Bioimpedance-based real-time wearable physiological monitoring

Robert Joseph Mathews

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BIOIMPEDANCE-BASED REAL-TIME WEARABLE PHYSIOLOGICAL MONITORING

Robert Joseph Mathews

A DISSERTATION

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in The Department of Electrical and Computer Engineering to The Graduate School of The University of Alabama in Huntsville

December 2023

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Abstract

BIOIMPEDANCE-BASED REAL-TIME WEARABLE PHYSIOLOGICAL MONITORING

Robert Joseph Mathews

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

Electrical and Computer Engineering
The University of Alabama in Huntsville
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Cardiovascular and respiratory diseases account for nearly forty percent of worldwide deaths. A critical factor in preventing these deaths is early detection, treatment, and monitoring of the diseases. Remote patient monitoring coincides with significant advances in integrated circuit technology resulting in greater performance and lower power consumption. In this work, novel monitoring configurations and frequency excitations are assessed across ten subjects to evaluate their suitability for monitoring cardiac and respiratory activity. A custom bioimpedance controller board was fabricated and integrated into the existing UAH euHy board. In the pilot experiment, the average inter-beat interval (IBI) derived from bioimpedance compared with Nexfin HD had an error of 3.9 ms, or 0.6%. We demonstrated that bioimpedance can be used to monitor breathing and heart activity in real time, in addition to body composition and fluid distribution. The proposed method is suitable for wearable monitoring applications.
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This dissertation is dedicated to my twin sons, Benjamin and Logan, who
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List of Acronyms

AC alternating current 13
BCM body composition monitoring 25
BIS bioimpedance spectroscopy 24
BP blood pressure 3
CCO continuous cardiac output 4
CO cardiac output 3
COPD chronic obstructive pulmonary disease 1, 5, 146
CPE constant phase element 17, 19
CT computed tomography 7
CVD cardiovascular diseases 1–6, 149
DC direct current 10, 13
ECF extracellular fluid 14, 17
ECG electrocardiogram ix, xiii, 2, 27, 29, 134–138, 148
ECW extracellular water 14, 60
FEV1 forced expiratory volume 4, 5
FVC forced vital capacity 4, 5
HSV heart stroke volume 27
I2C inter-integrated circuit 134, 135
IBI inter-beat interval ii, xv, 139, 143, 145
ICF intracellular fluid 14, 17
ICG  impedance cardiography 27
ICW  intracellular water 14
IPG  impedance pneumography 27
IRB  institutional review board 134
MRI  magnetic resonance imaging 7
PCB  printed circuit board 50, 150
PEF  peak expiratory flow 5
PEP  pre-ejection period 27
PLL  phase-locked loop 137, 177
PPG  photoplethysmogram xiii–xv, 3, 134–139, 142–145, 148
RD  respiratory diseases 1, 4–6, 149
RPM  remote patient monitoring 5, 146, 149
SPI  serial peripheral interface 135
SV  stroke volume 4
SVR  systemic vascular resistance 4
TBW  total body water 60
UAH  University of Alabama in Huntsville 134, 135, 137
WHO  World Health Organization 1
Introduction

1.1 Cardiovascular Disease and Respiratory Disease Monitoring

Cardiovascular diseases (CVD) and respiratory diseases (RD) are two major public health issues that affect millions of people worldwide. The World Health Organization (WHO) reports that CVD are responsible for 17.8 million deaths each year [1] and RD causes 3.2 million deaths annually [2]. CVD represents a group of conditions that involves the heart and blood vessels, including coronary artery disease, heart attack, and stroke [3]. RD, on the other hand, refers to a group of diseases that affect the respiratory system, including asthma, chronic obstructive pulmonary disease (COPD), and pneumonia [4]. These diseases have a significant impact on quality of life and are leading causes of death globally. There is both a medical and economic need for earlier identification, intervention, and treatment of cardiorespiratory diseases. Early healthcare interventions are crucial to improve patient outcomes, provide effective treatments, and achieve cost savings. They empower individuals to take control of their health and make informed decisions. The use of technology can further facilitate early intervention through continuous monitoring and data collection, making healthcare more proactive rather than reactive. Bioimpedance analysis, which assesses fluid in the body, is a promising non-invasive, low-cost, and well-researched method for identification and monitoring of many diseases, including but not limited to cardiorespiratory disease [5]. Recent advances in integrated circuit manufacturing have brought research
grade accuracy to bioimpedance devices that can be integrated into wearables. Bioimpedance-based wearables have the potential to revolutionize healthcare by offering real-time, personalized health monitoring, improved management of chronic conditions, and offer quantitative assessment of therapies to refine treatment plans.

1.1.1 Cardiovascular Disease

CVD is a significant, worldwide health problem, with an estimated 17.8 million deaths each year, accounting for 31% of all deaths globally. The primary causes of CVD include high blood pressure, high cholesterol, smoking, obesity, and physical inactivity [6]. These risk factors can be managed through lifestyle changes and medical intervention. A critical factor for the management and intervention in CVD is early identification and diagnosis, which leads to more favorable treatment outcomes. The cost associated with treating CVD is significant. In the United States, the total cost of CVD was estimated at $351 billion in 2016 [1], including both direct and indirect costs. Direct costs include medical expenses such as hospitalization and prescription drugs, while indirect costs include lost productivity due to disability and premature death. There are various non-invasive methods used to assess CVD, including but not limited to: ECG, Holter monitoring, and echocardiogram. ECG is a non-invasive test that records the electrical activity of the heart [7], while Holter monitoring uses a portable ECG device for 24-72 hours to monitor heart activity and rhythms [8]. An echocardiogram is an ultrasound test that creates images of the heart to assess its structure and function [9]. It can also be used to assess heart stroke volume (HSV), which is a measure of how much
blood is pumped with each heartbeat. Other methods, such as simple heart rate and blood pressure monitoring can be done with a PPG sensor or a blood pressure cuff. PPG sensors measure blood volume changes in the skin by shining light into the skin and detecting changes in light reflection caused by changes in blood volume [10]. This measurement is then used to determine the heart rate. Blood pressure cuffs, on the other hand, measure the force of blood against the walls of the arteries, which is an indirect measurement of the cardiac output and the force generated by each heartbeat [11]. These methods are not used to diagnose CVD but can be used to track changes and trends over time that may warrant further investigation. A recent review found that while significant advances have been made in the monitoring of CVD, further improvement in overall outcomes is a major unmet need [12].

Multi-sensor monitoring provides significant promise for the assessment of the autonomous nervous system and cardiovascular function [13]. The Nexfin HD monitor [14] is a device that measures cardiac output (CO) continuously in a totally noninvasive manner by an inflatable finger cuff which is the only interface with the patient. The Nexfin HD measures continuous CO by combining continuous blood pressure (BP) monitoring and a novel pulse contour method (Nexfin CO-Trek) which is based on the systolic pressure area and a physiological three-element Windkessel model. The patient’s age, gender, height, and weight are important input parameters for the measurement algorithm. The CO is calculated without external calibration although it can be calibrated externally. The parameters that are measured by the Nexfin HD include continuous BP (systolic, diastolic,
mean), heart rate, continuous cardiac output (CCO), stroke volume (SV), systemic vascular resistance (SVR), and an index of left ventricular contractility (dp/dt). The Nexfin monitor was used in this research to assess cardiovascular function and correlate with measures of bioimpedance of the upper body measured using this wearable sensor.

1.1.2 Respiratory Disease

RD is also a major health issue, affecting approximately 235 million people globally [4]. The primary causes of RD include smoking, air pollution, and genetics [4]. These diseases can be managed through lifestyle changes and medical intervention, including medications and oxygen therapy. Similar to CVD, early identification and intervention is critical for assuring positive treatment outcomes. The cost associated with treating RD is also significant. In the United States, the total cost of RD was estimated at $157 billion in 2016 [2], including both direct and indirect costs. Direct costs include medical expenses such as hospitalization and prescription drugs, while indirect costs include lost productivity due to disability and premature death. There are several monitoring methods used to assess RD, including spirometry, peak flow meters, and oxygen saturation monitoring. Spirometry is commonly used as a method to assess lung function and diagnose various lung conditions. Spirometer records various metrics, including forced vital capacity (FVC), as the total amount of air exhaled during the forced breath, forced expiratory volume (FEV1) that represents the amount of air exhaled in the first
second of the forced breath, $\frac{FEV_1}{FVC}$ ratio, and peak expiratory flow (PEF). Oxygen saturation monitoring measures the amount of oxygen in the blood [10].

1.1.3 Remote Patient Monitoring

Remote patient monitoring (RPM) is a rapidly growing field in the healthcare industry [15]. The aim of RPM is to provide patients with a convenient and accessible way to monitor their health conditions, while also allowing healthcare providers to collect data and make informed decisions about treatment. With the increasing prevalence of chronic conditions such as CVD and RD, RPM has become increasingly important in providing patients with timely and effective care. RPM has been shown to be an effective tool in monitoring patients with CVD and RD, allowing for early detection and prompt treatment. A meta-analysis of 91 studies for RPM found that it was effective in reducing hospital re-admissions for COPD as well as CVD [16].

RPM can be performed using a variety of monitoring methods, including wearable devices, mobile health apps, and telemedicine. Wearable devices, such as smartwatches and fitness trackers, have become increasingly popular in recent years and have proven to be effective in monitoring both CVD and RD [17]. Mobile health apps have also been used for RPM, allowing patients to track their health data and receive timely and personalized feedback from healthcare providers. Telemedicine, which involves the use of remote technology for medical consultation, has also become increasingly popular in recent years and has proven to be effective in providing patients with access to medical advice and treatment.
Wearable technology and smartwatches have the potential to revolutionize the monitoring and management of CVD and RD [18]. These devices provide real-time data to healthcare providers, allowing for early detection and intervention, and can be used for remote monitoring of patients in their homes [19]. In addition, the continuous monitoring provided by wearables enables healthcare providers to obtain more accurate and detailed data compared to conventional monitoring methods [16]. Wearable monitoring and mHealth technologies can play a significant role in the management of public health crises like the COVID-19 pandemic [20]. mHealth technology could be utilized to predict exacerbations in COVID-19 patients experiencing mild symptoms and prioritize diagnostic testing in subjects who might have been exposed to a virus. The new generation of unobtrusive wearables, such as the Oura ring [21], can use continuous monitoring to generate increased risk scores as early as 6 days prior to diagnostic testing (2.3 days, on average), demonstrating the feasibility of a real-time risk prediction score using wearables to minimize workforce impacts of infection [22].

Despite the potential benefits of wearable devices, smartwatches, rings, and other wearables for monitoring respiratory and cardiac function, there is still a significant need for additional research in this area [23]. While recent reviews have found that wearable devices are generally accurate [24, 25], the methods and protocols used to assess the accuracy vary greatly [26], which limits the overall adoption rate.
1.1.4 Bioimpedance Analysis

Bioimpedance analysis presents an avenue to combine some aspects of diagnostic measures (lung volume, rate of peak respiration, heart stroke volume, breathing pattern) with the portability of a wearable device. As a low cost, low power, non-invasive sensing method, it can be incorporated into existing smart-wearable devices with few changes.

This work focuses on the assessment of bioimpedance monitoring for cardiac and respiratory monitoring in wearable devices. To do this, a pilot study was conducted to determine candidate excitation frequencies for the analysis. Then, a separate study was conducted with ten subjects to evaluate measurement configurations and frequencies to determine the best combinations. Finally, a custom hardware solution was built and validated against a clinically accepted device in a two-person pilot study. It is hypothesized that these wearable bioimpedance sensors could be used to detect various health indications, such as lung fluid accumulation, which is often a symptom of lung inflammation, before it can be detected by using X-ray, computed tomography (CT) scan, or magnetic resonance imaging (MRI) diagnostic imaging procedures. Critically, bioimpedance can simultaneously measure both heart and lung function, providing an excellent avenue for at-home monitoring of various chronic and acute diseases which impact cardiorespiratory function.
1.2 Contributions

This dissertation evaluates both frequencies and electrode monitoring configurations for future wearable devices using bioimpedance analysis. This work represents the largest frequency range studied for bioimpedance analysis of cardiorespiratory monitoring, which will enable future researchers to choose better excitation frequencies for physiological phenomena. The performance and frequency range of commercially available bioimpedance controllers was evaluated in configurations suitable for wearable monitoring applications. This work also contributes two novel electrode configurations for cardiorespiratory monitoring, which can be used in future wearable devices such as smartwatches, smart-wristbands, or smart textiles. This study used commercially available bioimpedance devices and commonly used electrodes for the evaluations to increase the applicability to future research and commercial applications.

1.3 Dissertation Outline

Chapter 1 provides the context and the motivation for this work.
Chapter 2 provides the background information needed to understand the problem, the technology, and the approach taken in this study.
Chapter 3 discusses the initial pilot study.
Chapter 4 discusses the results from a 10-person study.
Chapter 5 presents the custom bioimpedance hardware, real-time processing, and a validation pilot study.
Chapter 6 contains the conclusions of this paper and suggestions for future work.
2.1 Overview

This chapter presents an overview of the field of bioimpedance with a focus on continuous measurements and wearable applications. It begins with the basics of impedance, applies them to biological tissues, and discusses the excitation signals used. Then, an overview of sources of error in bioimpedance is followed by measurement equipment, the application of bioimpedance to wearables, and finally an overview of related work and studies.

2.2 Complex Impedance

The concept of resistance was first documented by Georg Simon Ohm in 1827 as a generalization of his law of electrical resistance [27, 28]. Ohm’s law states that the current through a conductor between two points is directly proportional to the voltage across the two points and inversely proportional to the resistance of the conductor. This relationship is usually represented mathematically as

\[ V = IR, \]  

(2.1)

where \( V \) is the voltage, \( I \) is the current, and \( R \) is the resistance. Ohm’s law as stated is applicable only to direct current (DC) circuits, however, as it does not take into account the effects of reactance, introduced by the energy storage
elements capacitors and inductors. The work of Steinmetz [29], Heaviside [30], and Kennelly [31] introduced complex representations of voltage and current to the equation, resulting in complex impedance. Here, complex refers to the numeric system including imaginary numbers, where the imaginary unit $j$, defined as $j^2 = -1$, is utilized to represent quantities on the complex plane. In electrical engineering, $j$ is used in place of the typical $i$ to prevent confusion with electrical current. Utilizing the complex representation, impedance can be described in Cartesian coordinates as

$$Z = R + jX,$$  \hspace{1cm} (2.2)

where $X$ is the reactance of the circuit and $R$ is the resistance of the circuit. Substituting back into Equation 2.1, this gives

$$V = IZ = I(R + jX).$$  \hspace{1cm} (2.3)

When $X$ is zero, this reduces back to Equation 2.1. Reactance can be further divided into the contributions from inductance and capacitance, as

$$X = X_L + X_C,$$  \hspace{1cm} (2.4)

giving

$$Z = R + j(X_L + X_C),$$  \hspace{1cm} (2.5)

where $X_L$ represents the reactance ($X$) of the inductor ($L$), and $X_C$ that of the capacitor ($C$). Both the inductor and capacitor have frequency dependent
impedance. This is more readily apparent in the forms \( X_L = \omega L \) and \( X_C = \frac{1}{\omega C} \). Here, \( \omega \), the angular frequency, is given by \( \omega = 2\pi f \), where \( f \) is the frequency. As \( \omega \) increases, the reactance of the inductor increases, while the reactance of the capacitor decreases.

An additional concept can be introduced alongside the reactance, phase. Phase refers to the fraction of a sinusoid period at a moment in time, given in radians or degrees. When a sinusoidal excitation passes through a reactive element, the voltage and current are affected differently than if passing through a resistor. The voltage will lag the current by a quarter wave \( (\frac{\pi}{2} \text{ radians}) \) when passing through an ideal capacitor, and will lead the current by a quarter wave \( (\frac{\pi}{2} \text{ radians}) \) when passing through an ideal inductor. Returning to Equation 2.2, the resistive (real) and reactive (imaginary) components are sometimes referred to as the in-phase \( (I) \) and quadrature-phase \( (Q) \) components of the signal. This information can also be represented in Polar coordinates as

\[
Z = |Z|e^{j\theta},
\]  
\[(2.6)\]

where the magnitude of the impedance \( (|Z|) \) is given by

\[
|Z| = \sqrt{R^2 + X^2},
\]  
\[(2.7)\]

and the phase angle of the impedance, \( \theta \), is given by

\[
\theta = tan^{-1}\frac{X}{R}.
\]  
\[(2.8)\]
The phase angle represents the phase shift between the voltage and current signals. The equations 2.2 and 2.6 are equivalent, and the representation used depends on the application. However, these equations are valid only for steady state alternating current (AC) signals. Utilizing the Laplace transform, these equations can be shifted to the $s$-plane, where $s = \sigma + j\omega$, so that arbitrary excitations can be used. This changes the Ohm’s law representation of Equation 2.1 to

$$V(s) = I(s)Z(s), \quad (2.9)$$

or

$$Z(s) = \frac{V(s)}{I(s)}. \quad (2.10)$$

This general form can be used to represent DC and AC analysis for sinusoidal or arbitrary excitation signals. For DC, $s = 0$, and for AC, $s = j\omega$. This general form simplifies analysis. Applied to a circuit, the elements reduce to $R = R$,

$$X_L = j\omega L = sL, \quad (2.11)$$

and

$$X_C = \frac{1}{j\omega C} = \frac{1}{sC}. \quad (2.12)$$

13
2.2.1 Frequency Dependence of Bioimpedance

The impedance of tissues is not constant, but varies with both time and frequency. In this section, the variance of tissue impedance with frequency is presented.

The impedance of the body or a body segment is a bulk property with multiple underlying contributions. It can be useful to consider the body (or segments thereof) as a cylinder with known area and length, composed of different tissues. The tissues that make up the body are composed of cells suspended in fluid. This is typically modeled by extracellular water (ECW) or extracellular fluid (ECF) and intracellular water (ICW) or intracellular fluid (ICF), separated by the cell membranes. ECW and ICW are composed of ions suspended in fluid, and as such are highly conductive, meaning that current flows easily. Cell membranes, on the other hand, behave similarly to capacitors in that they have a high impedance at low frequencies and a decreasing impedance as frequency increases [32]. The excitation current flows around the cells at low frequencies, with their high impedance membrane remaining in the ECW. The current begins to flow through the cell membrane and through the cell as the frequency across a tissue increases. At a sufficiently high frequency, the cell membrane has little contribution to the impedance. Therefore, the low-frequency impedance is primarily due to the ECW, the high-frequency impedance is due to the ECW plus ICW, and the change in impedance with frequency is due to the cell membrane. This phenomenon is shown in Figure 2.1. In a bioimpedance measurement beginning at a low frequency and
increasing in frequency, the resistance will steadily decrease, while the reactance will rise and fall, as shown in Figure 2.2. Note that the locus of the graph is located below the X-axis, due to the non-idealities of the tissue.

**Figure 2.2:** A Cole-Cole plot displaying the frequency dependent impedance of the model.

\[ Z = \frac{\rho L}{A} \]

or

\[ Z = \frac{\rho L^2}{\text{volume}} \]

**Figure 2.1:** A representation of the current flow through a tissue.
The frequency-dependent impedance of ions suspended in water is a large field of study [32], but the primary dispersions for bioimpedance applications are the $\alpha$ and $\beta$ dispersions. Here, dispersion is a term describing the grouping of frequencies where there are significant changes in the permittivity of a tissue, also known as dielectric relaxations [33]. In Figure 2.3, note the black line describing the change in permittivity, and the blue line at the bottom displaying the derivative. The peaks of the derivative are at the center of the dispersion band, and the width of the peak shows the frequencies contained. The $\alpha$, or ionic, dispersion is the phenomenon of ionic polarization and displacement in the presence of an alternating electric field. The external electric field interacts with the bound ions on the surface of tissue membranes and causes them to reorient [34]. This orientation change causes the impedance of the tissue to decrease with increasing frequency [35]. The $\beta$ dispersion is the most commonly used, as it describes the dielectric relaxation of tissues between 10 kHz and 1 MHz. This dispersion has been well studied and is described by the Maxwell-Wagner-Sillars [36] (MWS) effect. This effect arises at the interfaces (hence interfacial) between heterogeneous materials, where charges can accumulate and their movement is restricted. The precise frequency at which this occurs is highly dependent on the size of the cell membrane in comparison to the overall cell size. As an example, consider two cells, A and B, that are the same overall size. If cell A's cell membrane is larger than cell B's, cell A's relaxation frequency will be greater than cell B's. Tissues made up of heterogenous mixtures of cells will exhibit a bulk property containing contributions from all of them. Building on MWS, the Hanai mixture theory
approach models the cells as ideal spheroids suspended in fluid, which enables the application of computational analysis techniques. In the case of bioimpedance, it can be difficult to assign a specific frequency to a specific tissue, as the interfaces between different tissue types necessarily mean that any measurement of them together exhibits a different response than the two tissues measured separately.

Bioimpedance parameters are often decomposed into a circuit model for analysis and comparisons, a process called equivalent circuit modeling. Equivalent circuit modeling is widely used in electrical engineering for simplifying complex systems in easily quantified and comparable parameters. The most common model in bioimpedance is the Cole-Cole model [33] developed as the simplest circuit representation of the ECF (resistor), ICF (resistor), and cell membrane (capacitor). The Cole-Cole model can be represented in the Laplace domain by:

\[
Z = R_1 + R_2 \| C = R_1 + \frac{R_2}{1 + sR_2C}.
\] (2.13)

The Cole-Fricke model [37], given by,

\[
Z = R_1 \|(R_2 + C),
\] (2.14)

is similar but rearranges the connections between the resistors and capacitor. A comparison of the two is given in Figure 2.4. A more modern version of the Cole-Cole model uses a constant phase element (CPE) [38] in place of a capacitor for modeling [39]. A constant phase element is a fractional order circuit component that exhibits both resistive and capacitive properties, and uses an \( \alpha \) term that
Figure 2.3: A description of the four major dispersions of water. The $\alpha$ and $\beta$ dispersions are most relevant to bioimpedance applications.
varies between zero (resistive) and one (capacitive) to represent the behavior between resistive and capacitive. This can be represented by a modification to Equation 2.12 to add the α term:

\[ X_C = \frac{1}{s^\alpha C}. \]  

(2.15)

Substituting into the Cole-Cole model, this gives:

\[ Z = R_1 + \frac{R_2}{1 + s^\alpha R_2 C}. \]  

(2.16)

An example of this model is given in Figure 2.5. Take note of how the peak reactance decreases with a reduction in the α parameter, and that the locus of the semicircles (except for α = 1) are below the x axis. These models allow for more realistic circuit fitting [40]. Constant phase elements are a common way to represent the non-ideal resistance and capacitance mixture present in tissues, and are more generally used to represent the bulk properties of heterogeneous mixtures [38]. CPE's are especially well suited to fit the β-dispersion.

Typical bioimpedance applications use a frequency range of 1 kHz to 1 MHz, though outliers exist in both directions. This frequency range is centered on the β dispersion, which gives significant insight into tissue composition due to its dependence on the interfaces between heterogeneous mixtures. The impedance measurements at these frequencies are often fitted to circuit models for ease of analysis. The use of models enables faster measurements and less processing for a relatively small decrease in accuracy. The largest benefit is the ability to
Figure 2.4: The Cole-Fricke (A) and Cole-Cole (B) tissue circuit models. These circuits are equivalent with the appropriate transform.

Figure 2.5: A modified Cole-Cole model with a constant phase element in place of the capacitor (a) and its associated frequency response to an excitation signal from 10 Hz to 1 MHz (b).
compare three values fitted to a circuit, rather than upwards of one hundred vector representations of impedance. However, researchers have moved increasingly away from equivalent circuit modeling in favor of using the raw impedance data [41].

2.2.2 Whole-body Impedance and Segmented Impedance

Continuing the analogy from section 2.2.1, consider the body as a group of connected cylinders. From there, parameters can be assigned to each and the relationships between them can be explored. Typically, larger volumes will have lower impedances (more paths for the current to take), while smaller volumes will have higher impedances (fewer paths for the current to take). The combination of segments will have contributions from each segment, which are affected by the makeup of the tissues, as well as any active physiological processes in the tissue. A model used in bioimpedance spectroscopy showing possible different segments is given in Figure 2.6.

The whole-body impedance is typically used in body composition applications. In this case, the electrodes are typically placed on one side of the body and separated between the hands and the feet on that side. In this case, the measured impedance includes one arm, the torso, and one leg. These could, of course, be subdivided into further segments. In this case, the impedance measured contains contributions from each segment. Torso-only measurements are the most common diagnostic application of bioimpedance, focusing on the heart and lungs. These measurements may be taken longitudinally (from the neck to the abdomen) or
Figure 2.6: An overview of possible segments for impedance measurements.
laterally (from the left to the right side, or vice versa), depending on the exact application [42].

Whole-upper-body impedance applications are used in some commercial body composition applications. The measured impedance includes contributions from both arms and the upper part of the torso [43]. However, this measurement location is important for wearable applications. Segments of the upper body can be used for various applications, such as cuffless blood pressure monitoring [44] and monitoring exercise-induced fatigue. Whole-lower body impedance is used in some at home body composition applications, such as smart weight scales. Segments of the lower body impedance can be and have been used for various applications, such as lymphedema detection, muscle injury, and osteoarthritis monitoring [5].

Bioimpedance measurements can only measure what is between the electrodes. For each application, the location of the electrodes must be carefully considered to collect the desired data. One must also be aware of any time-varying physiological processes that occur in the tissues that may be undesirable for the application. For example, measurements of segments with large blood vessels can be affected by heart activity, as fluid movement in the blood vessel can change the measured impedance. This generally leads to the standardization of measurement configurations [45] for certain diagnostic procedures to ensure that similar volumes of tissue are measured [46].
2.3 Excitation Signals

There are various methods to apply currents to a tissue and measure the voltage response. The most common method of bioimpedance analysis injects a small, sinusoidal current into the body and measures the voltage differential at the input and the output. Although any frequency may be used, the frequency of this sinusoidal current typically ranges between 1 kHz and 1 MHz. However, there are multiple other techniques to generate the excitation current. The two most common techniques after sinusoidal current injection are step function and noise signal techniques. The step function technique applies a step voltage and measures the time-varying current response, which is converted into a frequency domain representation via the Fourier transform. The noise signal technique generates a voltage signal with frequency components comprised of random elements from a previously determined frequency range that is applied across the measurement material, and the measured current is converted into the frequency domain similar to the step function technique. A less common technique is the chirp signal technique, analogous to the radar chirp signal, which sweeps through a frequency range in a short amount of time (micro- or milli-seconds) to obtain the near-instantaneous frequency response of a tissue. One of the most popular general techniques, bioimpedance spectroscopy (BIS), typically uses a sinusoidal current with a frequency sweep on a timescale of one second [47].
2.3.1 Discrete and Frequency Domain Measurements

Discrete measurements, as mentioned previously, are generally concerned with comparing the impedance of a tissue or system at two separate moments in time, typically separated by days, weeks, or months. The most commercially successful application of bioimpedance is body composition monitoring (BCM). BCM is a method to assess the makeup of the human body (or a segment of it) in terms of water, muscle mass, tissue, fat, and bone [48]. Each of these parameters can in turn be used for various applications. BCM is a useful indicator for general health [49] as well as tracking changes in muscle mass [50], body fat [51], and hydration status. BCM is commonly available in gyms for physical therapy [52]. One can purchase bathroom weight scales and wristwatches with BCM capabilities built in. Body composition monitoring typically returns three values which will be covered in detail later: intra-cellular water, extra-cellular water, (combined to give total body water) and fat free mass [49]. BCM is closely intertwined with the following applications, as they overlap in terms of health monitoring and funding for research, where research groups often publish in multiple areas at the same time.

Water, or hydration, monitoring is a leading method for the assessment of the hydration status of athletes before, during, and after training to increase performance and decrease the likelihood of injury. As mentioned previously, it is also a leading method for hydration assessment of hemodialysis patients where it is used to determine the correct amount of water to remove from the body during
a dialysis treatment [53]. Bioimpedance is also used to detect lymphedema, or limb-swelling, by detecting the increased fluid buildup before it visibly impacts the tissue [54]. Muscle mass monitoring is primarily used in bedside applications to assess the changes in lean tissue for cases of malnutrition from acute and chronic illnesses [55] or to monitor the progress of certain treatments such as radiation, chemotherapy, sarcopenia, cachexia, etc. [56]. Tissue monitoring can be used alongside muscle mass monitoring to determine the recovery from exercise [57, 40], to assess muscle injury and recovery from injuries [58], as well as monitoring joint health [59].

Measurements of the bones or skeleton are also possible. Recent developments use bioimpedance to diagnose and monitor bone fractures [60]. Cell proliferation monitoring [61], fibrosis detection and monitoring [62], cancer cell discrimination [63], myoblast growth/differentiation [64], myocardial infarction/scar formation [65], and the identification of pulmonary nodules [66] are other applications of this technique.

### 2.3.2 Continuous and Time Domain Measurements

Continuous measurements are typically used for applications where the timescale of tissue changes to be measured is on the order of seconds or minutes. Impedance plethysmography is a method using bioimpedance to assess volumetric changes in the body. The two primary applications of this method are to measure the heart (impedance cardiography) and the lungs (impedance pneumography). Other applications of impedance plethysmography include monitoring of cerebral
fluids, arterial, and venous diagnosis. Impedance cardiography (ICG) has been an active area of research for more than fifty years. ICG measures the change in impedance due to a heartbeat primarily by measuring the effects of muscle contraction and fluid flow [67]. Other biological processes in the heart (such as the alignment of red blood cells in the arteries [68]) impact the impedance measurement, but these two are generally accepted to account for the majority of the inter-heartbeat impedance change [69]. Impedance pneumography (IPG) has a similar history to ICG. IPG measures the change in impedance due to respiration, primarily due to the mechanical movement of the lungs contracting during exhalation, decreasing the impedance due to the tissues being contained in a smaller volume, and conversely increasing the impedance with inhalation due to the increased distance current must travel, leading to a highly linear change in impedance with respiration [70].

ICG and IPG have many clinically relevant applications. ICG can be used in conjunction with additional information about the patient to estimate the amount of blood pumped with each heartbeat (heart stroke volume (HSV)), cardiac output, heart rate variability, and pre-ejection period (PEP) for autonomic activity estimation [71]. A typical electrode configuration for ICG/IPG monitoring is shown in Figure 2.7, and a time-aligned ECG and ICG comparison is shown in Figure 2.8. Note that the PEP and ejection time are both easily identified. The derivative of this ICG graph can be used to calculate the total volume of fluid. IPG is used to assess pulmonary flow [72] and to monitor respiration rate [73]. Preliminary studies have observed changes in lung function due to COVID-19 [74].
This method is also used to assess tidal flow in premature infants [75]. Due to their proximity, measurements of the heart and lungs often contain contributions from both sources. This is one of the main benefits of bioimpedance (simultaneous heart and lung activity), but it is also a detriment for those interested in one but not the other [76]. Fortunately, multiple methods exist to decouple these factors [77].

2.3.3 Signal Generation

There are two primary groups of methods for signal generation, single-frequency and multi-frequency. Single-frequency refers to measurements of the
Figure 2.8: The result of an impedance cardiography measurement, aligned with an ECG measurement.
response at one frequency over time. This also includes multiple single frequency measurements in rapid succession, called a frequency sweep. Multi-frequency, or broadband, is the measurement of more than one frequency at a time, typically relying on advanced signal decomposition methods to determine the response at the individual component frequencies. Single frequency (and frequency sweep) measurements are most commonly used in bioimpedance analysis, but wideband measurements have been increasing in popularity with the increase in available computing power to generate and decompose the necessary signals.

2.3.3.1 Single Frequency

The simplest and most common method for measuring impedance is the application of an excitation current at a single frequency. The shape of this signal is typically a sinusoid [78], but under certain criteria, square wave [79, 80] and triangle wave [81] excitations have been explored as approximations of the sinusoidal frequency. Sinusoidal wave generation circuitry is mass produced and used in countless applications. This makes it an attractive option for low-cost systems. The largest advantage that single-frequency measurements have is the commercial availability of ready-made bioimpedance sensing circuitry designed for single-frequency measurements, available from manufacturers such as Analog Devices and Texas Instruments.

There are three main steps to applying a single-frequency current to a system: signal generation, filtering, and the voltage-current transform. First, the signal must be generated; then it must be filtered to remove any spurious
harmonics and enhance the linearity of the signal. Common methods to generate the excitation signal include Digital-to-Analog (DAC)-based, oscillator-based, and square-wave-based techniques. Square wave generation is the simplest method, where a single bit DAC generates a square wave at the desired frequency and applies it to a filter network to transform it into a sine wave. This method has the advantage of being cheap and easy to implement, but it has high levels of noise and requires significant filtering. DAC-based methods generate an approximation of a sine wave in a series of steps, the number of which is determined by the resolution and oversampling ratio of the DAC. This sine-wave approximation is then applied to a filter to smooth the steps. This method requires less filtering than the square wave method, at the expense of more hardware. These two DAC-based methods are together often referred to as (direct digital synthesis (DDS)) [82]. The final primary method for signal generation is oscillator-based. Oscillators can be used to generate sinusoidal or triangular signals, the latter of which is easily transformed into a sine wave signal. The benefit of oscillator-based generation is its relatively high linearity, requiring less filtering. However, the frequency generation is reliant on multiple components that are susceptible to drift and temperature changes. This can lead to a mismatch between the desired frequency and the generated frequency. Finally, the filtered signal is passed into a voltage-to-current converter. There are various methods and integrated circuits for this purpose, but the most common method uses an operational amplifier (such as the LM 741) in a Howland current source configuration [83]. Direct application of sinusoidal voltage signals
is also possible, but current is typically used for safety reasons, as it is simpler to limit current directly than to limit the voltage applied to an unknown impedance.

Certain measurement techniques use a series of single-frequency measurements to evaluate the impedance. In this case, a frequency range of interest is defined, and a set of frequencies covering the range is chosen. Similarly to the broadband case, the objective is to evaluate the body’s response to a wide range of frequencies. The frequency sweep method referred to here uses multiple discrete frequencies sequentially. These measurements often take between thirty and sixty seconds. A common example of a bioimpedance device using this method is the Impedimed SFB7, which measures 256 logarithmically spaced frequencies from 3 kHz to 1 MHz in approximately thirty seconds on the default settings.

### 2.3.3.2 Multi-Sine

Multi-sine measurements generate multiple single-frequency sine waves at the same time to cover more frequencies in parallel while reducing measurement time [78]. This method gives a high signal-to-noise ratio, but is susceptible to spectral leakage peaks, where power is wasted at unusable frequencies outside the range of interest. This method is increasing in usage for short-term measurements. The circuitry to generate these signals often has to be custom-made or implemented on a field-programmable gate array (FPGA). Significant research is still actively seeking the best algorithms to optimize the frequency and phase relationships of multi-sine signals to maximize the signal-to-noise ratio and reduce wasted energy.
Figure 2.9: An eight tone multi-sine excitation. The top figure shows the time domain representation, while the bottom figure shows the frequency domain representation.

[84]. In Figure 2.9 (a) the time domain representation of a multisine signal is shown, while in (b), the frequency domain representation is shown.

2.3.3.3 Frequency Chirps

The chirp is a function in which the instantaneous frequency varies continuously over time. This is differentiated from the previously mentioned frequency
sweep due to its continuous frequency variation rather than step-wise frequency variation. A linear chirp is distinguished by a frequency that varies linearly (at a constant rate) over time. A nonlinear chirp is where this time-frequency relation varies in a nonlinear fashion. A comparison of a linear and non-linear chirp is presented in Figure 2.10. Generally, longer chirps contain more energy and have a higher signal-to-noise ratio, while shorter chirps will have greater temporal resolution for time-varying processes [85]. Under certain conditions, the exact shape of these chirps can also be varied to slightly enhance the signal-to-noise ratios. Sine-wave-based chirps are the most common, using a sine wave as the base signal component [86]. However, signum chirps, using a square wave as the base signal component, also exist [79]. All of these signals are typically generated in FPGAs, limiting their application to wearable systems at this moment.

### 2.3.4 Summary of Excitation Signals

There are a few broad topics of interest when choosing a signal excitation method. For a wearable system, size, weight, and power (SWaP) requirements are the most pertinent criteria. For research or exploratory methods, one might seek to optimize a particular facet of the signal excitation, such as the signal-to-noise ratio, power spectral density, measurement speed, or power consumption. A low-frequency bound in the hundreds or tens of Hertz requires large passive components, which influences the size of the sensor. A large frequency range covering multiple orders of frequencies requires more advanced signal filtering (to suppress harmonics only outside of the desired range) and current output circuitry (to maintain a high
Figure 2.10: A comparison of linear and non-linear (logarithmic) chirp signals. (a) contains the time domain representation, while (b) shows the frequency change profile.
output impedance across the entire frequency range). Ultimately, the application itself determines the acceptable combination of tradeoffs.

For a single frequency, the generated frequency on board the device can be applied to the measured response through a quadrature demodulator, allowing the separation of the real and imaginary parts of the impedance spectra in hardware. Since the frequency is known, only the amplitude of the in-phase and quadrature-phase components need to be recorded. For a complex signal, such as the chirp or multi-sine, a discrete Fourier transform must be used to decompose the signal into its relative frequency spectra. For a resource-limited system, such as a wearable, this prompts the use of more signal processing on the device itself, increasing power consumption of the processor, or the transmission of more data back to a central processing device, increasing power consumption of the communication modules. This issue is less relevant for research-only purposes, but is still a concern for real-world wearable monitoring applications.

In a single-frequency excitation, the entire applied energy, except noise, is directed toward that frequency. This leads to a high signal-to-noise ratio, enabling higher-precision measurements. In multiple frequency or broadband measurements, the excitation energy is spread over the frequency spectrum, reducing the signal-to-noise ratio of the system and leaving it more susceptible to noise. Additionally, broadband signals require the pre-generation of the excitation signal. Multi-sine excitation algorithms, for instance, are measured in minutes for the time it takes to simply generate the signal [87]. Similarly, chirps require significant processing to generate the signal [88]. Broadband signals to date have mostly been implemented
in FPGAs, where significant amounts of system resources (hardware blocks) can be allocated to decomposing the FFTs [89, 90]. These steps are important for future systems to understand the hardware requirements for real-time bioimpedance monitoring. The hardware limitations for the implementation of broadband signals in wearables are slowly relaxing, but for now the broadband signal generation requirements are too complex for wearable devices.

Other than single-frequency sine waves, the primary excitation signals used are multi-sine and chirp excitations. Other methods, such as pseudo-random signals, exist, but they are in the minority. Nearly any signal shape or generation method has the potential to be used, and many have been investigated by some researchers, but the majority are the ones covered in this section. The primary tradeoffs for broadband techniques are the increased signal processing required and the more complex generation circuitry. In addition, single-frequency devices are commercially available, whereas broadband devices must be custom made. However, the increased speed required to measure rapidly changing biological processes across a large frequency range may warrant the use of these signals.

2.4 Sources of Error in Bioimpedance Monitoring

There are three significant sources of error in bioimpedance: electronics, parasitic capacitances, and electrode-skin interface [91]. Each of these will be covered in detail in this section. The impacts of electronics are typically constant, while parasitic capacitance occurs primarily at high frequencies and the electrode-skin interface mostly changes due to motion. These sources come into play for
different applications. For example, a seated study at low frequency (an ideal case)
is limited only by electronics, but a high-frequency measurement of an athlete
performing an activity would be impacted by all three sources of error. Typical
commercial devices claim errors around 1% across the frequency spectrum for
ideal cases (SFB7, B4000), with errors as low 0.05% in certain cases.

2.4.1 Parasitic Capacitance

In bioimpedance, parasitic (or stray) capacitance typically refers to unwanted coupling between the body and the environment, though coupling between wires and the equipment to ground is sometimes included. Estimates of parasitic capacitance values range from 10-100 pF in most cases. The effects of these parasitics are frequency dependent. At low frequencies, the impact is negligible, but the effect increases with frequency as the impedance of the parasitic path decreases. This causes high frequency (above 100 kHz) currents to pass outside of the measurement area and into the environment or to the ground. This "lost" current is still used in the calculation of total impedance, though, and the impact on the measured impedance is an increase in the estimated reactance with increasing frequency, commonly referred to as a hook artifact [92]. A visual representation of parasitics in a circuit is shown in Figure 2.11. Note that the capacitors \( C_p1 \) and \( C_p2 \) have the currents \( i_p1 \) and \( i_p2 \) associated with them, and these determine the decrease in accuracy. This artifact in some cases resembles the impedance change associated with a dielectric relaxation or dispersion, as the phase of the current lost resembles that of a capacitor. Recent advances in bioimpedance analog front
ends include features to reduce the effect of parasitic capacitance by exciting a ring current around the sense electrode traces on the board, but the impacts of these traces are still under investigation. The primary mitigation for this effect is the use of frequencies below 100 kHz, and a significant number of articles cite parasitic capacitance as the reason for limiting the frequencies chosen to study [39, 57, 80]. The parasitic effect causes a decrease in the estimation of the absolute impedance of a tissue, sometimes as high as 10-15%. However, high frequencies can still be used for measurements where the relative value or change of the impedance, such as during respiration, is the parameter under study.

**Figure 2.11:** A modified Cole model, with a constant phase element in place of the capacitor.
2.4.2 Tissue-Electrode Interface

Electrode impedance mismatch is an additional source of error for bioimpedance applications. The ideal case for a bioimpedance measurement assumes that all four electrodes have identical impedances. In practice, there are slight variations in the skin-electrode interface that lead to changes in impedance. Hair, skin oil, sweat, and different cleaning protocols can cause small differences in the interface between the body and the electrode. While these variations can cause the measured impedance to be distorted across the frequency spectrum, the typical electronics used have sufficiently high input impedances and common-mode rejection ratios to minimize the effects of small variations. However, the largest source of error comes from time-dependent electrode impedance mismatches in the form of motion artifacts. Motion artifacts in ECG and bioimpedance applications are an active area of study, but it is typically agreed that these mainly come from skin stretching, which dynamically alters the electrode-skin interface [93]. This interfacial change is often distributed unevenly across electrodes, leading to further errors. Often, motion artifacts can cause the skin-electrode impedance interface to increase by several times, rendering the impedance measurements taken at that time useless [39]. Significant research has been conducted in the fields of ECG and bioimpedance to reduce motion artifacts [94, 95]. Reliable error identification is important to know which error correction method to apply. The errors associated with a motion artifact require outlier removal or the removal
of entire segments of data. Hook artifacts require curve fitting methods such as particle swarm optimization or non-linear least squares fitting to be applied.

There are three types of electrodes used in bioimpedance, each with benefits and drawbacks. First, wet electrodes are composed of an Ag/AgCl gel that adheres to the body. These electrodes have excellent contact quality, but they are single-use only and typically can be used only for a few days without replacement. They are excellent in the lab, but they are unusable for any sort of wearable application. The aforementioned motion artifacts are less significant with wet electrodes, as the gel interface has some tolerance to movement. Dry, textile electrodes have been a relatively recent development. These textiles are often made of high-performance synthetic materials, such as polyester, with conductive metal threads woven in. These threads can be connected to an electrical measurement system and used for sensing. These electrodes can then be woven into clothing for use. Textile electrodes are commonly used for biopotential signal acquisition applications other than bioimpedance, primarily ECG measurement [96]. These electrodes can be used for wearable applications that do not require high fidelity. They often need to be integrated into compression-style clothing to have sufficient contact pressure for bioimpedance measurements. Finally, there are dry, metal electrodes [97]. These electrodes are often made of stainless steel, but gold or platinum are also common. These electrodes have the advantage of being quite durable, especially compared to single-use wet electrodes and textiles. However, these have the disadvantage of needing to be integrated into a wearable or standalone electronic device.
The electrode and its impact on impedance measurements are an active area of study. Electrode placement, geometry [98], material [99], and electrode-skin interface [100] can reduce the accuracy of any impedance measurements by obscuring the tissue under study. In the ideal case, with tetrapolar electrodes, the impedance of the electrodes and the electrode-skin interface are completely removed from the measurement. Realistically, slight variations in these impedances cause measurement errors. A recent study by Fu and Freeborn [101] isolated a few of these factors and found that large electrode impedances, such as those found in Ag/AgCl type electrodes, can significantly limit the usable frequency range with certain impedance analyzers, though this range is still within the frequency range commonly used for bioimpedance analysis.

Various models exist for the electrodes themselves as well as the electrode-skin interface. A few electrode types and their corresponding circuit models are shown in Figure 2.12. Since wet-type Ag/AgCl electrodes are the primary interface method for bioimpedance measurements [102], the bulk of this discussion will be focused on these electrodes. Here, wet refers to the use of a gel solution containing free ions to carry charge between the electrode and the skin to increase the contact quality [103]. It is useful to consider the path of current excitation from the measurement device to the body. The signal exits the measurement device through a cable that is attached to an electrode. The signal enters this electrode through a metal-to-metal contact, which is assumed to have nearly zero impedance. From the metal part of the electrode, the signal passes into the gel and then into the body. Each of these interfaces brings opportunities for modeling and for error.
The two primary interfaces in a single wet electrode are metal electrode to gel and gel to skin [99]. The electrode-gel interface is between the metal connection, the electrode, and the gel solution itself. This interface is typically modeled as an RC (resistor and capacitor) parallel circuit. After entering the gel, the signal passes through it and enters the skin. The gel itself has an impedance, typically modeled as a resistor. The gel-skin interface is subject to the most scrutiny. One common approach is to model the skin-electrode interface as a resistor in parallel with a capacitor. The value of these components depends on the type of electrode used. Separately, any interface-enhancing material (gel) can be modeled as an additional RC pair. For the common Ag/AgCl electrode, these two separate values are often combined into a single 2R-C (two resistors, one capacitor) circuit that approximates the impedance response of the electrode. In Figure 2.12, a few models are shown for the electrodes and the skin-electrode interface, while Figure 2.13 shows a more explicit model of the interfaces.
The skin-electrode interface is highly variable [104]. Multiple studies have investigated the effects of noise resulting from the electrode-skin interface and surrounding elements [105, 100, 106] and their impact on impedance measurements. Interfacial thermal noise, amplifier $1/f$ noise, and interface $1/f$ noise are all subjects of research in the pursuit of ideal impedance measurements [107]. Factors such as movement [108], skin preparation, the presence of hair, temperature variations [109], and time [110] also have an effect. Motion artifacts, caused by micro-scale stretching of the gel-skin interface [111], are the largest source of noise in the entire bioimpedance measurement process. However, additional factors contribute to overall noise and can contribute to the presence of motion artifacts. A typical human skin model contains the epidermis, dermis, and subcutaneous layers. Here, the epidermis is the outermost layer and continually grows new
cells and sheds old, dead cells. These outer cells form a layer called the stratum corneum on top of the epidermis. The stratum corneum differs from the epidermis beneath in many ways, the most notable being a lack of water. When a gel-based electrode is placed on the skin, the stratum corneum forms a separating layer between the two aqueous solutions of the gel and the epidermis. This formation is referred to as the "skin capacitor" [112]. The effect of this skin capacitance is a large increase in the resistance of the skin-electrode interface at low frequencies. For this reason, surface preparation (exfoliation) of the skin in the form of an alcohol wipe is critical to ensure precise measurements [113]. In one study, the skin electrode interface impedance dropped from tens of kΩ to hundreds of Ω with surface preparation [112]. This effect can be completely mitigated with skin-puncturing electrodes, but these are undesirable for most studies due to their invasiveness and potential for infection. Additionally, the skin will often react to the application of an electrode. This resolves as a change in the impedance at the electrode-skin interface over time [110, 106]. Various electrode types, specifically on-skin electrodes, are being investigated to reduce these effects and increase re-usability, sensitivity, and resistance to motion artifacts for better wearables [114].

Electrode impedance mismatch can cause significant issues with impedance measurements. For instance, power line coupling can cause the body to have a certain common-mode potential. If the electrodes are not perfectly matched, there is a potential difference between the sense nodes, and a voltage will be measured [115]. The size of the electrodes also has an effect on the impedance. A
Figure 2.13: A model of the electrode-skin interface for wet and dry electrodes. Notice that the skin contact (SC) model in both wet and dry electrodes has the same capacitance (10 nF) while resistance changes.

A larger surface area allows the electrode to sample the potential distribution across multiple points, where the measured value is an average of all of these points, which can result in decreased noise [116].

Bipolar (two electrode) measurements were the first electrode configuration investigated for bioimpedance measurements, but tetrapolar (four electrode) measurements have become the dominant measurement modality due to their increased accuracy. A bipolar electrode measurement setup places the electrodes in series with the tissue under study and, therefore, measures the impedance of the electrode in addition to the tissue. In Figure 2.14, note that the voltage sense interface is directly connected to the current source. Therefore, the measured voltage differential is caused by the current, which passes through the impedance of both electrodes in addition to the tissue. In addition to the tissue, the electrodes themselves possess a frequency-dependent impedance, leading to further inaccuracy. The Maxwell-Wagner-Sillars effect, covered previously, also occurs at the electrode-skin interface, leading to an additional, non-tissue-related dispersion.
called "electrode polarization" [38] at very low (sub-100 Hz) frequencies. The bipolar configuration is especially prone to errors from this polarization. For these reasons, bipolar electrode configurations are typically not used when absolute accuracy is needed. However, they can still be useful for tracking changes in impedance, such as those due to respiration or cardiac activity. A tetrapolar (four electrode) setup separates the current source and sink electrodes and the voltage source and sink electrodes into pairs. In this case, only the current electrodes are in series with the tissue. This allows the voltage electrodes to sense only the current that has already passed through the electrode, removing the impact of the current electrode impedance and eliminating the polarization effect. Note in Figure 2.15 how the voltage-sensing electrodes are connected directly to the tissue under study. Additional electrode configurations exist, such as tripolar and octopolar, but they are relatively rare and do not exhibit any real benefits over the ones discussed above.
An important consideration for any bioimpedance study is electrode placement. Previously, the tissue under study was represented as a cylinder with a certain length. The movement of the electrode system causes the parameters of this cylinder to change. Theoretically, one can consider measurements taken without perfect electrode alignment to be of different tissues. Practically, perfect electrode repeatability is simply not possible, and the effects of electrode positioning are minor for most applications as long as the total volume of the cylinder is not significantly changed, and the positioning of the electrodes is within a few millimeters.

The primary source of error in bioimpedance analysis is the electrode-skin interface. This error occurs mostly due to motion, which changes the interface between the subject and the measurement device. It is largely unavoidable but
can be mitigated with proper preparation and techniques. Parasitic, or stray, capacitances impact impedance measurements above 100 kHz, especially where absolute accuracy or circuit fitting is needed. However, for relative analysis, it can be treated as a constant. Finally, the electronics themselves limit the precision and accuracy of any bioimpedance system. In the ideal case, the analog-to-digital converter resolution would determine the total error. In practice, other factors come into play well before the precision limitations of the electronics.

The impact of electrodes on impedance measurements of the body cannot be overstated. Electrodes are the only interface between the human body and measurement systems. They are the largest source of noise and error in the measurement schema, and significant amounts of research is focused on modeling and improving the electrode-skin interface. The Ag/AgCl electrodes, which serve as the primary electrode type in bioimpedance studies, are severely limited in wearable applications, leading to the development of textile and other dry electrodes. However, these suffer from a different set of problems, mainly a lack of contact quality. As a result, many studies trial novel measurements with Ag/AgCl electrodes before switching to dry electrodes for integration into wearables.

2.4.3 Electronic Noise

Noise in impedance measurements can come from a variety of sources. The most important sources of electronic noise, listed in approximate descending order of severity, are:

- the electrode-skin interface and motion artifacts
- power line noise
- power supply noise
- clock noise
- quantization errors
- thermal noise

The most significant uncertainty comes from the electrode-skin interface, detailed in the previous section, but the limiting factor for overall precision in bioimpedance measurement is the electronic signal chain. As mentioned previously, oscillators can be a source of noise and sampling frequency uncertainty. Various random noise sources, such as thermal noise, play a small role in the overall measurement schema for bioimpedance measurements. Their effect is certainly non-zero, as they impact every measurement, and analog-to-digital converters (ADC) can be particularly sensitive to thermal noise. However, their contribution is minimal compared to other factors in the measurements [117, 118]. Power line interference, occurring at a frequency of 60 Hz in the United States, is a concern for many bioimpedance systems. While battery-powered systems eliminate the pass through of 60 Hz through the power electronics, these potentials still exist in the electromagnetic environment around the measurement system. This noise can couple with sensitive electronics and cause increased noise, primarily through the printed circuit board (PCB) layout. As mentioned in the electrode section, potentials can also couple to the human body and cause small voltage differentials in unbalanced electrode configurations [115].

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In battery-powered bioimpedance devices, the conversion of the battery voltage to a usable integrated circuit voltage can have negative impacts on impedance measurements. For example, switch-mode voltage converters have high levels of high-frequency noise, which then powers the rest of the components, where it can cause deviations in the true signal. ADCs and amplifiers are particularly sensitive to power supply noise. In the same way, the voltage reference used by components such as the ADC can vary with environmental factors and cause errors in the measurement. Amplifier noise can also impact impedance measurements. Amplifiers themselves can be impacted by temperature variations and electromagnetic coupling, contaminating the signal with noise. Amplifier $1/f$ and broadband noise also require mitigation through careful component selection. In general, amplifiers with the minimum amount of bandwidth to effectively measure the signals of interest should be chosen to limit noise.

Clock noise in a system may cause frequency instability, known as jitter, leading to noise in the output. A typical clock used in a bioimpedance wearable system will be of piezoelectric design, though others may be used. The construction of the crystal determines the frequency at which it oscillates when a voltage is applied to it. However, these crystals can exhibit small changes in size due to temperature, which causes the frequency of oscillation to vary, which leads to variable errors in the DACs and ADCs. Additionally, vibrations can also cause changes in the frequency generated, which is a concern for wearable devices, especially those measuring the movement of athletes, children, or active adults.
These effects can be mitigated with phase lock loops, among other methods, but come with increases in cost [119].

The conversion of analog signals into digital signals and vice versa is a critical enabling factor for bioimpedance measurements. In most measurement scenarios, the electrode-skin interface is the limiting factor for total precision in determining the impedance. However, in ideal cases, such as in a laboratory setting, small errors from the electronics can become the primary noise sources. All analog to digital converters (ADC) and digital to analog converters (DAC) suffer from quantization errors, also referred to as quantization noise, as it is difficult to describe continuous signals with discrete steps. DAC quantization errors mostly result in non-ideal signals, which contain contributions from frequencies higher than the selected frequency. The steps in the DACs approximation of a signal result in spurious harmonics, which can impact signal quality. ADC quantization errors occur when converting the analog signal back into its digital representation. This comes from mapping the continuous signal to a discrete value, where the analog value is mapped to the nearest discrete bin. ADCs with higher numbers of bits have more of these discrete values to assign signals to, leading to more accurate approximations. However, quantization errors or noise can occur with any finite number of bits. Many ADCs and DACs employ oversampling to decrease errors. Oversampling means deliberately sampling a signal at a rate higher than the Nyquist rate to increase the signal-to-noise ratio [120]. This in turn decreases the effective sampling rate of the system. Effective number of bits (ENOB) is a measure often used to generate an approximation of the real-world performance
of ADCs. A simple approximation for the quantization error can be made with the equation \( Error = \frac{1}{2}(LSB) \), where \( LSB \) stands for least significant bit. The formula \( SNR = 6.02N + 1.76dB \), [121], where \( N \) = number of bits, can be used to describe the ideal signal-to-noise ratio (SNR) of an ADC. Calibration is often used (and, in some cases, required) to remove the effects of factors such as temperature, clock drift, and measurement setup. Newer devices may have an internal calibration routine for temperature and clock drift errors, but most devices require an external calibration with a known impedance to remove the impact of the measurement setup (that is, the traces on the board, the components in the signal chain such as capacitors and switches, as well as the cables and connectors to interface with the subject). With proper calibration, research grade impedance analyzers claim accuracy down to 0.05% [122], while commercial devices such as the MAX30009 claim accuracies of 0.1% [123].

While the skin-electrode interface is the largest source of error in bioimpedance measurements, noise in the electronics also contributes. In analog electronics, thermal noise, quantization noise, jitter, switching noise, and layout noise can all contribute to the noise floor of measurements of bioimpedance. It is important to carefully consider component selection when a bioimpedance system is specified. The use of specially made and mass-produced circuits, such as analog front ends (AFEs), can significantly reduce noise and reduce system design time.
2.5 Bioimpedance Measurement Systems

At the heart of any wearable bioimpedance study is the sensing circuitry, often called a bioimpedance controller, sensor, or analog front end (AFE). The bioimpedance device, or chip, determines the limitations of the study. This specialized bioimpedance integrated circuit (or set of circuits) sets the minimum and maximum frequency, the possible current excitations, and the maximum accuracy of the bioimpedance study. Therefore, it is important to understand the limitations of bioimpedance controllers, especially compared to research-grade impedance analyzers. A complicating factor is that many bioimpedance controllers do not offer easily comparable measures for their noise and accuracy figures, which necessitates research verifying manufacturers' claims.

Many bioimpedance studies are conducted every year. These studies typically use one of the following bioimpedance devices:

- Impedance analyzers
- Commercial off the shelf
- Commercial off the shelf with additional circuitry to extend impedance or frequency range
- Custom circuit designs

For pilot studies, impedance analyzers, such as the one shown in Figure 2.16 are often used. Impedance analyzers, such as those by Zurich Instruments and Keysight, are typically built for commercial electrical impedance spectroscopy
applications and, as such, offer high levels of precision across a frequency range larger than what is typically needed for bioimpedance. These devices are typically large (20x20x20 cm) and costly, with entry-level models starting around $12000 at the time of writing. Typical accuracy specifications claim a 0.05 percent error in the measured magnitude of impedance across the majority of the frequency range [122, 124]. Impedance analyzers are often used as a reference device to evaluate COTS bioimpedance devices [80].

There are two types of commercial off-the-shelf (COTS) bioimpedance devices. The first are integrated commercial sensing solutions such as the Impedimed SFB7 [125], shown in Figure 2.17 and SOZO [126]. These devices are specially built for applications such as body composition monitoring. They provide access to the raw impedance data, but there is limited customization of the waveforms or frequencies used. The other type of COTS bioimpedance devices are the bare chips, sold by manufacturers such as Analog Devices, Maxim Integrated, and Texas Instruments. These chips can then be added to a wearable device for use. These manufacturers often offer an evaluation kit, such as the one shown in Figure 2.18 that serves as a self-contained test platform to evaluate their bioimpedance solution in a ready-made solution. The first widely used standalone bioimpedance chip
was the Analog Devices (AD) AD5933, which is still used in studies today. Maxim Integrated has offered two solutions in the past three years, the MAX30001/2 and the MAX30009. Texas Instruments (TI) offers the AFE4300, shown in Figure 2.19 and AFE4500. The TI AFE4300 [127] and AD5933 are the most widely used standalone bioimpedance controllers. These two controllers are often slightly modified to extend the frequency range, extend the impedance sensing range, or convert to a four-electrode sensing configuration [128, 129]. Finally, custom designs are sometimes built by researchers who have specific needs that are not met by the options available on the market, be it frequency range, current excitation, or cost [130]. These chips are typically not reproducible by the general public and therefore it is difficult to verify their performance.

The commercially available bioimpedance analog front ends (AFEs) today have measurement accuracy that rivals that of research-grade impedance analyzers in certain scenarios [131]. With the increasing commercialization of bioimpedance AFEs, other features and refinements have been added that drastically reduce
Figure 2.18: A MAX30009 EVKIT, or evaluation kit.

Figure 2.19: A bare TI AFE4300 controller, shown in the LQFP-80 package.
the development time for researchers. For instance, the MAX30009 is the first commercial AFE to offer simultaneous IQ (In-phase and Quadrature) demodulation in the device. This advance alone effectively doubles the sampling rate of the device, as other AFEs need to switch between I and Q demodulation in successive samples to monitor these parameters. This is critical for any application where the magnitude of impedance alone is not sufficient and phase data is crucial, such as impedance cardiography and pneumography. Additional features that are becoming more common are on-board calibration and general circuit configuration options such as bypassable high-pass filters and multiple output options. This increased circuit complexity has not resulted in increased costs, as in the past decade the cost of integrated circuit components has greatly benefited from economies of scale and progress in related fields.

2.6 Applications of Bioimpedance Monitoring

Bioimpedance monitoring applications depend on the type of monitoring that can be used and applied. There are two primary types of bioimpedance monitoring: discrete and continuous. The first method measures the impedance for a short period of time, typically with multiple frequencies, to capture a "snapshot" of the tissue under study. Often, this is a series of short (e.g., one second) measurements at different frequencies. This snapshot can then be compared to others taken at different points in time to comparatively assess changes in tissue properties. This is especially useful for measuring properties of the tissue that change on long time scales (days, weeks, months), such as body fat percentage,
muscle mass, and bone mass. This is the most commonly used method and is present in most body composition applications, such as body composition weight scales [132]. The other method, continuous monitoring, measures the tissue impedance continuously at a single frequency, or a small set of frequencies, for a relatively longer period of time at a high sample rate to capture the effect of biological processes on the tissue that change on the order of seconds or minutes, such as breathing and heart rate. However, the lines between continuous and discrete measurements can overlap, with applications such as single-frequency bioimpedance analysis (SF-BIA), which estimates body composition with only a single frequency. It can be useful to consider these as general categories rather than hard-and-fast rules. Bioimpedance is a versatile technology, and most systems can measure using either method, depending on the application or circuit configuration.

In addition to the impedance plethysmography applications previously mentioned, there are a multitude of other applications for bioimpedance monitoring. Bioimpedance monitoring is itself a subfield of a larger field called electrical impedance spectroscopy. Electrical impedance spectroscopy is a widely used technique with numerous applications in many fields, including the monitoring of concrete curing [133], detection of foodborne bacteria [134], corrosion monitoring [135], air quality monitoring through the detection of nitrogen-In thin films [136], and tracking plant health [137]. As covered in earlier sections, the impedance of the body is a passive, frequency-dependent property composed of the contributions of tissues, fluids, and bones. This property and the changes in it over a period of time can give insight into the underlying biological processes as well as the
composition of the body. Bioimpedance is among the cheapest physiological sensing methods, as the circuitry used greatly benefits from advances in other fields and industries where economies of scale drive down research and development costs. However, bioimpedance is typically not quite as accurate as specialized methods for sensing, and commercial uptake of bioimpedance technology has been slow. Bioimpedance is multifunctional and often competes with specialized equipment in hospital settings, where the strongest advantages of bioimpedance (low cost and non-invasiveness) are nullified by large budgets and the acceptance of invasive procedures. Bioimpedance is more commonly used in research studies as a way to investigate biological phenomena without using invasive techniques and expensive equipment.

There are various medically successfully applications of bioimpedance, such as:

- Non-invasive total body water measurement during hemodialysis, leading to a decrease in patient mortality by reducing errors in the total amounts of water being removed during the procedure [53].

- Body composition monitoring, which uses several frequencies to determine total body water (TBW), ECW, muscle mass, bone mass, etc.

- Electrical impedance tomography, which uses repeated impedance measurements to generate 3-D representations of tissue [138]. This method can also be used as an alternative to a biopsy when the electrodes are placed on a needle tip [139, 65].
• Various bedside applications, such as the use of body composition monitoring to assess muscle mass changes in bed-bound patients [140].

• Arthritis monitoring [80].

• Impedance cardiography, measuring the changes in impedance of the heart, and including heart rate monitoring.

• Impedance pneumography, measuring the changes in impedance of the lung, and including respiratory monitoring.

2.6.1 Assistive Surgery

Bioimpedance monitoring can also be used during surgical procedures. In one instance, bioimpedance was used in a robot assisted minimally invasive surgery to detect tissues of interest (e.g., tumors, cancer, etc.) through the skin non-invasively [141]. In multiple studies [142, 143, 144, 145], impedance cardiography was assessed alongside traditional thermodilution cardiac output monitoring during multiple points in a cardiac surgery (anesthesia induction, mediastinum opening, cardiopulmonary bypass, and post surgery), and found to generally agree with traditional monitoring methods. Other studies used similar methods during surgeries such as a liver transplant [146]. In another study, bioimpedance fluid analysis was assessed to guide fluid management in high risk abdominal surgery [147]. Other studies focused on the assessment of bioimpedance methods for post surgery monitoring [148].
2.6.2 Wearable Bioimpedance Monitoring Applications

A clinical setting will often have specialized equipment that is highly accurate for routine measurements such as heart rate, blood oxygenation, blood pressure, etc., limiting the attractiveness of bioimpedance devices. However, outside of the clinical setting, opportunities abound for bioimpedance measurements. As mentioned previously, most bioimpedance systems can be used in both the discrete and continuous time domains. Therefore, any bioimpedance system capable of performing measurements in both domains can be used for any of the applications discussed above. Wearable devices and at-home systems are excellent use cases for a multipurpose technology such as bioimpedance. While a doctor’s office or hospital can easily afford to have specialized equipment, a standalone user would greatly benefit from a general health measurement device that enables the measurement of key health indicators without the need to go to the doctor or use multiple expensive, specialized devices. Wearable devices such as the Samsung Galaxy Watch 4+ already include a bioimpedance based body composition measurement, opening the door for the increased use of bioimpedance for additional health measurements at home and on the go. Remote patient visits have become increasingly common since the beginning of the COVID-19 pandemic. One key issue with these visits, though, is the lack of basic health markers such as heart rate and blood pressure, which typically only occur in the office. Bioimpedance could see increased uptake as an at-home, all-in-one solution to measure vital signs and reduce the need to physically visit the doctor. With an increasing number of
applications and continued reductions in cost, there is a strong possibility that the
cost will not occur in the hospital
or doctor’s office, but everywhere else.

Wearables in general increase the amount of data available to researchers
and inspire questions that would not be asked without them. For example, a
pre-print paper published by WHOOP, a wearable device manufacturer, discovered
a link between heart rate variability (HRV) and both full-term and pre-term births,
indicating that it may be possible to predict and intervene in a pre-term birth
[149]. Collecting HRV data such as this in a conventional way, such as in the
hospital, would be difficult for a large study. However, in this case, the study
did not require any participation other than to wear the device and opt-in to the
study. Findings such as these spur the development of better wearables, and it is
imperative that these technologies and algorithms be developed. Doing so will
not only lead to better treatments and improved outcomes for patients, but also
earlier detection and intervention for those at risk of developing diseases.

Various research groups focus on wearable bioimpedance sensing. The
Jafari research group at Texas A&M has published many articles on bioimpedance
sensing. Impedi-Bands [150], for example, are a wearable bioimpedance device
that could be used in a similar fashion to a Holter monitor. Cuffless blood-
pressure monitoring on the forearm [44] is another novel application of a wearable,
that could also be used in a smartwatch-style wearable. The group also has
produced significant research on the topic of non-invasive cardiac and respiratory
changes [70], which is cited heavily in this work. The Freeborn research group at
The University of Alabama conducts research into exercise induced changes in bioimpedance parameters [112], conducts wide bioimpedance parameter studies [80], and researches the association between pain and bioimpedance parameters [39]. The works by Blanco-Almazan further characterized the linear relationship between impedance and breathing and its application to respiratory monitoring [151, 152, 153, 154, 155, 156, 75]. Their study, Breathing Pattern Estimation Using Wearable Bioimpedance for Assessing COPD Severity [152], was the first study to use only bioimpedance for respiratory monitoring.
3.1 Overview

This chapter introduces a pilot study that evaluated the effectiveness of four candidate electrode configurations and ten candidate excitation frequencies suitable for bioimpedance-based wearable monitoring applications. The electrode configurations and excitation frequencies are analyzed; the data processing techniques and experimental results are presented in detail. From these results, an additional study with ten subjects, detailed in the next chapter, was performed with a subset of the frequencies and system configurations.

3.2 Pilot Study

In the single person pilot study, four electrode configurations were evaluated: chest, forearm, wrist-to-wrist, and wrist-to-finger. For each configuration, ten frequencies were evaluated: 1, 2, 4, 8, 16, 32, 64, 128, 256, and 512 kHz. These frequencies were chosen to cover commonly used bioimpedance stimulation frequencies supported by off the shelf bioimpedance controllers, while also extending the frequencies into those less commonly used, such as 256 and 512 kHz.
3.3 Electrode Configurations

There are four primary electrode configurations used in this study, shown in Figure 3.1. The first configuration is placed on the chest. The second configuration is placed on the left forearm. These two configurations are commonly used in studies and were used in the pilot study for comparative evaluation. The third configuration places the source electrode pair on the left forearm, and the sink electrode pair on the right forearm. The fourth and final configuration places the source electrode pair on the left forearm, like the third, but places the sink electrode pair on the fingers of the right hand. The third and fourth electrode configurations are novel contributions which have not been studied for cardiorespiratory monitoring before this study.

3.3.1 Chest Electrode Configuration

The chest electrode configuration places the four measurement electrodes on the chest. The source pair is placed on the left side of the chest, while the sink pair is placed on the right. The electrodes are aligned vertically, with the current electrodes on the bottom and placed at the 7th rib. The voltage sense pair is placed above the current electrodes with a half inch separation between the edges of the electrodes. This measurement configuration is commonly used in impedance cardiography and pneumography. The majority of the current excitation passes through the bottom two thirds of the lungs, the heart, and the central arteries. The movement of the diaphragm increases and decreases
**Figure 3.1:** The system block diagram (left) and the electrode configurations (right). Note that the electrodes on the wrist on the right side of the figure closest to the hand labeled V+ and I+ are used as the source electrodes for the forearm, wrist-to-wrist, and wrist-to-fingers electrode configurations.
the impedance during inhalation and exhalation, respectively, as it modulates
the distance the current must travel as well as the density of the tissue between
measurement electrodes. The movement of fluid generated by the heart beating
results in a change in impedance, as does the contraction of the heart muscle.
Impedance cardiography and pneumography applications typically capture both
heart activity and respiration and filter out the unwanted signal. In this study,
both are captured and separated for analysis. This electrode configuration is used
for a reference measurement and a point of comparison with other works.

3.3.2 Forearm Electrode Configuration

The forearm electrode configuration places all four electrodes in a line on
the left forearm above the radial artery. The source pair is placed near the wrist,
while the sink pair is placed nearer to the elbow. The electrodes are separated
by a minimal distance, with the edge of the electrodes touching one another. In
this electrode configuration, the heart and lungs are not directly contained in the
tissue between the electrodes. However, the radial and ulnar arteries located in the
forearm provide an opportunity for physiological measurements and assessments.
The arterial blood pulse can be sensed as it passes through the tissue under study
and the heart rate can be measured through the changing impedance due to fluid
flow. This electrode configuration has been previously used by the Jafari research
group [44] and is used here as point of comparison to their work.
3.3.3 Wrist to Opposite Wrist Electrode Configuration

The wrist to opposite wrist measurement configuration places the source electrode pair on the left wrist and the sink electrode pair on the right wrist. Both the source and sink electrode pairs are placed near the radial artery with the edge of the electrode at the wrist flexion crease, with the current electrode pair closest to the respective wrists.

3.3.4 Wrist to Opposite Fingers Electrode Configuration

The final electrode configuration, the wrist to opposite finger measurement, places the source electrode pair on the left wrist and the sink electrode pair on the fingers of the right hand. Specifically, the current sink is placed on the forefinger, while the voltage sense sink is placed on the thumb. The source electrode pair, similar to previous measurements, is placed on the radial artery of the left wrist flexion crease with the current source closest to the wrist. This measurement configuration is intended to replicate a wearable smartwatch-style measurement setup, such as the Samsung Galaxy Watch 4+ [157].

3.4 Frequency Selection

A critical part of this work is the evaluation of multiple measurement frequencies. As discussed in Section 2.2.1, the impedance of tissues varies with frequency as well as physiological processes. Therefore, a wide range of frequencies must be evaluated for their response to physiological phenomena to characterize
their sensitivity. The frequencies chosen cover the low, medium, and high ranges of a typical Cole-Cole curve, described in Section 2.2.1.

3.5 Protocol

To ensure proper electrode-skin contact, the skin at the chosen electrode site is thoroughly cleaned with an alcohol wipe and allowed to dry. The electrodes, typically stored in a sealed bag, are removed from the bag, and carefully applied, one-by-one, to the chosen electrode locations. After the electrodes are applied, they are pressed into the skin to ensure proper adherence at the edges. The marked electrode cables are attached to the proper electrodes and then to the device. Care is taken to eliminate cables tangles to reduce the impacts of parasitic capacitance between cables.

A deep breathing routine is used to induce the maximum possible impedance change. This represents the best case for the research study. The deep breathing routine is a two-second inhale, four-second breath hold, and two-second exhale, immediately continuing back to the inhale. This protocol forces breathing rate of 7.5 breaths per minute, which is slow but still a comfortable breathing rate for most users. This process is repeated for sixty seconds for each measurement.

3.6 Data and Analysis

MATLAB was used extensively for the data processing. The raw output from MAX30009 was a N row, four column matrix, where N = number of samples
and columns 1-4 represent time, sample number, In-phase (I), and Quadrature (Q) data.

### 3.6.1 Calibration

The MAX30009 EVKIT software GUI has a built-in calibration function which corrects for the measurement configuration. A 99.7 Ω resistor was used between the 3M Red Dot 2560 electrodes to account for the impedance of the electrode. One thousand samples were taken for each frequency combination, and the resulting impedance was calculated from the average.

The MAX30009 outputs the I and Q data, which must be calibrated using the above coefficients. The magnitude, phase, real, and imaginary components at each sample were calculated and added to columns alongside the original data. This resulted in a N row, eight column matrix, where N = number of samples and columns 1-8 represent time, sample number, In-phase (I), Quadrature (Q), Magnitude (Ω), Phase (Θ), real-part of impedance (Ω), and imaginary part of impedance (Ω).

### 3.6.2 Data Cleaning and Filtering

The data collection was relatively error free. However, a few individual measurements contained errors and motion artifacts. These were manually identified and removed using a manual removal/replacement. Then, the data was lowpass filtered at 10 Hz to remove high frequency noise. A Savitsky-Golay filter of order three and frame length 15, `sgolay(signal,3,15)`, was applied to smooth
the remaining signal. Finally, a trim function was used to remove the first and last tenth of a second from the matrix to remove impulse effects from the filtering.

### 3.6.3 Breathing and Heart Rate

To assess an average breath for a particular measurement, a custom function was written to identify the peaks of bioimpedance caused by breathing, and a similar function with different parameters was written to identify the heartbeats. A similar method was used in [152]. Once the peaks were identified, a window of values before and after the peak was added to obtain a full view of the activity. For instance, each breath cycle is approximately eight seconds long; therefore, a ten second window was used. These windows were shifted down to eliminate the baseline through the detrend function, and then each breath in the measurement was averaged together to generate typical change of bioimpedance as a response to each breath. The mean, median, and standard deviation were measured for each average breath or heartbeat window.

The heartbeats are easily identified due to the sharp decrease in impedance with the fluid output from the heart. This results in sharp derivative peak which can be used for heart beat detection, even in the presence of breathing and other physiological phenomena. In Figure 3.2, notice in part (c) the derivative, showing 74 clear heartbeats. In particular look closely at second 23. Here, the subject is in the middle of an exhalation, and in the magnitude (a) and phase (b) components, a heartbeat is not clearly seen. However, there is a clear peak in the derivative
(c), indicating a heartbeat. On careful inspection of (a), one can see the heartbeat overlaid on the down-slope of the breath.

In Figure 3.2 (d), the heart rate throughout the measurement is shown. This is calculated from the distance between the peaks shown in (c) of the same figure. Here, the respiratory sinus arrhythmia is clearly seen, where the heart rate increases with inspiration and decreases with exhalation. From this plot, heart rate variability (HRV) can be calculated using the standard deviation of the differences.

### 3.6.4 Fast Fourier Transform

For the time series analysis, a fast Fourier transform (FFT) was used to identify the primary component frequencies. Due to the slight movements of the subjects, a large DC component was often present. A simple mean adjustment in the form of \( \text{signal} = \text{signal} - \text{mean(signal)} \) was insufficient to remove all of this component. Therefore, the data were also high-pass filtered at 0.1 Hz. The primary respiration frequency range widely used in the literature, 0.15-0.4 Hz, is unaffected by the filter [158].

### 3.7 Results

Here, the results from the pilot study are presented. These results are separated by measurement location and changes due to heartbeats and breathing.
Figure 3.2: This is the time series of the Wrist to Finger configuration for one subject measured at 64 kHz, magnitude (a), phase (b), derivative of magnitude (c), and heart rate interval (d). The points of peak exhalations are marked in (a), and the derivative peaks for heart activity are marked in (c).
3.7.1 Chest Measurements

Chest measurements of bioimpedance are widely used to monitor breathing. Figure 3.3 shows a representative sample of one full recording of a bioimpedance measurement for the chest location at 128 kHz. Here, the repeating patterns of impedance increase with inhalation, constant with breath hold, and decrease with exhalation represent the change in impedance corresponding to respiration, while the smaller spike-like variations show the change corresponding to individual heartbeats. The magnitude component of the impedance, Figure 3.3a, is dominated by changes corresponding to respiration, while changes corresponding to heart activity are relatively more visible in the phase, Figure 3.3b. The phenomenon of visible changes corresponding to heart activity in the phase component were found to occur primarily at 128 kHz and above. The relative changes caused by breathing and heart activity for different locations suitable for wearable monitoring are presented in the following sections.
Figure 3.3: Changes in the magnitude (a) and phase (b) components of recorded bioimpedance at the chest location. The stimulation frequency used was 128 kHz and the recording time was 60 seconds.

The relative change in measured bioimpedance caused by cardiac activity is presented in Figure 3.4. The figure shows the relative change (y-axis) of the magnitude, Figure 3.4a, phase Figure 3.4b, real part, Figure 3.4c, and imaginary part, Figure 3.4d, of the impedance across 10 candidate frequencies (x-axis). Here, the relative change in most categories is highest in very low frequencies and frequencies of 64 kHz or above. The highest relative changes are in the imaginary and phase components.
**Figure 3.4:** Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to heart activity measured across the chest for selected frequencies.

Relative change in measured impedance corresponding to the average breath depth as measured on the chest is shown in Figure 3.5. The figure shows the
relative change (y-axis) of the magnitude, Figure 3.5a, phase, Figure 3.5b, real part, Figure 3.5c, and imaginary part, Figure 3.5d, of the impedance across 10 candidate frequencies (x-axis). Generally, the changes are consistent across frequencies, but there is a smaller change in the frequencies of 2–16 kHz.
Figure 3.5: Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to respiration measured across the chest for selected frequencies.
3.7.2 Forearm Measurements

Forearm measurements are commonly used in research studies for respiratory and heart activity monitoring. Figure 3.6 below presents a representative sample of a full sixty second measurement with a stimulation frequency of 8 kHz on the forearm. Here, the magnitude representation, Figure 3.6a, has no clear trends, but the phase, Figure 3.6b, shows clear changes corresponding to heart activity in the form of small spikes corresponding to arterial pulsing as well as to respiration in the form of the mild, inverted trapezoidal modulation, most noticeable between the peaks in phase at 29 and 38 seconds. This may suggest that the phase and quadrature components are more sensitive to changes due to the measured physiological activities. In this section, the evaluated stimulus frequencies are all strong candidates for monitoring heart activity, though increasing the stimulation frequency showed slightly higher percent changes in the phase.
Figure 3.6: Changes in the magnitude (a) and phase (b) components of recorded bioimpedance at the forearm location, stimulation frequency of 64 kHz recorded for 60 seconds.

The measurements corresponding to heart activity for the forearm are presented in Figure 3.7. There are consistent relative changes (y-axis) across all stimulation frequencies for the magnitude, Figure 3.7a, real, Figure 3.7c, and imaginary, Figure 3.7d, parts of the impedance. However, the phase, Figure 3.7b, change increases with frequency (x-axis), though it is still a small relative change. This is due to the absolute value of the real part decreasing relative to the imaginary part, causing a larger relative change in phase with increasing frequency.
Figure 3.7: Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to heart activity measured on the forearm measured for selected frequencies.

Presented in Figure 3.8 are the relative changes (y-axis) corresponding to respiration at various stimulation frequencies (x-axis). Similar to the heartbeats,
there are higher relative changes in the phase, Figure 3.8b, due to the decreased magnitude of the real part relative to the imaginary part. With the exception of the phase, there is a consistent change across all frequencies for respiratory activity measured at the forearm. Only the imaginary part, Figure 3.8d, exceeds 0.1% change, for three stimulation frequencies.
Figure 3.8: Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to respiration measured on the forearm for selected frequencies.
3.7.3 Wrist-to-Wrist Measurements

Measurement with the novel wrist-to-wrist measurement location are presented in this section. A representative sample of a sixty second recording at this location with a simulation frequency of 2 kHz is presented in Figure 3.9. The magnitude component of the impedance, Figure 3.9a, is dominated by the trapezoidal changes corresponding to respiratory activity, though heart activity is visible as a small sinusoidal variation. Changes in the phase component, Figure 3.9b, correspond strongly with respiration. For this section, AFE4300 results are added at 8, 16, and 32 kHz.

![Figure 3.9: Changes in the magnitude (a) and phase (b) components of recorded bioimpedance at the wrist-to-wrist location, stimulation frequency of 2 kHz recorded for 60 seconds.](image)

The relative changes (y-axis) in the magnitude, Figure 3.10a, phase, Figure 3.10b, real, Figure 3.10c, and imaginary, Figure 3.10d, components of bioimpedance
corresponding to heart activity for the wrist-to-wrist sensing location are presented in Figure 3.10. The highest relative changes occur in stimulation frequencies (x-axis) between 32 and 128 kHz. The frequencies above 32 kHz have an average change of nearly double that of frequencies below 32 kHz, though 8 kHz shows a stronger response than 1–4 kHz and 16 kHz. The AFE 4300 measurements provided a similar response, but only for 8, 16, and 32 kHz.
Figure 3.10: Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to heart activity measured across the body from left wrist to right wrist for selected frequencies.
3.7.3.1  Respiration

The relative changes (y-axis) corresponding to respiration are presented in Figure 3.11. Generally, the relative change increases with higher stimulation frequencies (x-axis). The frequencies above 8 kHz have an average change of nearly double that of frequencies below 8 kHz in all components, except for phase. The AFE 4300 measurements provided a similar response for the breathing, but only for 8, 16, and 32 kHz.
Figure 3.11: Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to respiration measured across the body from left wrist to right wrist for selected frequencies.
3.7.4 Wrist-to-Finger Measurements

Measurements taken with the novel wrist-to-finger electrode configuration are presented in this section. A representative time series measurement is presented in Figure 3.12. Similar to the chest measurements, the changes corresponding to respiratory activity are clearly identified by the trapezoidal pattern in the magnitude component, Figure 3.12a, while the changes corresponding to heart activity are less visible. The phase component, Figure 3.12b, shows clear heart activity, and some weakly correlated changes with breathing.

![Figure 3.12](image)

**Figure 3.12**: Changes in the magnitude (a) and phase (b) components of recorded bioimpedance at the wrist-to-finger location, stimulation frequency 64 kHz recorded for 60 seconds.

3.7.4.1 Heart Activity

The relative changes (y-axis) due to heart activity measured from the left wrist to the right index finger is presented in Figure 3.13. Note that stimulation
frequency 256 kHz is missing (due to data corruption). Generally, lower stimulation frequencies (x-axis) have higher relative changes in all components. The large change in the imaginary component is due to the smaller absolute value of this component, relative to the other components, Figure 3.13.
Figure 3.13: Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to heart activity measured across the body from left wrist to right thumb and forefinger for selected frequencies.
3.7.4.2 Respiration

Figure 3.14 shows the relative changes (y-axis) corresponding to respiration between stimulation frequencies (x-axis) for this location. Note that frequency 256 kHz is missing (data corruption). There seem to be no clear trends in the frequencies in this location. The relative change in the imaginary component is larger than that of the real, but the overall magnitude of it is much smaller.
Figure 3.14: Relative changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to respiration measured across the body from left wrist to right thumb and forefinger for selected frequencies.
3.8 Discussion

Based on the results of this study, which are discussed further in [159], a subset of these frequencies (16, 32, 64, 128, and 512 kHz) along with a subset of electrode configurations (wrist to wrist and wrist to finger) were chosen to be evaluated with a larger population sample. The results of this larger study are discussed in the next chapter.
Experimental Evaluation of Methods Suitable for Wearable Real-time Physiological Monitoring

This chapter presents the primary experimental results of bioimpedance monitoring for wearable physiological monitoring applications. First, details of the subjects in the study are given. Then, the overall results for each evaluated electrode configuration are presented. Next, an overview of each individual frequency is given. Finally, heart activity and respiration results are presented. The summary section contains a condensed version of the heart and breathing activity monitoring as a function of the stimulation frequency.

4.1 Subjects

Ten subjects were evaluated in this study. Age: 51.3 ± 17.53 years. Height: 66.9 ± 3.2 inches. Weight: 171 ± 26.15 pounds. Five male and five female subjects were included. This study was approved by the UAH IRB document (EE202284, 5 December 2022).

4.2 Evaluation of Bioimpedance Magnitude by Electrode Configuration

4.2.1 Wrist to Opposite Wrist Electrode Configuration

In this section, a broad overview of the time series measurements for all ten subjects and frequencies in the wrist-to-wrist configuration is presented. In each
figure, the x-axis (time) displays the time during a one-minute experiment. The y-axis (impedance), displays the magnitude of the impedance ($|Z(\Omega)|$) during the measurement. Notice that the mean value of the impedance varies significantly between subjects, and, with few exceptions, the general ordering of subjects (noted by the color of the line) is similar in each plot.

**Figure 4.1:** The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Wrist configuration for all ten subjects at 16 kHz.
Figure 4.2: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Wrist configuration for all ten subjects at 32 kHz.

Figure 4.3: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Wrist configuration for all ten subjects at 64 kHz.
Figure 4.4: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Wrist configuration for all ten subjects at 128 kHz.

Figure 4.5: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Wrist configuration for all ten subjects at 512 kHz.
4.2.2 Wrist to Opposite Fingers Electrode Configuration

In this section, a broad overview of the time series measurements for all ten subjects and frequencies in the wrist-to-finger configuration is presented. In each figure, the x-axis (time) displays the time in seconds during a one-minute experiment. The y-axis (impedance), displays the magnitude of the impedance $|Z(\Omega)|$ during the measurement. Notice that the mean value of the impedance varies significantly between subjects, and, with a few exceptions, the general ordering of subjects (noted by the color of the line) is similar in each plot. Note that the 512 kHz measurement of subject 3 in Figure 4.10 is cut short, due to the high amount of discontinuities (missed values) removed during the data processing.

**Figure 4.6:** The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Finger configuration for all ten subjects at 16 kHz.
Figure 4.7: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Finger configuration for all ten subjects at 32 kHz.

Figure 4.8: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Finger configuration for all ten subjects at 64 kHz.
Figure 4.9: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Finger configuration for all ten subjects at 128 kHz.

Figure 4.10: The time series of the magnitude $|Z(\Omega)|$ measurement of the Wrist to Finger configuration for all ten subjects at 512 kHz.
4.3 Measurement Sensitivity as a Function of the Excitation Frequency

In this section, the FFT’s of the bioimpedance signal for each subject are presented. Specifically, each pair of plots shows the FFT evaluated for each excitation frequency in a given configuration. These figures present a comprehensive spectral analysis of power spectra, spanning a range of 0 to 5 Hz, for each FFT. This selected range is relevant for the changes generated by breathing and heart activity. Each FFT provides valuable insight into the individual nature of the subject’s vital signs, with specific emphasis on primary respiration frequencies of 0.125, 0.25, and 0.5 Hz and primary cardiac frequencies that vary between 1 and 1.6 Hz depending on the subject. The spread spectra around the heartbeat peak is a measure of heart rate variability, where a higher variance in heart rate will result in a shorter, wider peak. Throughout these figures, take note of the respiration and heart beat spectra. While the respiratory peak is always the strongest, there is significant variance in the heart beat range in regards to the size of the peak compared to the surrounding noise.

For subject 1, the FFT’s in Figure 4.11 and Figure 4.12 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT varies between 1 and 1.5, corresponding to 60-90 BPM. The primary difference between these two configurations is the significant noise (vertical offset) of the 32 kHz excitation in the wrist-to-wrist configuration. The wrist-to-wrist location generally has a stronger heartbeat spectrum, between 1 and 1.5 Hz, other than the outlier of 32 kHz. In neither configuration does the 512 kHz
excitation have a strong heart beat spectrum. All candidate frequencies have strong respiration-induced spectral components.

**Figure 4.11**: Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 1.
For subject 2, the FFT’s in Figure 4.13 and Figure 4.14 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT varies between 1.1 and 1.6, corresponding to 66-96 BPM. Here, the primary difference between the two electrode configurations is the strong secondary peak at 0.4 Hz for the wrist-to-wrist configuration, Figure 4.13, which does not occur as strongly in the wrist-to-finger configuration of Figure 4.14. Upon further inspection of the time series, this subject did not strictly follow the breathing protocol, instead approximating a square wave with their breathing pattern, causing the changes in the FFT. Additionally, there are two peaks in the heartbeat range between 1 and 1.5 Hz.
**Figure 4.13:** Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 2.

**Figure 4.14:** Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 2.
For subject 3, the FFT’s in Figure 4.15 and Figure 4.16 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT can be clearly identified as 1.1 Hz, corresponding to 66 BPM, and with a low heart rate variability. Here, there are no significant differences in the peaks identified between the two electrode configurations.

Figure 4.15: Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 3.
For subject 4, the FFT’s in Figure 4.17 and Figure 4.18 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT is not easily identified above noise, likely due to a high rate variability. However, this individual exhibits a strong respiratory response. Otherwise, there are no significant differences between the two electrode configurations.

**Figure 4.16**: Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 3.

![Magnitude vs Frequency graph]
Figure 4.17: Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 4.

Figure 4.18: Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 4.
For subject 5, the FFT’s in Figure 4.19 and Figure 4.20 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT can be identified as 1.25 Hz, corresponding to 75 BPM. Here, there are no significant differences between the two electrode configurations, other than the outlier of 64 kHz in the wrist-to-finger configuration. Note the higher peak at 0.125 Hz and increased noise between 0.3-0.7 Hz for the wrist-to-finger configuration.

**Figure 4.19:** Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 5.
Figure 4.20: Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 5.

For subject 6, the FFT’s in Figure 4.21 and Figure 4.22 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT can be identified as 1.15 Hz, corresponding to 75 BPM, with very low heart rate variability. Here, there are no significant differences between the two electrode configurations. In both configurations, the harmonics of the heart beat can be clearly identified (2.2-2.3, 3.3-3.5, and 4.3-4.7 Hz).
Figure 4.21: Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 6.

Figure 4.22: Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 6.
For subject 7, the FFT’s in Figure 4.23 and Figure 4.24 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT can be identified as 1.6-1.7 Hz, corresponding to 90-95 BPM, with a low heart rate variability. Here, there are no significant differences between the two electrode configurations. In both configurations, the harmonics of the heart beat are clearly identified around 3.2-3.4 Hz. In the wrist-to-finger configuration, the 512 kHz excitation has higher noise (between 2-3 Hz, specifically), which is the only major difference between the two configurations in this format.

**Figure 4.23**: Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 7.
Figure 4.24: Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 7.

For subject 8, the FFT’s in Figure 4.25 and Figure 4.26 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this subject, the heart rate from the FFT can be identified around 1.1 Hz, corresponding to a heart rate of 60-65 BPM. Here, there are only slight differences between the two electrode configurations. The 512 kHz excitation produces the strongest heartbeat response for both configurations. However, the noise is higher for 512 kHz as well. Generally, the wrist-to-finger configuration has lower noise for this subject. The harmonics of the heartbeat are also more clearly visible in the wrist-to-finger configuration, which is the primary difference between these configurations.
Figure 4.25: Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 8.

Figure 4.26: Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 8.
For subject 9, the FFT’s in Figure 4.27 and Figure 4.28 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this individual, the heart rate from the FFT is not clearly identified, but there are wide peaks around 1.25 Hz, corresponding to 70 BPM. Here, there are some differences between the two electrode configurations. Note that in Figure 4.27, the heartbeat peaks around 1.25 Hz are clearly identified, while in Figure 4.28, only 16 and 512 kHz have clear peaks.

Figure 4.27: Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 9.
Figure 4.28: Spectrum of the bioimpedance measured at the Wrist to Finger configuration for Subject 9.

For subject 10, the FFT’s in Figure 4.29 and Figure 4.30 clearly show the respiratory signals of 0.125, 0.25, and 0.5 Hz. For this subject, the heart rate from the FFT can be identified around 1.1 Hz, corresponding to a heart rate of 70 BPM. There are significant differences for this individual between the two electrode configurations. Particularly, the heartbeat peaks, clearly identifiable around 1.3 Hz in the wrist-to-wrist configuration, are surrounded by significant noise (specifically around 0.75 Hz) in the wrist-to-finger configuration and are not clearly distinct from the surrounding spectra. In the wrist-to-wrist configuration, there is a dip in the power at 1 Hz which is not present in the wrist-to-finger configuration. While all frequencies show similar respiration spectra, the heart beat spectra varies. In the wrist-to-wrist configuration, only the 512 kHz frequency
does not show a clear heart beat peak, which could be due to a number of factors, including increased heart rate variability, movement leading to decreased electrode adhesion, etc.

**Figure 4.29:** Spectrum of the bioimpedance measured at the Wrist to Wrist configuration for Subject 10.
4.4 Assessment of Changes in Bioimpedance Caused by Heart Rate

In this section, the impedance change due to a heartbeat is evaluated for all ten subjects and five frequencies across both electrode configurations. In Figure 4.31, the heartbeats are separated by frequency, with 16 kHz located at the top and the frequencies presented in ascending order to 512 kHz for the wrist-to-wrist configuration. Similarly, Figure 4.32 presents the heartbeats for the wrist-to-finger configuration. Each of these figures presents a two second window of all identified heartbeats averaged together. Therefore, the average change due to an average heartbeat for each subject/frequency/configuration can be evaluated. Notice that the heartbeats are centered at the point of peak change, or highest derivative,
during the heart beat, which occurs just after the peak impedance. Since the average heart rate of the subject sample is approximately 75 beats per minute, the previous and following heartbeats can be seen at the edges of the graphs (between -1 and -0.8 seconds and between 0.8 and 1 seconds, respectively).
Figure 4.31: Time series of an average bioimpedance measurement aligned with heartbeats for the Wrist-to-Wrist Configuration across all subjects; the frequencies 16 kHz, 32 kHz, 64 kHz, 128 kHz, 512 kHz are shown in subplots arranged from top to bottom.
Figure 4.32: Time series of an average bioimpedance measurement aligned with heartbeats for the Wrist-to-Finger Configuration across all subjects; the frequencies 16 kHz, 32 kHz, 64 kHz, 128 kHz, 512 kHz are shown in subplots arranged from top to bottom.
4.5 Assessment of Changes in Bioimpedance Caused by Breathing Rate

In this section, the impedance change due to individual breaths is evaluated for all ten subjects and five frequencies across both electrode configurations. In Figure 4.33, the breaths are separated by frequency, with 16 kHz located at the top and the frequencies presented in ascending order to 512 kHz for the wrist-to-wrist configuration. Similarly, Figure 4.34 presents the breaths for the wrist-to-finger configuration. Each of these figures presents a ten second window of all identified breaths averaged together. Therefore, the average change due to an average breaths for each subject, frequency, and configuration can be evaluated. Notice that the breaths are centered at the peak of the exhalation, the lowest impedance during the breath. Here, all subjects followed the same breathing protocol. In both configurations, subject 7 is a strong outlier, generating a noticeably larger impedance change in each subplot. Additionally, Subject 2’s deviations from the breathing protocol are clearly noticeable in the top two plots of Figure 4.33.
Figure 4.33: Time series of an average bioimpedance measurement aligned with breaths for the Wrist-to-Wrist configuration across all subjects; the frequencies 16 kHz, 32 kHz, 64 kHz, 128 kHz, 512 kHz are shown in subplots arranged from top to bottom.
Figure 4.34: Time series of an average bioimpedance measurement aligned with breaths for the Wrist-to-Finger configuration across all subjects; the frequencies 16 kHz, 32 kHz, 64 kHz, 128 kHz, 512 kHz are shown in subplots arranged from top to bottom.
4.6 Discussion

In this section, the changes in complex bioimpedance due to respiratory and cardiac activity are summarized for each configuration. These plots use the normalized relative value of the impedance, as values of the time series with the mean subtracted and divided by the mean of the time series. The results from all ten subjects are presented as time series plots in the previous sections.

In Figure 4.35, the summary of changes in the magnitude (a), phase (b), real (c), and imaginary (d) parts of the impedance for heart beats in the wrist to wrist configuration are presented. Similarly, Figure 4.36 shows the same for the wrist-to-finger configuration. For Figure 4.35, notice that 64 kHz and 128 kHz have the highest changes in phase and the imaginary part of the impedance, while 16 kHz has the highest change in real and magnitude components. In Figure 4.36, 16 kHz appears to be the frequency with the highest overall change due to heart activity for the wrist-finger configuration.

In Figure 4.37, the summary of changes in the magnitude (a), phase (b), real (c), and imaginary (d) parts of the impedance for respiration in the wrist to wrist configuration are presented. Similarly, Figure 4.38 shows the same for the wrist-to-finger configuration. In Figure 4.37, there is not a clear best frequency for evaluating breathing. However, 128 kHz and 512 kHz have the strongest changes in the imaginary part of the impedance. In Figure 4.38, 64 kHz appears to be the frequency with the highest changes across all four components, but the absolute change over the other frequencies is relatively small.
Figure 4.35: Mean absolute changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to heart activity measured across the body from left wrist to right wrist for selected frequencies.
Figure 4.36: Mean absolute changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to heart activity measured across the body from left wrist to right fingers for selected frequencies.
Figure 4.37: Mean absolute changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to breathing measured across the body from left wrist to right wrist for selected frequencies.
Figure 4.38: Mean absolute changes in the (a) magnitude, (b) phase, (c) real, and (d) imaginary components of bioimpedance corresponding to breathing measured across the body from left wrist to right fingers for selected frequencies.
Perhaps the most surprising result of this work is the small difference between wrist-to-wrist and wrist-to-finger measurements. While the absolute magnitude of the components was greater for wrist-to-finger configurations (typically 20 Ω higher for the real part and the magnitude of the impedance), the changes induced by breathing and heart activity were similar, typically within one percent. From a purely signal to noise perspective there would seem to be little advantage to choosing the wrist-wrist configuration over the wrist-finger. However, applications such as smart textiles with electrodes embedded in the sleeves could easily justify the trade-off.

The variations in measured impedance caused by breathing, on average, were 2.5 Ω, but one subject had a change as high as 8 Ω. The changes due to heart beats were less varied between subjects, with 0.25 Ω on average, an order of magnitude smaller than the changes due to respiration. This was consistent across all frequencies and candidate locations, an important result for future wearables and demonstrating the viability of high frequency bioimpedance monitoring of physiological activity. The primary difference between the evaluated frequencies was the change in phase, Θ, due to breathing. This work found that the three middle frequencies, 32, 64, and 128 kHz, showed higher changes in the phase and imaginary part of the impedance than the lowest (16 kHz) and highest (512 kHz) frequencies. This finding points to an underlying physiological phenomenon beyond the scope of this dissertation but is perhaps worth further investigation.

Generally, each candidate frequency is found to be suitable for cardiorespiratory monitoring. Generally, each candidate frequency is found to be suitable for
cardiorespiratory monitoring. However, there are some frequencies that may be better suited for specific wearable monitoring applications. The lowest frequencies in this study, 16 and 32 kHz, generally had lower noise as evaluated by the FFT. Simultaneously, they tended to have a lower magnitude of change. The highest frequency evaluated, 512 kHz, was typically suitable for cardiorespiratory monitoring, but, as expected, had the highest amount of noise. As discussed in Chapter 2, parasitic capacitance can heavily affect these measurements, and high frequencies may be more sensitive to motion.

Notably, the FFT plots capture nuanced variations in the breathing and heart rate activity for each of the ten subjects, highlighting the utility of bioimpedance for assessing both vital signs simultaneously. The twenty different FFT’s, two for each subject, and the overall spectral analysis presented provides an in-depth view of the individual nature of vital signs. These results emphasize the importance of personalized health assessments and the need to assess individual variations in physiological activity with bioimpedance.

A surprising result of this work is the identification of a potential source of error in Cole-Cole model-based body composition. Changes in impedance due to breathing, between 2 and 6 Ω for the range of subjects, can have significant impacts on the calculated body composition. Although this source of error is minimized by the subject refraining from deep breaths, it is unclear whether the full-lungs measurement may be closer to the "true" body composition than the empty-lungs measurements. However, variations caused by breathing must be taken into account during body composition analysis, that would require data
acquisition during multiple breathing cycles or modeling of the change using a single cycle.

As discussed in the introduction, remote patient monitoring (RPM) is a topic of increasing importance in today’s connected world, potentially bringing high-quality care to increasingly larger segments of the population. Building from the work of Blanco-Almazan [152] and Jafari [70], this dissertation extends the application of real-time bioimpedance to a smartwatch-style measurement. The primary differentiating factors for this work are the two electrode configurations studied, specifically aimed at enabling wrist-wearable applications, and the candidate frequencies evaluated, specifically evaluating 512 kHz as a candidate frequency, which is typically excluded from consideration in bioimpedance monitoring studies.
Implementation of the Wearable Real-time Physiological Monitor

This chapter details the design and implementation of a real-time bioimpedance monitoring system. After evaluation and experimentation of several existing controllers from Analog Devices, Texas Instruments, and Maxim Integrated, MAX30009 from Maxim Integrated was selected for sensor implementation. The MAX30009 bioimpedance controller is integrated as a daughter card for the existing low power euHy controller board. The board is software compatible with the Teensy LC based system, and contains a custom inter-integrated circuit (I2C) connector extension interfacing with a PPG/ECG sensor. This configuration allows synchronized physiological monitoring and assessment of changes in bioimpedance caused by heart beats and breaths. The final system is validated with a two subject pilot study. This study was approved by the University of Alabama in Huntsville (UAH) institutional review board (IRB) document (EE202284, 5 December 2022).

5.1 Hardware Implementation of Bioimpedance Monitoring

5.1.1 euHy Motherboard

A UAH euHy controller board was developed as a low power motherboard for application specific sensor boards, such as [160]. The board is powered by a LiIon/LiPolymer battery, a Teensy LC compatible primary processor
MKL26Z64VFT4, Cortex-M0+ with 48 MHz clock, Silicon Labs WiFi controller, on-board 3 axis accelerometer MMA8653, and application specific connectors for additional sensor boards. The board features a two-row, 10-pin header with a serial peripheral interface (SPI) connection for custom adapter boards and general purpose I/O pins for the controller of the daughter cards. The euHy controller features a five pin FPC connector with an I2C interface which can be used with any peripheral board. In this system, it is typically used with a custom PPG/ECG board with Maxim Integrated MAX 86150 controller [161]. Both boards are shown in Figure 5.1. Overall, this system was chosen for ease of implementation and software support developed in previous UAH projects [160]. A dedicated connector is used for connection with capacitance sensors, the main processor features high quality capacitive sensing and capacitance to digital conversion. Additional headers can be used for analog inputs, GPIO, and UART connections.

5.1.2 MAX30009 Daughter Board

The MAX30009 daughter board was specifically designed to interface with the euHy controller. Only two other integrated circuit devices are present on the board: a 1.8 V low noise power supply, and logic level shifter. These components allow the daughter board to be used with other boards in the future. The two-row, 10-pin header contains the SPI connection, power and ground, as well as an interrupt pin and external clock input. This allows the controller to generate custom clock signals for use in the MAX 30009 circuit. A 3-D model of this board is shown in Figure 5.2.
Figure 5.1: The euHy motherboard, MAX 81650 PPG/ECG board, and MAX 30009 bioimpedance board.

Figure 5.2: A 3-D model of the MAX30009 daughter board.
5.2 Software Implementation of Bioimpedance Monitoring

The primary goal of the software is to collect time-synchronized PPG, ECG, and bioimpedance signals using the euHy Teensy LC. The software primarily does this using the following high level tasks:

- Initialize sensors (MAX30009 and MAX86150)
- Set bioimpedance stimulation frequency and drive settings
- Collect bioimpedance calibration data
- Collect data at set sample rate
- Send data to UAH Serial App

The critical task for the software is the generation of the bioimpedance stimulation frequencies and drive settings. The stimulation frequencies and sample rates of the MAX30009 are derived from the clock frequency and manipulated through dividers and multipliers, and cannot be set arbitrarily. Therefore, some combinations of frequency and sample rate are not possible. Therefore, care must be taken to not violate the ranges of the ADC and phase-locked loop (PLL) clocks. A simple function to generate frequencies and sample rates within these constraints was written. After the frequency and sample rate is set, the program reads from the FIFO queues of the MAX sensors at set times. To ensure the data collected is the latest sample, the FIFO’s are routinely flushed. Finally, this data is collected and sent to the UAH serial app during debugging, or processed in real time to
determine heart rate, breathing rate, or complex bioimpedance of the tissue. The main controller allows real-time execution of simple processing tasks, but RAM limitations prevent analyses that require longer buffering of signals (only 8KB of RAM).

5.3 Subject Measurements

As a proof of concept and sensor operation, two subjects were measured with multimodal sensors. The experimental setup included three PPG sensors, two ECG sensors, bioimpedance, and a clinical quality Nexfin HD monitor [162]. For this study, the bioimpedance stimulation frequency was set to 64 kHz. Both the MAX30009 and MAX86150 were set to a 400 Hz sample rate. The change of bioimpedance during heart beats is similar to the change in PPG, as shown in Figure 5.5. Therefore, the same algorithms to detect heartbeats were used from changes in bioimpedance. Real-time assessment of the breathing rate was evaluated from periods of change of bioimpedance calculated between successive zero-crossings, as shown in Figure 5.3. The minimum peak distance and peak prominence arguments were adjusted to identify the candidate peaks while ignoring peaks too close together or too small. The interval between these identified breaths gives the instantaneous breathing rate.

A pilot study was conducted with two subjects (male, ages 63 and 28). The experiment included paced breathing with breathing rate varying from 15 BPM to 2 BPM and back to 15 BPM. The breathing was indicated using a custom program to guide the user: the LED turned on during inhale cycle and turned off
during exhale cycle. Paced breathing was used as a method to assess changes in bioimpedance during different phases of the breathing cycle. This synchronized monitoring allowed the precise annotation of the breathing phases.

5.3.1 Experimental Results: S1

In Figure 5.6, 67 total breaths from S1 are identified using the bioimpedance data. It is interesting to note that even short or interrupted breaths were correctly identified using bioimpedance, as demonstrated in Figure 5.6 at time around 6.5 minutes. In Figure 5.7, heart beat detection using the first derivative of the bioimpedance signal is demonstrated. The accuracy of the RR IBI assessment using bioimpedance and PPG measurements were compared with a clinically acceptable measurement from the Nexfin HD, as shown in Figure 5.4. The results of the analysis during a five minute experiment are shown in Table 5.1. The average IBI error is $-3.9 \pm 10.2 \text{ ms}$, similar to the error generated using PPG measurement ($-3.9 \pm 6.6 \text{ ms}$). Heart rate detection using bioimpedance did not miss any heartbeats during the experiment.

Two full inhalations and exhalations are shown in Figure 5.3 to illustrate the change of bioimpedance during a typical breath. For these deep breaths, a change in impedance of nearly $1.6 \Omega$ peak to peak due to breathing can be seen, equivalent to relative change of $1.75\%$. Three heartbeats are shown in Figure 5.5. The unfiltered and filtered bioimpedance data is shown alongside the PPG signal. The lag between the PPG and bioimpedance data is caused by the pulse arrival time at the finger.
Figure 5.3: A window of two full inhalations and exhalations for S1.

Figure 5.4: Comparison of heart rate derived from bioimpedance and Nexfin HD; subject S1; test duration = 300 s.
Figure 5.5: A window of three full heartbeats for S1.

Figure 5.6: The identified breaths (top) using bioimpedance and calculated instantaneous breathing rate (bottom) for S1 throughout the experiment.
Figure 5.7: The identified heartbeats (top) using bioimpedance and calculated instantaneous heart rate (bottom) for S1 throughout the experiment.

Figure 5.8: The identified heartbeats (top) using a PPG measurement and calculated instantaneous heart rate (bottom) for S1 throughout the experiment.
Table 5.1: Analysis of IBI intervals measured by bioimpedance, Nexfin HD, and PPG; subject S1; test duration = 300 s.

<table>
<thead>
<tr>
<th>Subject 1</th>
<th>Nexfin</th>
<th>BioZ</th>
<th>PPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IBI Interval [ms]</td>
<td>632</td>
<td>628</td>
<td>628</td>
</tr>
<tr>
<td>IBI Error/Nexfin (mean ± std) [ms]</td>
<td>-3.9±10.2</td>
<td>-3.9±6.6</td>
<td></td>
</tr>
<tr>
<td>Max IBI Error/Nexfin [ms]</td>
<td>37.5</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5.9: The identified breaths (top) using bioimpedance and calculated instantaneous breathing rate (bottom) for S2 throughout the experiment.

5.3.2 Experimental Results: S2

In Figure 5.9, 66 total breaths from S2 are identified using the bioimpedance data. In Figure 5.10, heart beat detection using the first derivative of the bioimpedance signal is demonstrated.
Figure 5.10: The identified heartbeats (top) using bioimpedance and calculated instantaneous heart rate (bottom) for S2 throughout the experiment.

Figure 5.11: The identified heartbeats (top) using a PPG measurement and calculated instantaneous heart rate (bottom) for S2 throughout the experiment.
5.4 Real-time Implementation

The MAX30009 bioimpedance sensor provided a higher quality of signal than previously used controllers. Therefore, simple signal processing algorithms were used for detection of heart rate and breathing rate. The algorithms can run in real-time on a low power microcontroller with only 8K of RAM, which makes it suitable for a wearable sensor with long battery life.

5.5 Discussion

This chapter detailed the implementation of a bioimpedance-based monitoring system. The system is able to successfully monitor heart rate and breathing rate in real time. The average IBI error was 3.9 ms, or 0.6%. It was demonstrated
that bioimpedance can be used to monitor breathing and heart activity, in addition to body composition and fluid distribution. The proposed method is suitable for wearable monitoring applications.

The findings of this work suggest that the bioimpedance monitoring system built could be immediately adapted and implemented in wearable monitoring configurations. This could be especially useful in RPM applications, where a simple wearable device such as a wristwatch could be used to continuously monitor the progression of COPD or other respiratory diseases. The ability to measure cardiorespiratory function using low-cost bioimpedance hardware in a wearable device could greatly improve the accessibility and affordability of RPM for patients and prevent unnecessary hospitalizations. There is significant potential for at-home monitoring of the progression of respiratory illnesses, such as pneumonia and COVID-19, due to the simultaneous monitoring of heart and lung function.

There is an opportunity for the integration of bioimpedance monitoring into clinical practice specifically for cardiorespiratory monitoring, while simultaneously enabling other applications of bioimpedance, such as body composition monitoring from the same device. In the future, a wrist-wearable device with bioimpedance and other sensors could serve as an invaluable resource for remote patient monitoring, enabling applications such as monitoring of blood pressure, heart rate, respiration, and body composition in a low-cost device. Other applications could also use such a device. Athletic training in particular could use these findings in conjunction with other devices to develop more advanced monitoring methods for fitness
progression and fatigue. Other consumer applications such as stress monitoring could use a similar method for evaluating the stress of an individual.

The electrode configurations studied in this work would primarily enable intermittent cardiorespiratory monitoring, which could be used in conjunction with continuous methods that only use one wrist. Intermittent monitoring could serve as a way to "calibrate" the continuous method without specific intervention, which would enable greater confidence in the measurements. The latest Samsung Galaxy Watch could likely enable this application with existing hardware, which means that this technology could be available to a wide range of consumers who own the device. Overall, these implications suggest that bioimpedance monitoring has the potential to revolutionize cardiorespiratory monitoring and RPM.

The primary limitation for adoption is the lack of wide-scale clinical trials and, historically, the existence of more accurate methods in a clinical or hospital setting. However, bioimpedance monitoring has greatly benefited from the increases in integrated circuit technology, and the accuracy and sensitivity of bioimpedance devices has increased while simultaneously the price has decreased. This suggests a promising future for bioimpedance monitoring in ambulatory settings.

A primary limitation of this work in terms of applicability is the small sample size. A more thorough evaluation realistically would need approximately one hundred subjects of varying ages, sizes, and fitness levels to make a true approximation of the fitness of these methods to the general population.

This study only evaluated five candidate frequencies across a wide range. A more thorough study should evaluate significantly more candidate frequencies
or utilize a wide-band excitation for simultaneous evaluation. This would allow for a more nuanced analysis of the physiological phenomena measured.

These measurements were taken in the same setting, but not simultaneously. While this was unavoidable, it was minimized with rapid serial testing. The only gap between the measurements with the same electrode configuration was the time to reconfigure the measurement device excitation frequency, averaging about fifteen seconds. A longer gap of approximately one minute was used to swap the measurement cables to the other electrode location. A future study may opt to have a separate device and to measure some of the frequencies or configurations simultaneously.

The most significant limitation of the study is lack of funding, leading to a lack of equipment (spirometers, impedance analyzers, etc.) which would make the analysis more medically relevant. An ideal study would use a reference impedance analyzer, spirometer, PPG, ECG, and candidate wearable device simultaneously. This would allow a more thorough analysis to be performed.
Conclusions

CVD and RD are responsible for more than twenty million deaths each year. Early detection and intervention are critical for improving patient outcomes. Bioimpedance-based wearable monitoring provides a promising RPM avenue for continuous monitoring of CVD and RD conditions. This work explored bioimpedance-based methods for heart rate and breathing rate monitoring, using novel electrode configurations, and implemented a custom bioimpedance controller to implement them. This system was validated in a pilot study compared to a clinically validated device.

6.1 Contributions

This work evaluated five candidate excitation frequencies and two candidate electrode configurations for ten separate subjects, and revealed that signals from all candidates were sufficiently good quality to detect both respiratory and cardiac activity, although some outliers were present. Utilizing readily available hardware, it is shown that cardiorespiratory monitoring is achievable with bioimpedance analysis in a smartwatch or other wrist-based device. Additionally, this study filled a gap in the literature by assessing two novel electrode configurations for cardiorespiratory monitoring, as well as higher frequencies (namely, 512 kHz) than what had been studied in the open literature previously. Furthermore, it is shown that deep breathing can influence impedance measurements and hinder body
composition monitoring, making it unclear whether full or empty lungs should be used for such analysis. Finally, a custom PCB was built to implement the MAX30009 bioimpedance controller into the existing euHy controller. This system was evaluated in a two subject pilot study and is able to accurately measure heart rate and breathing simultaneously in real time, validated by the Nexfin HD multimodal monitor. In summary, the individual contributions of this work are the:

- Evaluation of novel electrode configurations for bioimpedance-based wearable monitoring
- Evaluation of stimulation frequencies suitable for bioimpedance-based wearable monitoring
- Custom hardware implementation of MAX30009 bioimpedance controller
- Real-time processing of heart rate and breathing rate
- Demonstrated use of bioimpedance for real time heart rate and breathing rate compared with clinically validated device

6.2 Future Work

While this study used wet Ag/AgCl electrodes, future studies could replace these with metal or textile electrodes for evaluation. The signal to noise ratio of the respiratory signal should be sufficiently high to enable respiratory monitoring, if not also cardiac monitoring.
A study using a wideband excitation could take advantage of measuring multiple frequencies simultaneously at a high sample rate to effectively evaluate the spectral response of the body, rather than measuring them sequentially. While a high sample rate would be crucial to effectively capture physiological phenomena, this is becoming increasingly achievable with advances in integrated circuits.

Future studies would do well to partner with a clinician for this type of evaluation. This could enable a wider population to be evaluated, and also provide some insight into the applicability of the work. Are the candidate configurations, specifically wrist-to-finger, natural enough for a patient or consumer to use effectively? This was beyond the scope of this work, but is a consideration for the applicability of future work.
References


[109] E. T. McAdams, J. Jossinet, A. Lackermieier, and F. Risacher, “Factors affecting electrode-gel-skin interface impedance in electrical impedance to-
mography,” *Medical and Biological Engineering and Computing*, vol. 34, pp. 397–408, Nov. 1996.


[144] A. Guha, D. Arora, and Y. Mehta, “Comparative study of cardiac output measurement by regional impedance cardiography and thermodilution method in


Appendix A: Custom Bioimpedance Controller Hardware

The MAX30009 is only offered in a 2.03 mm x 2.03 mm, 25-pin, 0.4 mm pitch wafer-level package (WLP). This WLP is a sub-type of the ball-grid-array (BGA) package where no bond wires or interposer connections are required. In some cases, BGA devices with pin pitches below 0.5 mm are referred to as micro-BGA devices, but there is no hard definition. BGA devices with pitches as low as 0.3 mm or 0.25 mm can be found in current generation smart phones. While this small pitch size enables this chip to occupy only ≈ 4.09 mm$^2$ of board space, this tradeoff comes with increased manufacturing cost. The small pitch size leads to less total area for the ball joints, and requires more advanced inspections to insure consistent contact quality. Other issues will be covered in this section as well.

A typical PCB layout recommendation for BGA components includes using a fan-out method (colloquially referred to as "dog-bone") to route inner pin traces beyond the BGA component where they can be increased to the appropriate size or transitioned to another layer by a via. However, this method depends on the PCB manufacturer having the minimum trace width requirements to route a trace between BGA pins. For many BGA components, the pin pitch is around 1 mm (≈ 39 mils), and this is not an issue. However, the pins of the MAX 30009 (and other micro-BGA components) are spaced 0.4 mm apart while being .27 mm in diameter. This results in 0.14 mm (≈ 6 mils) of space between pads, not accounting for any keep-out distance.
Many PCB manufacturers have a minimum trace width of six mils, not accounting for keep-out distance around traces and pins, which can itself typically be another six mils. This results in roughly 12 mils (0.28 mm) of space required between BGA pins. In short, many PCB manufacturers today could not route traces from the inner pins out to the rest of the board.

However, other methods exist specifically for micro-BGAs of this size. A leading method is to use via-in-pad construction to transition the connection directly to another layer without routing a trace first. Via-in-pad construction involves drilling a hole through the board, coating it with a conductive layer, and then filling (also known as plugging) the center of the hole with a non-conductive material, often an epoxy. The outer copper layers can then be formed on top of the via, which will conduct the signals to the proper layer. These vias can be quite small. (while certain sizes can be drilled, many via-in-pads are laser drilled, adding costs). This technology comes at an added cost.

Blind vias, which do not penetrate the entire layer stack, can be used to route micro-BGA pins to internal layers. This technique is expensive, as it is can be difficult to precisely drill the via without over-penetrating into undesired layers. While this is a viable technique for high layer count boards, it was not used in this work. With only nine of the twenty-five pins considered internal, a via-in-pad construction transitioning these internal pins to the back layer was sufficient to route all traces.
A.1 Schematic

Because this design is primarily an adapter board, only a few primary components were needed: the MAX30009, a voltage regulator to convert battery voltage to the needed 1.8 V, a ten pin 2.54 mm adapter, and the electrode connections. Maxim Integrated, part of Analog Devices, provides a few schematic variations in the MAX30009 datasheet, and includes the layout files for the MAX30009 EVKIT in its datasheet as well. The PCB schematic is shown in Figure A.1.

A.2 Layout

The board is a four layer stackup in a signal-ground-ground-signal configuration, meaning that the outer (visible) layers carry any signals, while the two inner layers are ground. This configuration is commonly used, and provides excellent noise reduction for a moderate price increase over a two layer board.

3-D renderings of the MAX30009 adapter board are displayed in Figure A.2 and Figure A.3.
Figure A.1: The schematic for the MAX30009 adapter board.
**Figure A.2:** A 3-D model of the designed board.

**Figure A.3:** The backside view of the 3-D model of the designed board.
Appendix B: Processing Code

A primary limitation of the MAX30009 is that the stimulation frequencies and sample rates are both derived from the PLL clock, and only integer divider values are possible. This means that the frequencies and sample rates cannot be set independently of one another, rendering certain configurations impossible. It is critical to not violate these timings. Below, a set of functions written to set the stimulation frequency and sample rate on the MAX30009 are provided.

This process is derived from the MAX30009 datasheet. This is provided here for reference:

```plaintext
To make a BioZ measurement, set the following parameters, and then BIOZ_Q_EN[1](0x20) and BIOZ_I_EN[0](0x20) as needed.

The BioZ sample rate and stimulus frequencies depend on the state of the following fields:

MDIV[9:0](0x17, 0x18)
NDIV[7](0x17)
KDIV[4:1](0x17)
BIOZ_ADC_OSR[5:3](0x20)
BIOZ_DAC_OSR[7:6](0x20)
CLK_FREQ_SEL[5](0x1A)
REF_CLK_SEL[6](0x1A)

The BioZ sample rate is calculated as follows.
SR_BIOZ = PLL_CLK
```
NDIVxBIOZ_ADC_OSR

BIOZ_ADC_CLK = PLL_CLK

NDIV (must be between 16.0kHz and 36.375kHz)

PLL_CLK = MxREF_CLK (must be between 14MHz and 28MHz)

REF_CLK is either 32.0kHz or 32.768kHz depending on the state of the CLK_FREQ_SEL and REF_CLK_SEL bits, and

M = MDIV +1.

The BioZ stimulus frequency is set by the following equation.

F_BIOZ = PLL_CLK

KDIVxBIOZ_DAC_OSR

BIOZ_SYNTH_CLK = PLL_CLK

KDIV (must be between 4096Hz and 28MHz)

The ratio of F_BIOZ to SR_BIOZ must be an integer, so that each BioZ sample is integrated over a given number of stimulus cycles. This ratio, C_BIOZ, is calculated by the following equation.

C_BIOZ = F_BIOZ

SR_BIOZ = NDIVxBIOZ_ADC_OSR

KDIVxBIOZ_DAC_OSR

The procedure for setting the BioZ timing parameters is as follows:

First decide the target stimulus frequency (F_BIOZ) for the BioZ measurement.
If $F_{\text{BIOZ}} < 54,668 \text{Hz}$:
1. Set $\text{BIOZ\_DAC\_OSR} = 256$.
2. Set $\text{KDIV}$ to get $\text{PLL\_CLK}$ in range.
3. Calculate $\text{MDIV} + 1 = \text{ROUND}(\text{PLL\_CLK} / \text{REF\_CLK})$.
4. Set $\text{NDIV}$ to get $\text{BIOZ\_ADC\_CLK}$ in range.
5. Set $\text{BIOZ\_ADC\_OSR}$ so that $C$ is an integer.
6. If $F_{\text{BIOZ}} = \text{BIOZ\_ADC\_CLK} / 8$, set $\text{BIOZ\_CH\_FSEL} = 1$, otherwise set to 0.
7. If $F_{\text{BIOZ}} = \text{BIOZ\_ADC\_CLK} / 2$, set $\text{BIOZ\_INA\_CHOP\_EN} = 0$, otherwise set to 1.

If $F_{\text{BIOZ}} > 54,668 \text{Hz}$:
1. Set $\text{KDIV} = 1$.
2. Set $\text{BIOZ\_DAC\_OSR}$ to get $\text{PLL\_CLK}$ in range.
3. Calculate $\text{MDIV} + 1 = \text{ROUND}(\text{PLL\_CLK} / \text{REF\_CLK})$.
4. Set $\text{NDIV}$ to get $\text{BIOZ\_ADC\_CLK}$ in range.
5. Set $\text{BIOZ\_ADC\_OSR}$ so that $C$ is an integer.
6. Set $\text{BIOZ\_CH\_FSEL} = 0$.
7. Set $\text{BIOZ\_INA\_CHOP\_EN} = 1$.

The code itself is provided here:

```c
uint16_t calculateMDIV(uint32_t pll_clk, uint32_t ref_clk) {
    return (round((pll_clk + ref_clk - 1) / static_cast<double>(ref_clk) - 1));
}

// Function to calculate the NDIV value based on pll_clk
uint8_t calculateNDIV(uint32_t pll_clk) {
```
if ((pll_clk / 512) >= 36375) {
    return 0;
} else {
    return 1;
}
}

// Function to configure BioZ timing parameters
void configureBioZTiming(uint32_t target_stimulus_freq) {
    // Calculate PLL_CLK based on target stimulus frequency
    uint32_t pll_clk = target_stimulus_freq * 256;
    uint16_t mdiv = calculateMDIV(pll_clk, 32768);
    uint8_t ndiv = calculateNDIV(pll_clk);
    uint8_t kdiv = 0;
    uint16_t bioz_dac_osr = 1;
    uint32_t bioz_adc_clk;
    bioz_adc_clk = pll_clk / ndiv;

    if (target_stimulus_freq < 54668) {
        bioz_dac_osr = 256;
        pll_clk = target_stimulus_freq * bioz_dac_osr * 1;
        if ((pll_clk / kdiv) > 28000000) {
            while ((pll_clk / kdiv) > 28000000) {
                kdiv <<= 1;
            }
        }
    }
    else{
}
while ((pll_clk / kdiv) < 14000000) {
    kdiv >>= 1;
}

pll_clk = target_stimulus_freq*bioz_dac_osr*kdiv;
mdiv = calculateMDIV(pll_clk, 32768);
ndiv = calculateNDIV(pll_clk);
kdiv = log(kdiv)/log(2);
}
else{
    kdiv = 1;
    // pll_clk = target_stimulus_freq*1;
    bioz_dac_osr = 32;
    if((target_stimulus_freq* bioz_dac_osr) > 28000000){
        while ((target_stimulus_freq * bioz_dac_osr) > 28000000) {
            bioz_dac_osr >>= 1;
            Serial.println("2");
        }
    }
    else if((target_stimulus_freq* bioz_dac_osr) < 14000000){
        while ((target_stimulus_freq* bioz_dac_osr) < 14000000) {
            bioz_dac_osr <<= 1;
            Serial.println("3");
            Serial.println(bioz_dac_osr);
        }
    }
}

pll_clk = target_stimulus_freq*bioz_dac_osr*kdiv;
mdiv = calculateMDIV(pll_clk, 32768);
ndiv = calculateNDIV(pll_clk);
kdiv = 0x00;
}

Serial.println("mdiv: ");
Serial.println(mdiv);
Serial.println("kdiv: ");
Serial.println(kdiv);
Serial.println("pll_clk: ");
Serial.println(pll_clk);
Serial.println("ndiv: ");
Serial.println(ndiv);
// Set the registers
uint16_t mdivUP = mdiv >> 8;
writeMaxRegister(PLL_CONFIG_1, ((mdivUP << 6) | (ndiv << 5) | (kdiv << 4) | 1));
// writeMaxRegister(PLL_CONFIG_1,0x52);
writeMaxRegister(PLL_CONFIG_2, mdiv & 0xFF);
writeMaxRegister(PLL_CONFIG_3, 0x01);
writeMaxRegister(PLL_CONFIG_4, 0x20); // Additional PLL configuration
// writeMaxRegister(BIOZ_CONFIG_2, (bioz_dac_osr << 6));
Serial.println("3");
// Calculate C_BIOZ
uint16_t c_bioz = (ndiv * 8 * bioz_dac_osr) / 256;

// Set BIOZ_ADC_OSR so that C is an integer
uint8_t bioz_adc_osr = 1;
while (((ndiv * bioz_adc_osr * bioz_dac_osr) % 256) != 0) {
    bioz_adc_osr ++;
}
if(bioz_adc_osr!=1){
    bioz_adc_osr= log(bioz_adc_osr)/log(2);
}

Serial.println("biozDacosr: ");
Serial.println(bioz_dac_osr);
Serial.println(" biozadcosr ");
Serial.println(bioz_adc_osr);
writeMaxRegister(BIOZ_CONFIG_1, (bioz_dac_osr << 6) | (bioz_adc_osr << 3) | 0x7);

writeMaxRegister(BIOZ_CONFIG_2, 0x00);
Serial.println("4");
// Set BIOZ_CH_FSEL based on target stimulus frequency
uint8_t bioz_ch_fsel = (target_stimulus_freq == (32000 / 8))? 0x80 : 0x00;
writeMaxRegister(BIOZ_CONFIG_6, bioz_ch_fsel);

// Set BIOZ_INA_CHOP_EN based on target stimulus frequency
uint8_t bioz_ina_chop_en = (target_stimulus_freq == (32000 / 2)) ? 0x00 : 0x04;
writeMaxRegister(BIOZ_CONFIG_7, bioz_ina_chop_en);
writeMaxRegister(BIOZ_MUX_CONFIG_1, 0x02);
}
Appendix C: Institutional Review Board Approval
Date: 2 February 2023

PI: Emil Jovanov
PI Department: ECE
The University of Alabama in Huntsville

Dear Emil,

The UAH Institutional Review Board of Human Subjects Committee has reviewed your proposal titled: *Evaluation of Novel Bioimpedance Electrode Configurations for Future Wearable Applications* and found it meets the necessary criteria for approval. Your proposal seems to be in compliance with these institutions Federal Wide Assurance (FWA) 00019998 and the DHHS Regulations for the Protection of Human Subjects (45 CFR 46).

Please note that this approval is good for one year from the date on this letter. If data collection continues past this period, you are responsible for processing a renewal application a minimum of 60 days prior to the expiration date.

No changes are to be made to the approved protocol without prior review and approval from the UAH IRB. All changes (e.g. a change in procedure, number of subjects, personnel, study locations, new recruitment materials, study instruments, etc) must be prospectively reviewed and approved by the IRB before they are implemented. You should report any unanticipated problems involving risks to the participants or others to the IRB Chair.

If you have any questions regarding the IRB’s decision, please contact me.

Sincerely,

Ann L. Bianchi
IRB Chair
Associate Professor, College of Nursing