Department of Electrical, Computer, and Software Engineering

Part IV Research Project

Literature Review and

Statement of Research Intent

Project Number: 34

Pacemakers for

Gastrointestinal Diseases

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Declaration of Originality

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ABSTRACT: Gastroparesis is a medical condition that affects gastric emptying and causes chronic symptoms. Gastric Electric Stimulation (GES) through a gastric pacemaker is a promising treatment for gastroparesis. However, current open-loop systems are suboptimal, and closed-loop systems are limited to clinical settings. Wang et al. have addressed these issues in their works, but their animal experimental results are not convincing. This project aims to design a prototype embedded system to implement the detection and GES algorithm and use machine learning to detect activation of the GI tract's slow wave propagation, thus improving the efficacy of closed-loop GES for gastroparesis.

1. Introduction

Gastroparesis is a clinical syndrome characterised by delayed gastric emptying without any mechanical obstruction preventing the GI system from emptying properly, which results in chronic symptoms such as nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain[1 2]. There are various etiologies of gastroparesis, including idiopathic, diabetic, post-surgical, neurologic, and medication-induced. The most common cause of gastroparesis is idiopathy (~36%), followed by diabetes(~29%) [3][54]. Dysfunction of ICC is usually present in most patients and contributes to gastroparesis's pathophysiology[5][54]. One way to treat these symptoms and gastroparesis is By Gastric Electric Simulation (GES), which has shown good results in patients' health and quality of life[4]. These GES is delivered through a device called a gastric pacemaker, which is surgically implanted into the wall of the stomach. Gastric pacemakers do not have significant side effects, unlike medicines. Moreover, compared to surgical options such as pyloroplasty or gastrectomy, gastric pacemakers are less invasive and have a lower risk of complications[6]. Thus the development of gastric pacemakers is vital in treating gastroparesis. Although such pacemakers are available for the heart, no such (FDA) approved pacemaker is available for the gut, as knowledge in gastric electrophysiology lags behind that of cardiac electrophysiology. Open-loop pacing of the (GI) tract is the current standard for modulating dysrhythmic patterns, but it is known to be suboptimal and inefficient[7].

Open-loop systems pacemakers could deliver a fixed frequency and amplitude of electrical stimulation to the stomach to improve its motility. Still, they risk overstimulation and cannot respond to changing conditions. In contrast, closed-loop systems use sensors to monitor the stomach's activity and adjust the stimulation accordingly. Closed-loop systems are considered more advanced, precise, complex, and expensive. Current (GI) systems testing is limited to a clinical setting [8] as they are either inefficient or accurate enough[9][10]. Some research in this field has been done, but a scalable (GES) that can sense, process, and actuate the ICC network in a closed-loop manner is unavailable. These issues have been addressed in works wang2019formal, wang2020design, wang2020novel and wang2022framework from Wang et al. Although simulation results are good from the wang2022framwang2022 framework work, experimental animal results are not convincing. This project aims to extend this work by designing a prototype embedded system to implement the detection and GES algorithm and use machine learning to detect activation of the GI tract's slow wave propagation.

2. Literature review

2.1. Gastrointestinal System and GI Motility

The gastrointestinal, or digestive, system is responsible for breaking down and digesting food and eliminating waste products from our bodies. The gastrointestinal system is regulated by a complex network of nerves, hormones, and muscles, including the ICC cells mentioned earlier. The GI tract is part of this system. This long, muscular tube begins from our mouths to our anuses, responsible for the digestion and absorption of food. The GI tract includes various organs like the oesophagus, stomach, small intestine, large intestine, rectum, and anus. These all play key roles in motility as food travels down its pathway and aids nutrient absorption.

GI motility is an essential function of this system for optimal digestion and absorption of nutrients and is necessary for life itself. Motility begins with the contraction of smooth muscles, which is partially controlled by bio-electrical events known as slow waves - smooth muscle cells alone do not possess this power to cause movement within the GI tract[7]. The motility of the gastrointestinal (GI) tract is an intricate process governed by an enteric nervous system (ENS), which coordinates smooth muscle contractions and relaxation to propel food from the mouth to the anus. It involves complex interactions among neural, hormonal, and mechanical factors[11]. This network consists of two major types of neurons: intrinsic primary afferent neurons (IPANs) and interneurons. IPANs receive sensory information from the GI tract and relay it to interneurons; in turn, these regulate smooth muscle cells and secretory cells' activity to maintain balance [12]. Smooth muscle cells alone do not possess the capability of producing or propagating slow waves. Instead, intestinal contraction controllers (ICC), acting as pacemakers in the GI system, generate and propagate them while smooth muscle cells produce phasic waves [7].Myocytes contract in response to slow wave depolarisation. These contractions are regulated by motor input from the enteric nervous system, hormones, and myocytes [7].

2.2. Mechanics of Gastric Pacemaker

Wang et al. have developed a closed-loop GES s[13,14,15] to modulate gastric slow waves. A key component of such a device is its feedback loop's detection algorithm to monitor their period, as detailed in [15]. The simulation was successful but failed during experimental trials. Wang et al. propose that the GES modulate bradygastria due to abnormal initiation and conduction block by sensing and processing the noisy extracellular potentials and pacing accordingly in a closed loop. The proposed GES algorithm filters noisy extracellular potentials. It detects slow wave activation using a slope and threshold method in real-time, using high-fidelity 2D ICC network models as noise generators to validate the efficacy of the proposed GES algorithm. Multiple leads may be used to detect unexpected slowdowns; pace can also be applied using this mechanism, and modulated dysrhythmia is addressed through multiple leads with pacemakers for dysrhythmia management.

The single-channel GES (gastric electrical stimulation) algorithm [7]is intended to sense and modulate an abnormal ICC network using extracellular potential amplitude and timing measurements as used in cardiac pacemakers, similar to how cardiac pacemakers sense and modulate abnormal cardiac situations.

Normal conduction occurs when an ICC network is entrained by its fastest cell, known as the Lowest Rate Interval (LRI). To detect abnormalities from this cycle, the GES algorithm monitors extracellular potential levels for slow wave activations, comparing it to LRI and noting any deviation from this rhythm by comparing activations times elapsed since the previous activation to this period - if no activation was seen within this time limit an external pace can be applied to rectify abnormal conduction. GES operates by computing its base time - that is. when the ICC near the probe first activates. The difference between this base time and current time allows us to detect abnormal slow wave activation patterns; when slow wave activations reoccur within Gastric Repolarization Interval (GRI) or LRI intervals, it is considered normal, and the base time reset accordingly; otherwise, if no such activation occurs after LRI period, then an external pace is applied correcting abnormal conduction by applying external pace thereby and forever perpetuate within GES.

Treating a slow wave conduction block may require more than one lead pacing. Hence, the GES should be able to sense and pace on multiple channels [13,14,15]. The developed GES pacing algorithm by Wang et al. [7]detects slow wave activation and applies pacing to modulate the delay if necessary. Each channel has its own LRI and GRI timers, and the offsets for non-dominant cells are considered. The algorithm applies to pace if there is no activation within the LRI period plus the corresponding offset for each channel.

2.3. Benefits of GES Over Other Solutions

Gastric pacemakers can help alleviate symptoms associated with gastropareses, such as nausea, vomiting and abdominal pain in patients. According to one study involving gastroparesis patients who received electrical stimulation of their stomachs, 89% saw improvements in symptoms[16]. Gastric pacemakers have been linked to reduced hospitalisations and fewer emergency room visits among those suffering from gastroparesis[17].GES helps in reducing nausea and vomiting symptoms, improves gastric emptying, and increases the quality of life in patients compared to other solutions[18].

Study findings published in Digestive Diseases and Sciences demonstrated that GES successfully relieved symptoms associated with gastroparesis in those who failed to respond to other treatments [19]. Surgery may be considered for patients with severe gastroparesis who have failed to respond to other treatments. Yet, surgery carries an increased risk of complications and may not be appropriate for all individuals. Compared to pyloroplasty, which widens the opening between the stomach and small intestine, GES has fewer complications and better symptom control. One advantage of gastric electrical stimulation is its flexibility; patients can program different patterns of stimulation to meet individual patient needs. This allows for personalised gastroparesis treatments as stimulation can be tailored specifically to address the severity of symptoms and response to therapy. Some GES devices can be programmed to deliver a high-frequency stimulation pattern that has been shown to improve gastric emptying and reduce symptoms in some patients with gastroparesis [20,21]. Meanwhile, other devices allow stimulation levels to be adjusted in response to changes in symptoms or function over time.. Gastric pacemakers may help reduce the need for medications among people suffering from gastroparesis or other digestive conditions by improving digestive function and alleviating symptoms. Studies have demonstrated that gastric pacemakers provide long-term relief to patients suffering from digestive disorders, remaining effective for over ten years or more.

Overall, the programmability of GES devices provides an advantage over other treatments for gastroparesis, such as medications or surgery; most of those do not allow for personalised therapy.

2.4. Advancements in Gastric Pacemaker Technology: A Look at the Progress Made So Far

The gastric pacemaker model by Wang et al. [7] developed is based on the Falling Edge Voltage Threshold (FEVT) algorithm[23]. The FEVT algorithm detects the falling edge of the signal and uses a threshold to determine when activation occurs. It was first proposed in 2009 as a method for ECG signal processing and was later adapted for use as an online algorithm in the context of GI slow-wave recordings by Wang et al. in 2022. In Wang2022's framework, one filtering stage and an online activation detection algorithm are utilised as feedback for the closed-loop GES system. The filter used is a second-order band-pass Butterworth filter with an approximate passband from 0.02Hz-1Hz, while its counterpart online activation detection algorithm relies on real-time signal analysis techniques. The algorithm works very well in simulation and shows good results in normal pigs ,but it fails in pigs with dysrhythmia.

Building on the work of Wang et al. an algorithm was proposed last year by Larissa Marr and D. Vanpraseuth[24]. The proposed algorithm integrates a method from [25] with techniques from [26,27] for artefact removal to be specifically applicable to gastric slow wave signals (Figure 1).

The algorithm proposed comprises three stages: filtering, artificial pacing artefact removal and detection signal. At each step in turn, low-pass and high-pass filters are utilised to remove noise and baseline wander; for pacing artefact detection, a simple thresholding method is employed and removed from the signal; finally, in the detection signal stage, a nonlinear energy operator and convolution with edge detection kernel are utilised simultaneously to detect natural activations of an ICC; finally, activations identification is accomplished using variable threshold method, making real-time analysis possible online or real-time use. The algorithm was done in Matlab, not on an embedded platform. On running various tests on this algorithm, it fails on specific data sets. Failed removal of an artefact will increase the frequency and intensity of false positives and false negatives (FPs and FNs), while using a cubic spline to replace it can produce spike-like curves that mark activation events. Thus this lead for a need of Machine learning algorithm to be done on top.

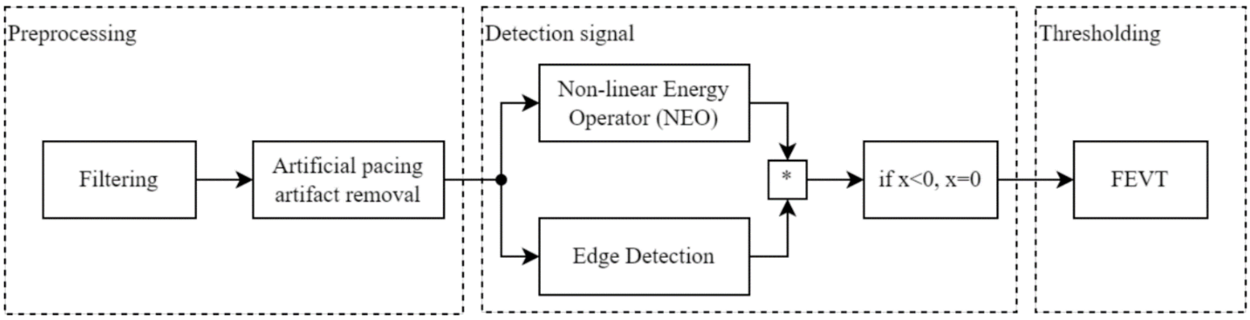

Figure 1

2.5. Machine Learning Algorithm and Embedded Platform

Machine learning algorithms may be applied to gut pacemakers using various machine learning approaches, including decision trees, random forests, support vector machines, neural networks and deep learning algorithms such as convolutional neural networks (CNNs) or recurrent neural networks (RNNs). These can help detect and classify gastrointestinal disorders while simultaneously predicting symptoms and optimising stimulation parameters for pacemaker use. However, in our case, it is a classification problem; thus, it narrows down the models we can use. Support Vector Machines (SVM), Random Forest, Naive Bayes, K-Nearest Neighbors (KNN), and Gradient Boosted Trees (GBT) are classification machine learning models utilised for classifying gut pacemaker data points. SVM uses hyperplanes to segment data points into distinct classes; Random Forest utilises an ensemble of decision trees; Naive Bayes relies on Bayes' theorem; KNN assigns class according to a majority vote of nearest neighbours, while GBT uses multiple decision trees in combination to correct errors and make predictions.

Y Li et al. [28]propose an intelligent system using machine learning algorithms and electrogastrogram (EGG) signals to control gastric pacemakers for patients suffering from gastroparesis. They note that current gastric pacemaker control methods utilize fixed-frequency stimulation which may result in inefficiencies and limited effectiveness when treating gastroparesis.To address this limitation, an intelligent system was designed which consist of a machine-learning algorithm that predicts when gastric slow waves will form and an adaptive closed-loop control mechanism to adjust pacemaker stimulation accordingly was designed. EGG signals were used as input and feature both time and frequency domain features to improve accuracy. It was tested on patients suffering from gastroparesis; results demonstrated significant improvements in symptoms and gastric emptying times compared with fixed-frequency stimulation.

SVM is the most promising of all models [29]. Y . C Lin et al. [29] trained the SVM classifier to classify EGG signals into two classes: active and inactive. Active class represented periods when the gastric slow wave was propagating; inactive class represented periods when the slow wave was not. For training purposes, SVM used features extracted from EGG signals like dominant frequency, power and coherence.

Template-matching algorithm was utilised to detect the beginning of gastric slow wave propagation. This procedure involved creating a template waveform from the EGG signal during gastric slow wave propagation periods and using this waveform as a reference point when searching for similar forms in EGG. When such waves were found, their presence indicated a possible start date of gastric slow wave propagation.

Although This algorithm is promising with good results, it is very slow and can impact our real-time implementation; thus there is another model that is recently emerging is gradient boost, and it is highly popular for its speed. If the above model doesn't seem to work, this can be used.

The embedded system we will be using is De1-soc. It has arm processor in it One of the many advantages of the DE1 board is its versatility. The FPGA chip can be programmed to implement custom logic, making the board suitable for use across various applications. Furthermore, its interfaces and input/output devices make it a convenient platform for designing and testing digital systems. Terasic Technologies provides extensive documentation, tutorials, and example projects to assist users in getting started with the DE1 board and its associated software tools. Furthermore, many universities and institutions have adopted it as a teaching platform for digital system design. Overall, the DE1 board provides an ideal digital system design and development platform. We will be using c/c++ for our software development. C and C++ have several advantages for embedded systems development, including efficiency, low-level hardware access, portability, reliability, and a large and active community of developers providing support and resources.

3. Research Intent

3.1. Project Scope and Objective

Our goal is to improve the work done in wang2019formal-wang2022framework. Improving the automatic activation detection algorithm (might need ML)and transferring the existing GES pacing algorithm to an embedded system.

3.1.1 Automation of removing wrong channels- Bad channels need to be detected automatically, which has not been done yet. Bull et al. [25] propose a method to achieve this.

3.1.2 Closed-loop gut pacemakers in embedded systems - The algorithm in Matlab should be converted into c /C++ and natively run on the embedded system. In our case, it is De1 soc. We will run it multiple times for real-time analysis and plot it as a histogram. The longest execution in that will be our worst-case scenario and will give an idea for real-time analysis.

3.1.3 ML model to detect correct activation of GI tract- For this we tend to implement SVM and train and run it on a native PC. If the algorithm improves, it will be implemented in an embedded system. For easier transfer, the current selection of language is c/c++. The model we will be using is SVM, as various research papers are supporting it thus making a strong contender for this. An SVM works by creating a hyperplane that separates gut activity data points into various classes that can then be classified. Gut pacemakers use SVM algorithms to train off data collected by pacemaker sensors to classify different forms of gut activity, including contractions or non-contractions, into groups. Once trained, this algorithm can be optimised by changing parameters such as its kernel function, regularisation parameter and kernel coefficient to find optimal solutions.

Once the SVM algorithm has been trained, it can be applied in the pacemaker to detect and respond to gut activity in real time. For instance, it could stimulate contractions detected or modify stimulation patterns to sync better with natural gut activity. Overall, SVM offers great promise as an accurate and efficient detection of gut activity for pacemakers. If it doesn’t, we will try SVM classifier and template-matching algorithm into a hybrid method for detecting gastric slow wave propagation. SVM classifier will be used to classify EGG signals into active and inactive periods, while the template-matching algorithm will detect when gastric slow wave propagation began during active periods.

3.2. Timeline

The proposed timeline for this is given below;-

28 April 2023	Literature Review
20 June 2023	Finishing algorithm in embedded systems
21 July 2023	Mid-year Report
22 July 2023	P4P seminar
15 August 2023	P4P display day
6 October 2023	Final day poster
13 October2023	Final day report
16 October2023	Compendium Submission
19 October2023	Exhibition Day

4. Conclusions

GI motility is one of the very important for proper digestion and excretion, and motility disorders can have a significant impact on quality of life. Closed-loop gastrointestinal electrical stimulation (GES) devices have been proposed, but the activation detection algorithm used as feedback needs improvement. Wang et al. designed the first closed-loop GES device, but animal trials showed the need for better activation detection. Adaptive threshold, wavelet transform and machine learning (ML) are potential methods for automatic activation detection. ML is challenging and is need for implementation as the filtering algorithm proposed doesn’t work on all data sets. A prototype embedded platform will be designed to implement the detection and GES algorithms.

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