (window size: 1.7 s, polynomial order: 9) was effective at eliminating high frequency noise. Noise sources such as respiration lie in the frequency range of the dominant harmonics of the slow wave, and cannot be eliminated using traditional signal filtering approaches without distorting the slow wave morphology. It is expected that such noise sources will be minimised during experimental recordings to minimise distortion to the recorded slow wave signals.

HR mapping utilises a large number of electrodes for mapping slow waves (typically 160–256 electrodes), providing a significant amount of information which is inefficient for manual analysis. Automated methods developed by Lammers et al. and Erickson et al. are capable of detecting slow waves, but are insensitive to noisy segments of data and recording data from sections of the stomach, such as the fundus, which exhibit no slow waves [53, 107]. A novel method was developed to eliminate incorrect fiducial slow wave markers by assessing the signals dominant frequency, amplitude, correlation and kurtosis characteristics. The algorithm was applied on experimental datasets and its results were compared to manual analysis, yielding a sensitivity of 91% and specificity of 82%.
8.1. Summary of findings & future directions

Methods were also devised to visualise the information in an intuitive manner via a static isochronal image map and via animated sequences of propagation. The framework of filtering the signals, detecting slow wave signals, and displaying the slow wave information, was used as a framework to build automated methods for quantification, detection of key characteristics, such the pacemaker activation, and display of succinct information about the experimental recording. It is anticipated that the methods developed in this framework will be used in other gastric HR mapping studies, and can provide the opportunity to translate HR mapping to analyse slow wave activity in other areas of the GI tract such as the small intestine.

Velocity and amplitude estimation

Reliable estimation of quantitative metrics from GI HR mapping is essential for defining slow wave patterns of interest in regional locations of the stomach. Methods of estimating the velocity and amplitude of the gastric slow wave propagation were developed that accounted for the noise levels in experimental GI HR mapping. Two newly developed methods of velocity estimation (FDSM and POLY4x4) and one newly developed method of amplitude estimation for gastric slow waves, were compared to current methods of velocity (FD) and amplitude (‘maximum-minimum’) estimation. The new velocity FDSM method was superior to the FD method currently used for velocity estimation of slow wave propagation. Under realistic synthetic conditions, the FDSM method resulted in a speed error of 6% and angle error of 3°, while the FD method resulted in a speed error of 12% and angle error of 7°. The new method of estimating the slow wave amplitude based on derivatives was superior to the current method (‘maximum-minimum’) of amplitude estimation. Under synthetic experimental conditions, the derivative based method resulted in an average error of 16 µV in estimating the slow wave amplitude accurately, while the ‘maximum-minimum’ method resulted in an average error of 44 µV.

With the use of the velocity and amplitude of the slow wave propagation regionally, a detailed spatiotemporal understanding of the stomach could take place in normal and abnormal conditions, as seen in [142, 144]. It was seen in pigs, that during
dysrhythmic gastric slow wave propagation, rapid circumferential propagation is associated with high-amplitude signals. The clinical relevance of these findings are yet to be determined.

It is anticipated that the utilisation of GI HR mapping along with the developed velocity and amplitude estimation methods will allow for an improved understanding of clinical motility disorders in patients. Gastric HR recordings in humans with various defined gastric dysmotility is pertinent to understanding the variations in velocity and amplitude profiles across various types of gastric dysmotility. A recent study by O’Grady et al. has illustrated in gastroparetic patients that during ectopic circumferential propagation patterns, the velocity and amplitude of the slow wave activity increased [138]. Further HR studies in other human gastric dysmotility are required to assess the similarities and differences in profiles and characteristics of propagation.

Electrophysiology of slow waves

An electrophysiological study was also undertaken to investigate recent claims by Bayguinov et al. [13] that in vivo extracellular slow wave recordings are contaminated by motion artefacts and motion controls are obligatory during in vivo slow wave mapping. An experimental comparison study was undertaken between surface PCB contact electrode (used for HR mapping) and suction electrodes (which are less affected by motion artefacts). The results showed that slow wave signals were faithfully represented in the surface PCB contact electrode as they were in suction electrode recordings, with both recording modalities recording a frequency of 3.6 cpm and an activation to recovery interval of 6.2 s. Thus, motion control is not obligatory for in vivo extracellular slow wave mapping studies which utilise surface contact electrodes.

An investigation was undertaken to illustrate the differences in normal and abnormal slow wave propagation by comparing the activation-recovery intervals of the slow waves. The study has shown that dysrhythmic spatiotemporal activation patterns have characteristic morphological changes, namely a reduction in the
activation-recovery interval in slow wave dysrhythmias (normal: 4.3 s, dysrhythmic: 3.3 s). It is hypothesised that during dysrhythmic slow wave propagation, the activation to recovery interval decreases, which reduces the potential for spike activity or mechanical contraction, thus potentially inducing gastric motility disorders.

The factors that are responsible for the initiation, maintenance and termination of gastric dysrhythmias need to be determined in order treat patients with gastric dysmotility in an effective manner. It is anticipated that analysing the intervals of gastric slow wave recordings in human patients suffering from motility disorders will aid in detailing the mechanisms behind various gastric motility disorders. This is essential to developing novel treatment options and drug therapies to treat motility disorders.

**Automated dysrhythmia detection**

For GI HR mapping to be translated in clinical use, automated methods of analysing and presenting summarised information to the clinician or researcher in real-time is imperative, as has been in the cardiac electrophysiological field [172]. Automated methods were developed for GI HR mapping which classifies patterns of propagation into similar clusters, identifies the type of propagation present and displays the characteristics of the propagation regionally [154]. The automated classification method was 96% accurate and the automated identification method was 95% accurate with a mean spatial error of 1.5 mm in comparison to manual classification and identification of slow wave propagations. The results of the automated methods were displayed in an intuitive format to provide a summary of the HR slow wave recording. These methods were computationally efficient, taking less than a second for offline analysis, and can be implemented online without a significant computational overload.

Incorporating these automated techniques of classification and identification to GI HR mapping studies will enable detection of key propagating patterns in real-time and may assist in providing a diagnosis or prescribing a treatment strategy, potentially in real-time, such as determining stimulus protocols for gastric stimulation.
treatment. It is anticipated that these automated methods can be translated and adapted to other GI HR mapping configurations such as the use of laparoscopic devices \cite{140}, which can allow for clinical trials, development of treatment options and novel diagnostics that are less invasive.

**EGG analysis**

Body surface EGG signals typically have a low signal to noise ratio compared to ECG recordings due the low amplitude of the slow wave and the presence of noise in vicinity to the fundamental frequency of slow wave. An improved approach to estimate the frequency and amplitude of the EGG trace which is capable of detecting noisy sections of the signals is presented. With synthetic and experimental EGG traces (manually analysed by an expert in the EGG field), the automated method resulted in an average error of 0.33 cpm in estimating the frequency of the EGG trace, and 0.03 mV in estimating the amplitude of the EGG trace.

The use of reliable automated methods for frequency and amplitude of the EGG trace will allow the clinician to assess the viability of EGG as a clinical utility. It is anticipated that these methods will be trialled in EGG recordings from patients at the University of Mississippi Medical Center and the University of Louisville, that have gastric motility disorders such as gastroparesis and chronic nausea and vomiting.

To further validate the usefulness of EGG recordings, simultaneous HR electrical mapping from the serosal and body surface is required \cite{136, 148}. A recent EGG forward modelling study by Du et al. \cite{44} have highlighted potential key features in body surface EGG recording that could be useful clinically, such as the presence of multiple wavefronts, and when slow waves were activated in the antrum region of the stomach. Multi-scale mathematical modelling techniques can provide a crucial input to develop novel methods of experimental design and analysis that could extract key metrics and quantifications that can potentially be clinically useful.
8.2 Concluding remarks

It has become clear that slow wave activity plays a vital role in coordinating motility. Recent research efforts, particularly with an improved understanding of ICC and slow wave activity, and with the development of GI HR mapping, has started to provide a comprehensive view of GI electrophysiology. Novel treatment options such as “Enterra” stimulation therapy offered by Medtronic, Inc. are becoming available as a result, in an effort to replicate the methods used in cardiac electrophysiology. However, care must be taken in order to understand the similarities and differences across cardiac and GI electrophysiology, and how it impacts therapy accordingly. In particular, pathways and mechanisms of initiation, maintenance and termination of normal and dysrhythmic gastric slow wave activity are yet to be fully elucidated, along with the effects of co-regulation.

In conclusion, the methods and results of this thesis present a significant step forward in understanding slow wave activity and in pursuing the goal of incorporating the use of slow wave information into a clinical utility for diagnosis, prognosis, and for development and assessment of treatment strategies.
Appendix A

This section lists the peer-reviewed publications, book chapters, conference abstracts, award and achievements, and patent during the course of the PhD.

A.1 Peer-reviewed publications

If the peer-reviewed publication work has been included in this thesis, the chapter incorporating the work is listed after the publication details.

A.1.1 First Author Publications


### A.1.2 Co-Author Publications


A.2 Book chapters


A.3 Conference abstracts


A.4 Awards and achievements

Maurice and Phyllis Paykel Travel Grant (2013)
To present research and attend the 2013 annual IEEE Engineering in Medicine and Biology Conference in Osaka, Japan.

Best Student Communicator Award (2012)
Riddet CORE Annual Scientific Meeting 2012, Palmerston North, NZ.
“Automatic detection of spurious fiducial markers for gastric slow wave events,”

Top 25 research posters (2012)
EXPOSURE 2012 - Auckland University Postgraduate Research Exposition
“Detection of recovery times in gastric extracellular high-resolution electrical recordings”

Third place in Multimedia and Live Performance (2011)
EXPOSURE 2011 - Auckland University Postgraduate Research Exposition
“GEMS: a tool to understand the gut”

Sir John Logan Campbell Travel Grant (2011)
To present research and attend the 2011 annual IEEE Engineering in Medicine and Biology Conference in Boston, USA.

Third place at SPARK $100k Challenge (2010)
The University of Auckland Entrepreneurship Challenge

Best Biotechnology Idea - Chiasma I-Volve Award (2010)
The University of Auckland Entrepreneurship Challenge

Ideas Challenge Winner, SPARK (2010)
The University of Auckland Entrepreneurship Challenge

A.5 Patent

Appendix B

B.1 High-resolution electrical mapping of gastric slow waves

The prime asset of HR bio-electrical mapping is that it provides a detailed spatio-temporal view of the electrical activity. HR electrical mapping has been widely used in the cardiac and neuro-electrophysiological fields and has recently been used in GI electrophysiology. A brief overview of GI HR methods employed in an experimental setting are discussed.

B.2 Experimental methods

The animal data used in this thesis were acquired at the University of Auckland following ethical approval from the University of Auckland Ethics Committee. HR gastric mapping was performed on cross-breed weaner porcines using the International Guiding Principles for Biomedical Research Involving Animals. The serosal stomach surface of the subject was exposed via a mid-line laparotomy after the subject was anaesthetised and intubated. The method of anaesthesia and physiological monitoring was performed as previously described by Egbuji et al. [49]. Flexible PCB arrays (192-256 electrodes; 0.3 mm diameter gold contacts, 7.62 or 4 mm inter-electrode distance spacing) were tessellated and held in place with Tegaderm (3M, Minneapolis, MN), after which they were gently placed on the serosal surface of the stomach to minimise handling as shown in Figure [B.1]. The flexible PCB arrays achieved good contact with the serosal surface of the stomach via placement of warm saline filled gauze on top of the flexible PCB electrode.
array. A five minute period of stabilisation was allowed prior to a fifteen minute recording period.

The human data used in this thesis was acquired at Auckland City Hospital following ethical approval from the NZ National Ethics Advisory Committee. The method of anaesthesia and physiological monitoring was performed as previously described by O’Grady et al. [139]. The International Guiding Principles for Biomedical Research Involving Humans were followed.

Figure B.1: Gastric high-resolution electrical mapping setup. (a) shows the schematic of a flexible PCB electrode array with an inter-electrode distance of 4 mm. (b) shows the placement of a eight tessellated PCB electrode arrays on the surface of the stomach on the antrum region. In total 256 electrodes have been positioned on the serosal surface of the antrum. (c) shows the Biosemi system used to record the analogue signals and covert them to digital signals for display on the screen on the laptop as seen on (d) and storage of data for further analysis.

Unipolar recordings were acquired using the ActiveTwo system (Biosemi, Amsterdam) at a sampling frequency of 512 Hz. Each PCB electrode array was connected
B.2. Experimental gastric high-resolution mapping

to the ActiveTwo System via a 1.5 m, 68 way ribbon cable, which in turn was connected to a Dell M1450 laptop via a fiber-optic cable (Figure B.1). The common mode sense (reference) electrode was placed on the body surface of the lower abdomen, 5 cm below the incision for all recording sessions and the right-leg drive electrode (ground) was placed on the right hind leg. The recorded data was viewed online, as shown in Figure B.1 during gastric electrical mapping where the data was stored for off-line analysis. See Appendix C for details on the software used for off-line analysis. The acquisition software was coded in Labview 8.2 (National Instruments, Texas).
Appendix C

C.1 Software platforms for high-resolution slow wave mapping

One of the major complexities with HR mapping in comparison to sparse recording techniques is that a large amount of data needs to be processed and analysed. This can be time-consuming and laborious. Two software platforms have been developed to efficiently process the data and automate the analysis step: (i) SmoothMap and (ii) Gastrointestinal Electrical Mapping Suite (GEMS). The techniques developed as part of this thesis have been incorporated and used in the GEMS software framework.

C.1.1 SmoothMap

Lammers et al. [105] created a software called “SmoothMap” that was written in the Delphi programming language for use in GI HR mapping [103]. As seen in Figure C.1, this software performs all of the analysis in a single window. Some of the notable features of SmoothMap are as follows:

- Channel selection
- Marking and clustering of slow wave events
- Display of an activation time map
- Computation of amplitudes and velocities
- Exporting values of interest as a text file
This software has been used in experimental GI HR studies from both the Al-Ain group and the Auckland group.

Figure C.1: SmoothMap graphical user interface. Two windows are docked in the screen panel, with the top panel showing gastric slow wave signals with vertical fiducial markers. In the lower panel, the electrode map is shown along with the activation time which is colour coded.

C.1.2 Gastrointestinal Electrical Mapping Suite

As part of the thesis, contributions have been made to a software package Gastrointestinal Electrical Mapping Suite (GEMS). It was developed in Matlab 2011b (Mathworks, Natick) to address some of the shortcomings of the SmoothMap software. Two of the main hindrances with SmoothMap were that it required significant manual interactions, and did not have signal filtering capabilities [198]. An overview of the design considerations in GEMS are given followed by the features in GEMS.

Design considerations

GEMS main premise is a GI HR data processing tool that employs graphical tools and command line interface. Several design aspects were considered during its implementation.
At its heart, GEMS incorporates an intuitive graphical user interface to make it user friendly to clinicians and researchers alike. Command line interface tools were also developed, such as batch conversion of recorded data files. One of the important aspects to this software framework was the ability to add new methods and techniques to the existing framework.

Matlab is dynamically typed language, which offers numerical computing, plotting and visualisation, graphical user interface creation, algorithm development and implementation and interfacing to other programming languages [4]. One of the drawbacks of the native Matlab language is that it can be slow to execute due to it being an interpreted programming language. However Matlab has options for developers to implement compiled C++ code in the Matlab environment as a Matlab Executable (MEX) format, which speeds up the computational process. Key areas in the GEMS software that were computationally intensive were converted to MEX code for computational efficiency.

Good software documentation and source control is essential to any software development. A user manual is provided along with the GEMS software which shows the user how to load and analyse the recorded data in a step by step process. A detailed description is given for all of the options present in the GEMS software. To keep an up-to-date record of the source files, a git version control system was utilised. The git version control system was chosen for three main reasons. Firstly, it is a distributed system, which allows users to have a complete copy of the repository and share changes among colleagues, as seen in Figure C.2 [27]. Also with the distributed system, if the server were to breakdown, the repository will be alive in the developers machine and they can coordinate updates and releases without the requirement of the server.

The second advantage of git is that it efficiently handles and scales large projects. Git has been successfully used in large software projects such as the development of the Mozilla Firefox web browser and the Android operating system. It has been reported that the Mozilla repository took 12 GB in hard drive space using a subversion control system (another popular version control system) compared to 420 MB in hard disk space using a git version control system - around 30
Figure C.2: Illustration of distributed version control in git. Each developer has a copy of the repository on their computer and can communicate with each other and the central computer for source updates and releases. Reproduced from [27]
times less in hard disk space \cite{157}. At the current stage, the GEMS source files on a git version control takes up only 4 MB of hard disk space. Thirdly, git is compatible with most communications systems for data transfer and updates. Git supports data transfer over a local network or disk, hypertext transfer protocol secure (HTTPS), File transfer protocol (FTP), secure shell (SSH) and a git defined transfer protocol \cite{27}. These communication protocols allow for additional security and provides flexibility when working with developers that are accustomed to a certain communication standard.

Platform independence opens up the avenue for clinicians and researchers to use the software without the hindrance of installing various operating systems. Using Matlab as the programming language solves this issue, with the exception of minor syntantical commands. To get around the issue the GEMS software executes appropriate syntantical commands based on the operating system. The GEMS software is currently distributed as a executable, which is enabled through the use of the Matlab Compile Runtime (MCR) provided by Mathworks \cite{198}.

Features

As opposed to the SmoothMap software which is a single window software, GEMS is a multi-window environment as shown in Figures C.3 and C.4 \cite{198}. GEMS was designed in a manner that new methods and analysis techniques can be extended to the existing HR mapping framework. Some of the novel features (described in Chapter 4 and 5) of GEMS, in addition to the features by SmoothMap, are as follows:

- Automated conversion of native data format (*.bdf file to a *.mat file)
- Optimised filter setting which can be altered
- Automated clean-up of incorrect fiducial markers
- Improved computation of velocity and amplitude
- Improved visualisation of activation time maps
APPENDIX C

- Animation of slow wave propagation
- Exporting images of interest

The GEMS software is structured into three stages, (i) pre-processing, (ii) processing and (iii) post processing (Figure C.5). In the pre-processing stage, the recorded data gets converted from the recoded data format (*.bdf) to a format that Matlab can handle natively (*.mat). At this stage default parameters for the next stages are loaded and can be modified if necessary. In the processing stage, the signals are filtered, slow wave events are detected and grouped (see Chapter 3 for details). The data can be saved and be loaded for further analysis at a later stage. Quantitative metrics such as velocity and amplitude of slow wave propagation can also be computed (see Chapter 4 for details). In the post-processing stage, visualisation of the slow wave propagation takes place as an isochronal activation time map, velocity map, amplitude map or an interval map Figure C.6 (see Chapter 3 and 4).

C.2 Software platform for sparse cutaneous electrogastrography

A software platform was developed for the analysis of cutaneous EGG. This work performed was performed in collaboration with, and financially supported by, the University of Mississippi Medical Center and University of Louisville.

The methods described in Chapter 7 were incorporated into a graphical user interface (GUI) written in Python 2.7 and compiled as an executable program for research use to analyse sparse cutaneous EGG signal traces. The software has three major components to it; (i) data conversion (ii) data analysis and (iii) reporting. Each of the stages are described in the subsequent sections.
C.2. Software platforms for sparse cutaneous electrogastrography

Figure C.3: Graphical user interface for the GEMS software. Two windows are shown where (a) shows the slow wave signals with a red cross denoting the activation time of the slow wave event, while (b) shows the spatial location of the electrodes. The red column in (b) indicates the chosen electrodes to view in (a), whereby changes in window (b) affect window (a).
Figure C.4: Visualisation of porcine gastric HR mapping results using the GEMS software. Two windows are shown which correspond to the data shown in Figure C.3. (a) shows three consecutive activation time map of the slow wave propagation with 1 s interval (isochrone) as a colour map, while (b) shows three corresponding velocity maps of slow wave propagation, with the arrows indicating the propagation direction of the slow wave activity, and the speed of the slow wave propagation is shown as a graded colour map in mm s$^{-1}$.
C.2. Software platforms for sparse cutaneous electrogastrography

Pre-processing
- Data loading and conversion
- Parameters set up

Processing
- Filtering
- Event detection & clustering
- Quantitative metric calculation

Post-processing
- Visualisation of activity
- Data export

Figure C.5: GEMS architecture. GEMS is structured in three stages; pre-processing, processing and post-processing. In the pre-processing stage, the recorded data is loaded in the software, where it undergoes a change in format from a *.bdf file to a *.mat files so that it can be accessible. In the processing stage, the signals are filtered, slow wave events are detected and clustered accordingly, and quantitative metrics are computed. The final stage is the post-processing stage where the activity can be visualised and exported as necessary.
Figure C.6: Visualisation of slow wave activity. Activation isochronal time maps, velocity field maps, amplitude maps, and time-interval maps are shown for a sequence of 3 consecutive waves (left to right). The first wave ($t = 360$ s) demonstrates a normal wavefront propagating longitudinally (antegrade) (velocity $6.1 \pm 1.0$ mm s$^{-1}$; amplitude $422 \pm 194$ $\mu$V). The second ($t = 375$ s) and third ($t = 390$ s) waves demonstrate delayed activation of the right half of the mapped field, resulting in wavefront rotation and an abnormal area of retrograde propagation (velocity: $6.4 \pm 1.9$ mm s$^{-1}$; amplitude: $461 \pm 254$ $\mu$V). The mean frequency was $17 \pm 2$ cpm. Reproduced from [198].
C.2. Software platforms for sparse cutaneous electrogastrography

C.2.1 Data pre-processing

The EGG data was recorded using a Sandhill EGG recording system. Using the Sandhill system, the clinician has the ability to save clinical information to a certain EGG trace and also has the ability to mark events of interest during the course of the EGG recordings. The output of the EGG recordings from Sandhill system are usually two or three data files. The first data file has an extension *.S01 to denote the signal file, and the other two files have an extension of *.C01 and *.C02 to denote a configuration file where information about the patient is present, and the events recorded during the EGG recording.

The developed main GUI interface for EGG analysis is shown in Figure C.7(a), which allows the user to load up the EGG data (in *.S01 format), and configuration files (in *.C01 or *.C02 format). The configuration file typically includes information about the number of electrodes, the type of electrode recording, patient information, and key events such as coughs and breath holds. As soon as the user loads the signal file (*.S01), the associated configuration files are automatically loaded if they are located in the same folder (Figure C.7(b)). As a confirmation, the patient details are loaded up on the right hand side of the GUI so that the clinician can be sure which data set is being analysed. If the details are not correct, the correct files can be chosen before performing automated analysis.

The file name for the report (in *.pdf format) is set as default to the name of the input data file, but can be modified as necessary. Clicking “Generate report” starts the process of data conversion to an appropriate data format for analysis, and prompts the user to enter which signals are required for analysis (the first lead is selected as default) and what time periods are of interest (default is set to the whole recording) (Figure C.8(a),(b)). Once data analysis and reporting has been completed, it will display a message box advising that the process has taken place and what output files have been created (Figure C.8(c)).
Figure C.7: GUI for EGG data analysis. (a) shows the start-up screen of the GUI display where the clinical and researcher can input the relevant data files in S01 format and the configuration files in C01 format. (b) shows the GUI screen when the data files have been chosen. Patient and clinical information will be automatically be retrieved from the configuration files and be displayed on the right hand side.
C.2. Software platforms for sparse cutaneous electrogastrography

Figure C.8: GUI prompt screens for EGG data analysis. (a) shows the GUI prompt asking the clinician or researcher to choose which leads are to be chosen for analysis. (b) shows the GUI prompt asking the clinician or researcher what time frame of the EGG signal is to be analysed. (c) shows the GUI prompt advising the clinician or researcher that the automated frequency and amplitude estimation algorithm has finished running and has outputted the results in a pdf report format and a text file format.
C.2.2 Data analysis

The main parameters of interest are the frequency and amplitude of the EGG trace. The methods of computing the frequency, amplitude and other metrics of the EGG signals are described in Chapter 7.

C.2.3 Reporting

Once all of the metrics of the EGG trace are computed, a report in pdf format and a text file is generated. The report first lists the patient information, and other clinically relevant information such the attending doctor and nurse. Information about the name of the computer and the time the data was analysed, along with the version number is listed in the front page. A summary of the average frequency, amplitude and signal coverage is also reported in the first page. The text file contains detailed information about the amplitude and frequency over time, and can be opened using a text editor or using excel spreadsheet.

The subsequent pages of the report entail EGG signal plots and the associated metrics. All the information in the report is used as a guide for visual inference and for reviewing the results of the automated method of frequency and amplitude estimation. The output text file is in a tab-separated format which can be imported into MS Office Excel spreadsheet. The use of the text file is primarily for error checking, verification, and to perform statistical comparison across data sets or within sections of the signal.

Figures C.9–C.20 shows two example reports (each page as a figure) that have been generate with the software where the patient information has been erased for patient privacy. The two patient reports were arbitrarily named as Patient 1 and Patient 2. Figures C.15–C.20 shown an example report of Patient 1, where half of the EGG signal is contaminated by noise. Figures C.9–C.14 shows an example report of Patient 2, where the EGG signal is not contaminated by noise throughout the recording. The noisy and good quality sections are picked up the artefact detection method and depicted as a signal integrity measure (see Figures C.14 and C.20). The text file for Patient 2 is shown in Figure C.21 which has been imported into MS Office Excel for further analysis.
C.2. Software platforms for sparse cutaneous electrogastrography

**Figure C.9:** Patient 1 - Automated results of frequency and amplitude of the EGG signal. Page 1 of the report is displayed which shows the patient information and any listed clinician information. Average results of the automated frequency and amplitude estimation of the EGG signal trace is also listed.
Figure C.10: Patient 1 - Automated results of frequency and amplitude of the EGG signal. Page 2 of the report is displayed which shows the raw EGG trace.
Figure C.11: Patient 1 - Automated results of frequency and amplitude of the EGG signal. Page 3 of the report is displayed which shows the application of signal filters to remove the baseline wander and high-frequency noise.
Figure C.12: Patient 1 - Automated results of frequency and amplitude of the EGG signal. Page 4 of the report is displayed which shows the results of automated amplitude estimate over time in a green line with star markers.
**Figure C.13:** Patient 1 - Automated results of frequency and amplitude of the EGG signal. Page 5 is displayed which shows the results of automated frequency estimates over time in a red line with star markers.
Figure C.14: Patient 1 - Automated results of frequency and amplitude of the EGG signal. Page 6 of the report is displayed which shows the results of the artefact detection over time (as a blue line) which represents the signal integrity of the signal as a ‘good signal’ or a ‘noisy signal’.
Figure C.15: Patient 2 - Automated results of frequency and amplitude of the EGG signal. Page 1 of the report is displayed which shows the patient information and any listed clinician information. Average results of the automated frequency and amplitude estimation of the EGG signal trace is also listed.
Figure C.16: Patient 2 - Automated results of frequency and amplitude of the EGG signal. Page 2 of the report is displayed which shows the raw EGG trace.
Figure C.17: Patient 2 - Automated results of frequency and amplitude of the EGG signal. Page 3 of the report is displayed which shows the application of signal filters to remove the baseline wander and high-frequency noise.
Figure C.18: Patient 2 - Automated results of frequency and amplitude of the EGG signal. Page 4 of the report is displayed which shows the results of automated amplitude estimate over time in a green line with star markers.
Figure C.19: Patient 2 - Automated results of frequency and amplitude of the EGG signal. Page 5 of the report is displayed which shows the results of automated frequency estimates over time in a red line with star markers.
Figure C.20: Patient 2 - Automated results of frequency and amplitude of the EGG signal. Page 6 of the report is displayed which shows the results of the artefact detection over time (as a blue line) which represents the signal integrity of the signal as a 'good signal' or a 'noisy signal'.
C.2. Software platforms for sparse cutaneous electrogastrography

Figure C.21: Text file output for Patient 2 imported into MS Office Excel for further analysis. The frequency and amplitude metrics which have been automatically computed are displayed along with a summary with the average results at the end.
Appendix D

D.1 Velocity estimation

The five tables listed herein relate to Section 4.1.2. These tables relate to velocity errors under synthetic cases with various noise types and levels for different methods of velocity estimation. The noise types are activation time error (Tables D.1-D.3) relating to Figure 4.3 and electrode drop-out noise (Tables D.4-D.5) relating to Figure 4.4.

All of the data is presented in the form of the mean and standard deviation of the median difference of the velocity estimates. For each of the noise level, the random noise was tested multiple times (n = 100) for statistical robustness. The results of the ANOVA test are also represented at each level as a p value.

The results for velocity error under electrode drop-out noise with the linear case was not presented, as it did not yield any error with any of the velocity estimation methods.
APPENDIX D

Table D.1: Effect of increasing activation time error on speed and angle estimates when using FD, FDSM and POLY4x4 methods of velocity estimation with a linear plane wave. The noise level is the activation time error, which is the error in accurately detecting the most negative deflection in the signal, defining the activation time value in the map.
### Activation Time Error - Speed - Elliptical Wave

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<th>POLY4x4</th>
<th>p value</th>
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<td>Std(%)</td>
<td>Mean(%)</td>
<td>Std(%)</td>
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### Activation Time Error - Angle - Elliptical Wave

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<th>POLY4x4</th>
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<td>8.73</td>
<td>0.64</td>
<td>3.97</td>
<td>0.41</td>
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</tbody>
</table>

**Table D.2:** Effect of increasing activation time error on speed and angle estimates when using FD, FDSM and POLY4x4 methods of velocity estimation with an elliptical wave, with a single source of propagation. The noise level is the activation time error, which is the error in accurately detecting the most negative deflection in the signal, defining the activation time value in the map.
## APPENDIX D

### Activation Time Error - Speed - Elliptical Clashing Waves

<table>
<thead>
<tr>
<th>Noise Level (seconds)</th>
<th>FD</th>
<th>FDSM</th>
<th>POLY4x4</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(%)</td>
<td>Std(%)</td>
<td>Mean(%)</td>
<td>Std(%)</td>
</tr>
<tr>
<td>0</td>
<td>0.37</td>
<td>0.00</td>
<td>0.89</td>
<td>0.00</td>
</tr>
<tr>
<td>0.1</td>
<td>5.49</td>
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<td>2.58</td>
<td>0.21</td>
</tr>
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<td>0.45</td>
</tr>
<tr>
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</tr>
<tr>
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<td>18.91</td>
<td>1.41</td>
<td>9.09</td>
<td>0.79</td>
</tr>
<tr>
<td>0.5</td>
<td>22.84</td>
<td>1.64</td>
<td>11.79</td>
<td>1.18</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>12.12</td>
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<td>5.94</td>
<td>0.54</td>
</tr>
</tbody>
</table>

### Activation Time Error - Angle - Elliptical Clashing Waves

<table>
<thead>
<tr>
<th>Noise Level (seconds)</th>
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<th>FDSM</th>
<th>POLY4x4</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(%)</td>
<td>Std(%)</td>
<td>Mean(%)</td>
<td>Std(%)</td>
</tr>
<tr>
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<td>0.11</td>
<td>0.00</td>
<td>1.12</td>
<td>0.00</td>
</tr>
<tr>
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<td>2.72</td>
<td>0.24</td>
<td>1.76</td>
<td>0.18</td>
</tr>
<tr>
<td>0.2</td>
<td>5.37</td>
<td>0.53</td>
<td>2.77</td>
<td>0.31</td>
</tr>
<tr>
<td>0.3</td>
<td>8.11</td>
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<td>3.86</td>
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<td>0.72</td>
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<tr>
<td><strong>Average</strong></td>
<td>6.83</td>
<td>0.63</td>
<td>3.52</td>
<td>0.36</td>
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</table>

**Table D.3:** Effect of increasing activation time error on speed and angle estimates when using FD, FDSM, POLY4x4 methods of velocity estimation with an elliptical wave, with two sources of propagation. The noise level is the activation time error, which is the error in accurately detecting the most negative deflection in the signal, defining the activation time value in the map.
## D.1 Velocity estimation

### Electrode Drop-out - Speed - Elliptical Wave

<table>
<thead>
<tr>
<th>Noise Level (seconds)</th>
<th>FD Mean(%)</th>
<th>Std(%)</th>
<th>FDSM Mean(%)</th>
<th>Std(%)</th>
<th>POLY4x4 Mean(%)</th>
<th>Std(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
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<td>0</td>
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<td>0.00</td>
<td>0.24</td>
<td>0.00</td>
<td>0.23</td>
<td>0.00</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>5</td>
<td>0.23</td>
<td>0.02</td>
<td>0.31</td>
<td>0.03</td>
<td>0.22</td>
<td>0.02</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>10</td>
<td>0.23</td>
<td>0.03</td>
<td>0.37</td>
<td>0.05</td>
<td>0.22</td>
<td>0.02</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>15</td>
<td>0.24</td>
<td>0.05</td>
<td>0.44</td>
<td>0.06</td>
<td>0.22</td>
<td>0.02</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>20</td>
<td>0.24</td>
<td>0.06</td>
<td>0.50</td>
<td>0.07</td>
<td>0.23</td>
<td>0.02</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
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<td>0.25</td>
<td>0.08</td>
<td>0.56</td>
<td>0.09</td>
<td>0.24</td>
<td>0.03</td>
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</tr>
<tr>
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<td>0.14</td>
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<td>0.10</td>
<td>0.25</td>
<td>0.03</td>
<td>$p &lt; 0.05$</td>
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<td>0.14</td>
<td>0.26</td>
<td>0.03</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>40</td>
<td>0.29</td>
<td>0.15</td>
<td>0.72</td>
<td>0.14</td>
<td>0.26</td>
<td>0.03</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td><strong>Average</strong></td>
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<td><strong>0.07</strong></td>
<td><strong>0.49</strong></td>
<td><strong>0.08</strong></td>
<td><strong>0.24</strong></td>
<td><strong>0.02</strong></td>
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</table>

### Electrode Drop-out - Angle - Elliptical Wave

<table>
<thead>
<tr>
<th>Noise Level (seconds)</th>
<th>FD Mean(%)</th>
<th>Std(%)</th>
<th>FDSM Mean(%)</th>
<th>Std(%)</th>
<th>POLY4x4 Mean(%)</th>
<th>Std(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.42</td>
<td>0.00</td>
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<td>$p &lt; 0.05$</td>
</tr>
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<td>0.08</td>
<td>0.01</td>
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<td>0.14</td>
<td>0.01</td>
<td>$p &lt; 0.05$</td>
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<td>0.08</td>
<td>0.02</td>
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<td>0.01</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
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<td>0.03</td>
<td>0.50</td>
<td>0.06</td>
<td>0.14</td>
<td>0.01</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
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<td>0.03</td>
<td>0.57</td>
<td>0.09</td>
<td>0.13</td>
<td>0.01</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
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<td>0.04</td>
<td>0.64</td>
<td>0.10</td>
<td>0.13</td>
<td>0.01</td>
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</tr>
<tr>
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<td>0.10</td>
<td>0.05</td>
<td>0.69</td>
<td>0.14</td>
<td>0.13</td>
<td>0.01</td>
<td>$p &lt; 0.05$</td>
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<tr>
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<td>0.12</td>
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<td>0.20</td>
<td>0.14</td>
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<td>$p &lt; 0.05$</td>
</tr>
<tr>
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<td><strong>0.60</strong></td>
<td><strong>0.09</strong></td>
<td><strong>0.14</strong></td>
<td><strong>0.01</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Table D.4:** Effect of increasing electrode drop-out noise on speed and angle estimates when using FD, FDSM and POLY4x4 methods of velocity estimation with an elliptical wave with a single source of propagation. The noise level is the percentage of the array without an activation time value in the map.
### Electrode Drop-out - Speed - Elliptical Clashing Waves

<table>
<thead>
<tr>
<th>Noise Level</th>
<th>FD Mean(%)</th>
<th>Std(%)</th>
<th>FDSM Mean(%)</th>
<th>Std(%)</th>
<th>POLY4x4 Mean(%)</th>
<th>Std(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.37</td>
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<td>0.89</td>
<td>0.00</td>
<td>1.01</td>
<td>0.00</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>5</td>
<td>0.37</td>
<td>0.03</td>
<td>1.10</td>
<td>0.07</td>
<td>0.98</td>
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<td>p &lt; 0.05</td>
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<tr>
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<td>1.41</td>
<td>0.13</td>
<td>0.97</td>
<td>0.05</td>
<td>p &lt; 0.05</td>
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<tr>
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<td>0.07</td>
<td>1.69</td>
<td>0.18</td>
<td>0.95</td>
<td>0.07</td>
<td>p &lt; 0.05</td>
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<td>0.39</td>
<td>0.08</td>
<td>2.04</td>
<td>0.26</td>
<td>0.93</td>
<td>0.08</td>
<td>p &lt; 0.05</td>
</tr>
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<td>0.39</td>
<td>0.11</td>
<td>2.29</td>
<td>0.35</td>
<td>0.91</td>
<td>0.09</td>
<td>p &lt; 0.05</td>
</tr>
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<td>0.10</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
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<td>0.17</td>
<td>3.03</td>
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<td>0.88</td>
<td>0.11</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
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<td>3.38</td>
<td>0.69</td>
<td>0.88</td>
<td>0.13</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td><strong>Average</strong></td>
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<td><strong>0.11</strong></td>
<td><strong>2.06</strong></td>
<td><strong>0.29</strong></td>
<td><strong>0.93</strong></td>
<td><strong>0.07</strong></td>
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</tr>
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### Electrode Drop-out - Angle - Elliptical Clashing Waves

<table>
<thead>
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<th>Noise Level</th>
<th>FD Mean(%)</th>
<th>Std(%)</th>
<th>FDSM Mean(%)</th>
<th>Std(%)</th>
<th>POLY4x4 Mean(%)</th>
<th>Std(%)</th>
<th>p value</th>
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</thead>
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<td>1.12</td>
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<td>0.00</td>
<td>p &lt; 0.05</td>
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<tr>
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<td>0.01</td>
<td>1.25</td>
<td>0.05</td>
<td>0.33</td>
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<td>p &lt; 0.05</td>
</tr>
<tr>
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<td>0.02</td>
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<tr>
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<td>0.02</td>
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<td>0.32</td>
<td>0.02</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
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<td>0.03</td>
<td>1.72</td>
<td>0.17</td>
<td>0.31</td>
<td>0.03</td>
<td>p &lt; 0.05</td>
</tr>
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<td>0.03</td>
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</tr>
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<td>0.10</td>
<td>2.03</td>
<td>0.28</td>
<td>0.30</td>
<td>0.03</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
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<td>0.13</td>
<td>0.06</td>
<td>2.18</td>
<td>0.32</td>
<td>0.29</td>
<td>0.03</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>40</td>
<td>0.20</td>
<td>0.27</td>
<td>2.34</td>
<td>0.38</td>
<td>0.30</td>
<td>0.04</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>0.13</strong></td>
<td><strong>0.06</strong></td>
<td><strong>1.72</strong></td>
<td><strong>0.18</strong></td>
<td><strong>0.32</strong></td>
<td><strong>0.02</strong></td>
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</tr>
</tbody>
</table>

**Table D.5:** Effect of increasing electrode drop-out noise on speed and angle estimates when using FD, FDSM and POLY4x4 methods of velocity estimation with an elliptical wave with two sources of propagation. The noise level is the percentage of the array without an activation time value in the map.
References


REFERENCES


REFERENCES


REFERENCES


REFERENCES


REFERENCES


REFERENCES


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REFERENCES


REFERENCES


REFERENCES


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REFERENCES


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REFERENCES


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REFERENCES


REFERENCES


REFERENCES


REFERENCES


REFERENCES

