A Portable Bioimpedance Spectroscopy System for Congestive Heart Failure Management

by

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Submitted to the Department of Electrical Engineering and Computer Science
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Abstract

Congestive Heart Failure (CHF) is a chronic medical condition that causes reduced
exercise tolerance, shortness of breath, and fluid buildup in the lungs, legs, and ab-
domen. While CHF-related mortality has reduced in recent years, this reduction has
been accompanied by an increase in hospitalizations and readmissions. This thesis
takes the first steps toward developing a compression sock based bioimpedance mon-
toring system for patients with CHF to help reduce readmission rates. The primary
goals of the thesis were to better understand the calf bioimpedance measurement in
a controlled environment (hemodialysis) and to develop portable hardware to per-
form measurements. Calf bioimpedance was measured on 17 patients undergoing
hemodialysis using both a commercial measurement system and the experimental
system developed in this thesis. Measured calf bioimpedance data showed that more
fluid is recruited from the calf at higher ultrafiltration rates. Fluid shifts into or out of
cells also depended on the ultrafiltration rate. It was also observed that patients with
high calf fluid overload accumulate fluid in the calf, rather than lose it. Bioimpedance
measurements were also compared between the side of the leg and back of the leg.
Changes in calf bioimpedance were higher on the back in 4/7 patients measured, sug-
uggesting that ideal electrode placement depends on the individual patient. Finally, a
portable bioimpedance system was developed and verified against a commercial sys-
tem on the bench and during hemodialysis. The two systems measured bioimpedance
changes within 2 Ω in most cases, with outliers limited to patients with particularly
low calf bioimpedance. While the relationship between calf fluid status and total fluid
status is complex, there is likely utility in calf bioimpedance measurements for CHF
remote monitoring. In the ideal use case, patients will start out at dry weight and
gain comparable amounts of fluid compared with the fluid removed during hemodial-
ysis. This should result in measurable calf bioimpedance changes on the same order
of those measured here. Additionally, rates of both fluid accumulation and removal
will be an order of magnitude slower than hemodialysis, so volume compartments
should be in equilibrium, unlike immediately following hemodialysis as was measured
in this thesis.
Thesis Supervisor: Charles G. Sodini
Title: LeBel Professor of Electrical Engineering
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My partner Kendra Albert not only prepared cookies for my thesis defense (a promise made 3.5 years ago that they may have come to regret), but also supported
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Chapter 1

Introduction and Motivation

1.1 Background

Congestive Heart Failure (CHF) is a chronic disease affecting an estimated 5.7 million people in the United States and costing the US healthcare system over $30 billion [1,2]. Symptoms of CHF include fluid retention in the lungs, legs, and abdomen, shortness of breath, reduced exercise tolerance, and fatigue. CHF disproportionately affects African Americans, who tend to have more risk factors for CHF development and lower socioeconomic status [3]. CHF-related mortality has reduced over the years, but has been accompanied by an increase in hospitalizations and readmissions [4]. The disease must be managed carefully to prevent hospitalizations.

This thesis is the first step toward developing a wearable home monitoring system for patients with CHF. This chapter will provide an overview of CHF, outline the existing work in this area, describe the thesis aims, and provide an outline for the rest of the thesis.
1.2 CHF Overview

1.2.1 Classification

CHF occurs when the heart is unable to meet the metabolic needs of the body. Most cases of CHF are the result of impaired left ventricular (LV) myocardial function. Impaired LV function can be systolic (i.e. the heart has difficulty pumping) and/or diastolic (i.e. the heart has difficulty relaxing). Patients can also present with some combination of diastolic and/or systolic heart failure. The ejection fraction (EF), or the percentage of blood leaving the LV with each cardiac cycle, is used to distinguish patients with reduced ejection fraction (HF$_{r}$EF, i.e. systolic heart failure) and patients with preserved ejection fraction (HF$_{p}$EF, i.e. diastolic heart failure). A healthy EF is between 50 and 70%. An EF 40% or lower is considered to be a reduced EF, with an EF 40% to 50% considered borderline low. Patients with an EF of 50% or greater, but presenting with other signs of heart failure, are considered to have a preserved EF.

Severity of CHF is classified by two systems developed by the American College of Cardiology Foundation / American Heart Association (ACCF/AHA) and the New York Heart Association (NYHA). The ACCF/AHA stages of CHF focus on evidence of structural heart disease and the presence of symptoms, whereas the NYHA classification focuses on the influence of CHF on physical activity and the presence of CHF symptoms at rest and during exercise. The ACCF/AHA guidelines break CHF into Stages A through D, ranging from A (high risk for CHF but without any structural heart disease or symptoms of CHF) to Stage D (refractory CHF requiring specialized interventions). The NYHA classification focuses on the limitations CHF places on physical activity, ranging from Stage I CHF (no limitation of physical activity with no CHF symptoms on exertion) up to stage IV CHF (unable to carry on any physical activity without symptoms of CHF, or symptoms of CHF at rest).
1.2.2 Body Composition

Human body composition can be roughly divided into fat mass (FM) and fat-free mass (FFM, see Figure 1-1). FM and FFM are usually referenced as percentage of the total body weight. Body fat percentages can range from 5% in malnourished individuals to over 30% in morbidly obese individuals. FFM includes Muscle (50%), Bone (16%), Skin (14%), Blood (9%) and Organs (13%). FFM is typically 72-74% water (known as Total Body Water (TBW)), 19-21% Protein, and 7% Bone.

<table>
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<th>Total Body Mass (Weight)</th>
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<td><strong>Fat-Free Mass (FFM, 55-96% Weight)</strong></td>
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<tr>
<td>Muscle (50% FFM)</td>
</tr>
<tr>
<td>Skin (14%)</td>
</tr>
<tr>
<td>Organs (13%)</td>
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<tr>
<td>Total Body Water (TBW, 72-74% FFM)</td>
</tr>
<tr>
<td><strong>Bone (ON)</strong></td>
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</table>

Figure 1-1: Composition of the human body.

TBW is divided into intracellular (ICW) and extracellular water (ECW). ICW is a stand-alone compartment, and ECW is subdivided into interstitial fluid and plasma (see Figure 1-2). ICW is fluid located within cell membranes. Fluid can flow across the cell membrane to and from the ICW. Interstitial fluid is fluid that is located outside cell membranes (other than plasma). Interstitial fluid can flow across the cell membrane into the intracellular space, across capillary membranes to the plasma, or through the lymphatic system to the plasma. Plasma can flow out of the intravascular space through capillary membranes to the interstitial fluid. Ingestion of nutrients and fluids is the main input of plasma. Plasma can exit the body in the form of urine, sweat, excrement, etc.

1.2.3 Pathophysiology of CHF

CHF occurs when the heart is unable to meet the metabolic needs of the body. This often occurs as a result of a previous condition or incident, such as a heart attack or heart valve problems. Fluid overload in CHF patients is caused by a positive feedback
loop. The first thing that occurs in CHF is weakening heart muscle that results in a decreased cardiac output (Cardiac Output = Heart Rate * Stroke Volume). This in turn causes reduced arterial pressure as the Mean Arterial Pressure = Cardiac Output * Systemic Vascular Resistance. The body senses this decrease in Mean Arterial Pressure and a number of compensatory mechanisms go into effect to restore arterial blood pressure. These mechanisms may increase blood pressure and cardiac output in the short term, but they can cause weakened heart muscle in the long term due to the increased cardiac workload of the heart.

There are two main mechanisms in the body by which blood pressure and cardiac output are restored in CHF. In the first mechanism, decreased blood pressure is sensed by baroreceptors, which triggers increasing sympathetic tone. Increased sympathetic tone affects a number of parameters, such as systemic vascular resistance, heart rate, and contractility. In the second mechanism, the hormone Anti-Diuretic Hormone (ADH) is secreted and the Renin-Angiotensin Aldosterone System (RAAS) is activated. These both increase blood volume as another means of raising arterial blood pressure.
Increased sympathetic tone, ADH secretion, and RAAS activation all help restore blood pressure and cardiac output. However, these systems have consequences that leads to a positive feedback loop of worsening CHF. Increased blood volume leads to higher filling pressures in the heart, which increases the workload. Worsening perfusion to the heart weakens itself further. Additionally, worsening perfusion to the lungs and kidneys reduce the delivery of oxygen to vital organs and the elimination of toxins and fluid, which all in turn weaken the heart.

In addition to the impacts above, increased pressure in the intravascular space can cause fluid to seep out into the interstitial space, an outcome known as edema. Edema tends to occur in the lungs (left sided heart failure) and/or the legs (right sided heart failure). It may also occur in the abdomen in some patients (a condition known as ascites). Edema is not only a side-effect of CHF; it can also cause worsening CHF. Fluid buildup in the lungs themselves and in the left ventricle can increase pulmonary artery pressures, which can cause pulmonary hypertension and right sided heart failure.

1.2.4 Timeline to CHF Hospitalization

Implantable monitoring technology has provided insights into how CHF progresses before a hospitalization. Elevated circulating volumes cause filling pressures in
the heart to increase starting around 21 days before hospitalization (see Figure 1-4). Elevated filling pressures are seen in both patients with systolic CHF and patients with diastolic CHF [9]. Only small volume changes are required for elevated filling pressures, which might explain why some patients do not ultimately gain a significant amount of weight before hospitalization.

Alterations in cardiac autonomic control can be detected about a week after filling pressures increase, presumably due to the body’s attempt to maintain and/or increase cardiac output. Heart rate variability (HRV), an indirect assessment of the balance between the parasympathetic and sympathetic nervous systems, has been shown to decrease as patients retain fluid, suggesting increased sympathetic tone [10].

Elevated circulating volume and filling pressures result in pulmonary vasculature engorgement. Increased hydrostatic pressures may also cause fluid to build up in the lungs. Changes in pulmonary volumes can be detected by intrathoracic impedance measurements performed by an implanted device such as a pacemaker or an implantable cardioverter-defibrillator (ICD) up to 14 days before hospitalization [11]. Significant changes in weight and symptoms (if they appear at all), usually begin around a week before hospitalization.

Figure 1-4: Timeline of fluid overload before a CHF-related hospitalization. Each bubble indicates a physiological change before a hospitalization at zero days. Each image beneath represents an example monitoring device at that stage.
1.3 Remote Fluid Status Monitoring in CHF

CHF management involves maintaining and ideally improving heart function and minimizing fluid overload [8]. Fluid management is particularly important because more than 90% of patients hospitalized for worsening CHF present with signs and/or symptoms of fluid overload [12]. CHF patients typically have follow up visits on a regular (e.g. monthly) basis, where the physician will measure the patient’s weight and look for clinical signs of fluid overload through physical examination and auscultation. Patients with CHF are encouraged to weigh themselves regularly, monitor their blood pressure if they have hypertension, and maintain good medication and diet adherence.

At home fluid monitoring solutions for CHF patients include weight monitoring, heart pressure measurements (all invasive), and bioimpedance methods (both invasive and non-invasive). Daily weight monitoring has low levels of patient compliance (a weight measurement was made in 76% of days in [13]) and low sensitivity in predicting CHF decompensation (23% in [13]). Therefore, the focus of this section will be on heart pressure measurements and bioimpedance methods.

1.3.1 Pressure Based Methods

As discussed in section 1.2.4, increases in heart filling pressures are one of the first notable signs of CHF decompensation. Measuring heart filling pressures remotely requires surgery to implant a sensing device. Investigatory CHF pressure monitors include the Medtronic Chronicle (right ventricular pressure sensing), the St. Jude HeartPOD (left atrial pressure sensing), and the CardioMEMS Champion (pulmonary artery pressure sensing).

Despite measuring physiologically relevant information, implantable pressure monitors have not proved to be efficacious thus far. Medtronic’s application for premarket approval for the Chronicle was not approved, citing insignificant reduction in hospitalizations as a “lack of clinical effectiveness” [14]. A clinical study evaluating the safety and clinical effectiveness of the St. Jude HeartPOD was terminated early
“based on futility to reach the primary endpoint” and concerns over implant-related complications [15]. Of these three, the CardioMEMS Champion is the only device to have received FDA approval [16]. However, even the Champion is struggling, as although the device has been FDA approved, many insurers are refusing to offer reimbursements for implantation [17].

1.3.2 Bioimpedance Based Methods

Bioimpedance methods involve driving a small current through the body and measuring the resulting voltage. The measured voltage decreases as fluid increases. Bioimpedance measurements can be performed both invasively and non-invasively in variety of locations such as the thorax or the calf.

Medtronic’s Optivol system is the primary invasive bioimpedance system on the market. The Optivol algorithm uses intrathoracic bioimpedance measurements to predict CHF decompensation [11]. Optivol has been FDA approved, but has a high false positive rate (unexplained alerts rate of 79.6% and 1.27 unexplained alerts per person-year in [18]) and appears to increase hospitalizations and outpatient visits without improving clinical outcomes [19]. Additionally, one trial found that the sensitivity of the algorithm was less than 10% for the first 63 days after implantation and only improved to 42% when the device was implanted for 148 days or greater [20].

Wearable bioimpedance measurement systems show more promise. The Corventis PiiX and the toSense CoVa monitoring system have both been FDA approved [21,22]. The Corventis PiiX is a wearable adhesive patch that measures thoracic impedance, along with ECG and respiration. It was tested with patients undergoing hemodialysis and there was a strong correlation (r=0.98) between fluid removed and changes in bioimpedance. PiiX was also used in a study to develop multi-parameter CHF detection algorithms [23]. An algorithm that combined a fluid index, a breath index, and personalization parameters achieved a sensitivity of 65% and specificity of 90% with a false positive rate of 0.7 events per person-year. The CoVa monitoring system is a necklace worn by patients at home for 5 minutes a day that measures the same parameters as the Corventis PiiX. The CoVa necklace has been validated against a
A comparison commercial bioimpedance system, but peer reviewed data is not currently available.

It remains to be seen if wearable patches like the PiiX or once-a-day measurement systems like the CoVa necklace will reduce CHF readmission rates, though the use of e.g. monthly thoracic impedance measurements has been shown to reduce the number of CHF-related events and mortality \[24\]. Algorithms that reduce false positives will be essential in preventing unnecessary visits and procedures. Both devices use wet electrodes that can irritate the skin, which limit their potential for continuous long-term use. Additionally, in the case of the CoVa necklace, care must be taken to ensure a repeatable measurement day-to-day.

Exploratory research involving CHF or otherwise fluid-overloaded patients has been performed in hospital settings (e.g. \[25\]) and during hemodialysis (e.g. \[26\]). Researchers have also worked on wearable systems for at home monitoring (e.g. \[27\], \[28\]), though their performance remains to be seen. In patients with left sided heart failure, congestion forms in the lungs first, so most research has focused on lung based bioimpedance monitoring (e.g. \[27\], \[29\]). Monitoring of leg edema for CHF has been limited to use during dialysis (e.g. \[26\]). Measurements during dialysis have shown an increase of leg bioimpedance that correlates with volume removed. However, for accurate volume assessment, other parameters such as calf resistivity must also be estimated \[26\].

At this point, a long-term, non-invasive home bioimpedance measurement system is not yet available, though some patch-based systems are on the way. Commercially available systems are portable, yet expensive, and thus not suitable for home monitoring.

### 1.4 Problem Statement

This work will take the first steps toward designing a home monitoring system. Such a monitoring system would be a relatively low-cost, long-term, clinically relevant, wearable fluid status monitor for patients with CHF. The device will need to satisfy
the following functional requirements:

1. Distinguish between ECW and ICW.

2. Accurately determine changes in ECW or its correlates.

3. Classify a patient’s hydration status.

4. Perform robustly in an every day setting.

5. Integrate with a wearable system.


Ideally, the device will provide improvements beyond the standard of care. This may be achievable by combining bioimpedance data (the focus of this thesis), with other relevant information such as heart rate variability or activity. Additionally, the device is intended to provide feedback for the patient, caretakers, and healthcare providers (see Figure 1-5). Patients, along with their caretakers and healthcare providers would be able to use this information to titrate medications and schedule appointments.

1.5 Thesis Aims

There are four aims for this thesis:

1. Determine how changes in calf impedance are related to fluid removed during hemodialysis

2. Determine the best electrode placement to perform the calf bioimpedance measurement

3. Develop and verify a portable bioimpedance measurement system on the bench

4. Evaluate experimental system against a commercial system in a clinical setting
Figure 1-5: How this proposed thesis fits in with the bigger picture of CHF home management.

1.6 Thesis Organization

This thesis is organized into the following chapters:

- Chapter 2 introduces bioimpedance and contemporary bioimpedance techniques. The electrical properties of tissue, bioimpedance circuit models, and a specific literature review of bioimpedance methods are presented.

- Chapter 3 describes a clinical test that evaluates the relationship between calf bioimpedance and changes in patient fluid status (Thesis Aim 1). Results and proposed physiological explanations for this relationship are presented.

- Chapter 4 presents research to determine the ideal electrode placement of the electrodes on the calf (Thesis Aim 2). Both simulations and experimental results are presented.

- Chapter 5 describes a portable bioimpedance spectroscopy system and its verification on the bench and in a clinical setting (Thesis Aims 3 and 4).
• Chapter 6 concludes the work with a summary of the research contributions in this thesis and details opportunities for future work.
Chapter 2

Bioimpedance

2.1 Introduction to Bioimpedance

Bioimpedance is the response of the body to an externally applied electrical current. In the typical four electrode configuration known as a “tetrapolar” configuration, a known sinusoidal current is applied between a pair of electrodes and the resulting voltage is measured by another pair of electrodes placed between the current driving electrodes. The bioimpedance is the voltage divided by the current. Bioimpedance measurements can be performed at one or more frequencies and are used for a variety of applications, such as body composition analysis, impedance cardiography, estimation of hydration status, and monitoring regional fluid accumulation [30].

This chapter will provide an overview of tissue properties and modeling, explain how volume is estimated from bioimpedance measurements, provide a literature review of bioimpedance methods, and provide an overview of exploratory bioimpedance measurement techniques. At the end of the chapter, there will be a discussion of the selected bioimpedance techniques for this thesis.

2.2 Tissue Properties and Modeling

This section will provide a basic understanding of the electrical properties of tissue, and how tissue can be modeled using circuit components.
Low and high frequency current flow through the body. At low frequencies, current flows through the extracellular fluid. At high frequencies, current flows through both intra- and extracellular fluid \[31\]. Image not to scale.

Figure 2-1: A look at how tissue behaves electrically. (a) current flows through tissue; (b) an electric model of tissue.

2.2.1 Three Element Circuit Model

CHF results in volume changes that can be detected with bioimpedance measurements in the range of 1 kHz to 1 MHz. As discussed in Section 1.2.3, tissue has multiple fluid compartments that are separated by cell membranes. All fluid that is not within a cell is known as “extracellular” water (ECW). This includes both interstitial fluid and plasma. Fluid that is contained within a cell membrane is known as “intracellular” water (ICW). The sum of ECW and ICW is total body water (TBW).

ECW and ICW are both solutions of conductive ions in water, with the cell membrane acting as a dielectric. At low frequencies, an applied sinusoidal current will only flow through the ECW because the capacitive properties of the cell membranes prevent current flow into cells (see Figure 2-1a). At high frequencies, applied sinusoidal current will flow through both the ECW and the ICW. The change in resistance between low and high frequencies makes it possible to determine the resistance of the ECW and ICW in the measured volume.

The electrical properties of tissue, with current flowing through ECW at low
frequencies, and through both ECW and ICW at high frequencies, can be modeled as a network of two resistors and a capacitor (see Figure 2-1b). In this model, $R_e$ and $R_i$ represent the resistance of the ECW and ICW, respectively. The capacitor $C_m$ represents the capacitance of cell membranes. At low frequencies, $C_m$ looks like an open circuit and all current flows through $R_e$. At high frequencies, the capacitor $C_m$ looks like a short circuit and current flows through both $R_e$ and $R_i$, with an equivalent resistance of $R_\infty = \frac{R_e R_i}{R_e + R_i}$. An example bode plot of this circuit can be found in Figure 2-2. There are two “flat” parts of the bode magnitude and one transition period. The low and high frequency flat sections are dependent on the resistances $R_e$ and $R_i$, and the transition period is dependent on all three circuit elements.

![Bode Plot](image.png)

Figure 2-2: An example bode plot of the simple tissue body model consisting of two resistors and one capacitor. The magnitude starts out equal to $R_e$ and transitions to $\frac{R_e R_i}{R_e + R_i}$ at high frequencies.
2.2.2 Cole Model

The model in Figure 2-1b is an “explanatory” model that assumes tissue can be represented by a lumped model of three components. It holds true for dilute suspensions of cells, such as starfish and sea urchin eggs [32]. However, in practice this model does not sufficiently represent bioimpedance measurements in other types of tissue, including most human tissue. The cause of this deviation is not well understood (see Section 2.2.3). Researchers have since transitioned to “descriptive” models of tissue that are more consistent with measured bioimpedance data. However, because of their descriptive rather than explanatory nature, these parameters can not currently be directly related back to physiology.

The main descriptive model of tissue bioimpedance is the Cole Model [32]:

\[
Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^\alpha}
\]  

(2.1)

The Cole model expresses the bioimpedance in a slightly different form than the model in Figure 2-1b. It assumes that the capacitor in the three element model is actually what is known as a “constant phase element.” A CPE is a frequency dependent impedance that is modeled such that the phase of the impedance is independent of frequency and set by a parameter \(\alpha\) such that \(\theta_{CPE} = -\alpha\pi/2\). For example, for \(\alpha = 0\), the CPE behaves as an ideal resistor, and for \(\alpha = 1\) it behaves as an ideal capacitor. The CPE is not physical, but is used to fit the bioimpedance data to the actual measurements. The Cole model can be mapped back to the three element circuit model as follows:

\[
R_e = R_0
\]

(2.2)

\[
R_i = \frac{R_0 R_\infty}{R_0 - R_\infty}
\]

(2.3)

\[
C_m = \frac{\tau}{R_e + R_i}
\]

(2.4)
2.2.3 The $\alpha$ Term

Measured bioimpedance data of human tissue does not match the three element circuit model described in 2.2.1. Rather, the Cole model described in Section 2.2.2 is a better approximation of the bioimpedance spectrum. Though parameters $R_0$, $R_\infty$, and $\tau$ can be mapped back to the three element circuit model, the $\alpha$ term does not have a concrete physiological meaning. There have been many attempts to explain why the term appears in bioimpedance data, but there is no agreement on its meaning.

Some researchers suggest that the $\alpha$ term is caused by heterogeneity of cell sizes and shapes in living tissue. This heterogeneity would result in a distribution of relaxation times (i.e. time constants) that can produce a bioimpedance spectrum that replicates the effect observed in tissue (see e.g. [33]). However, Ivorra et al. argue that the amount of heterogeneity required to achieve an $\alpha$ term of 0.8 (typical for bioimpedance measurements), a non-physiologically broad distribution of cell sizes and shapes would be required [34]. They provide some evidence that the $\alpha$ term is related to extracellular morphology; however, their experimental results do not fully support their simulations.

2.2.4 Stray Capacitance in Bioimpedance Measurements

Bioimpedance measurements for fluid status are typically performed in a frequency range of 1 kHz – 1 MHz. Unfortunately, as with all systems, bioimpedance measurements have parasitic capacitances (referred to as “stray capacitance”) that impact measurements at frequencies above 100 kHz. Any parasitics from the cabling and instrumentation itself can be calibrated out, but stray capacitance from the body will remain and needs to be accounted for.

The impact of the stray capacitance can be modeled as a capacitor in parallel with the body (see Figure 2-3). This parallel capacitance causes significant negative phase deviations at frequencies above 100 kHz (see Figure 2-4). The magnitude is less affected by the stray capacitance, but can be impacted at frequencies above 500 kHz.
Figure 2-3: Stray capacitance in the bioimpedance measurement is in parallel with the body impedance.

Because the magnitude of the impedance is less affected than the phase, one approach to minimizing the impact of stray capacitance is to fit to only the magnitude. Other possibilities include correcting for the stray capacitance in some fashion, and/or extrapolating the desired parameters from lower frequency measurements.

2.3 Estimating Fluid Volume

While bioimpedance is related to volume status, it must be transformed to estimate actual fluid volume. Fitting bioimpedance data to the Cole Model (Equation 2.1) returns parameters $R_0$, $R_\infty$, $\alpha$ and $\tau$, which can be readily converted to $R_e$, $R_i$, and $C_m$ from Figure 2-1b. However, $R_e$ and $R_i$ only indicate the resistance of the measured tissue, rather than the fluid volume. In this section, the two main methods for estimated fluid volume from measured resistance are presented: bioelectrical impedance analysis (BIA) and bioimpedance spectroscopy (BIS).

2.3.1 Bioelectrical Impedance Analysis

BIA estimates TBW, ECW, and ICW for an individual from a population of similar individuals. Measurements include “whole body” (wrist-to-ankle) measurements and “segmental” measurements (measurements of individual body segments such as arm, trunk, leg, etc.) that are performed at a single frequency (SFBIA) or multiple
Figure 2-4: Calculated changes in magnitude and phase with the addition of stray capacitance values of 50 pF (red) and 100 pF (yellow). Stray capacitance acts in parallel with the body impedance and causes significant deviations in the phase at high frequencies (red and yellow lines) when compared with no stray capacitance (blue line).

frequencies (MFBIA). SFBIA is typically measured at 50 kHz. MFBIA is measured over a range of frequencies, typically from 1 kHz to 500 kHz.

Whole body BIA measurements assume that the body is a single conductive cylinder with homogeneous composition and constant geometry. The resistance of such a cylinder is:

\[ R = \frac{\rho H}{A} \]  \hspace{1cm} (2.5)

where \( \rho \) is the resistivity of the cylinder, \( H \) is the height of the individual (i.e. the length of the cylinder), and \( A \) is the cross sectional area. This equation can be rearranged to relate the resistance of the cylinder to the volume of the cylinder \( Vol \):
\[ R = \frac{\rho H}{A} \]  
\[ R = \frac{\rho H}{A} \cdot \frac{H}{H} \]  
\[ R = \frac{\rho H^2}{Vol} \]  
\[ Vol = \frac{\rho H^2}{R} \]  

Once the \( H^2/R \) values and other demographic information has been collected from a population of individuals, BIA uses regression analysis to generate empirically derived equations that combine measured \( H^2/R \) values at one or more frequencies with other parameters such as gender, age, and weight.

BIA has a number of limitations. First, BIA assumes the body is a cylindrical homogeneous conductor with a length equal to the height of the individual. In reality, the body is neither perfectly cylindrical nor homogeneous nor a perfect conductor. Additionally, BIA regression equations will only work for individuals similar to the population of individuals used to generate said equations. This causes issues when measuring patients with modified fluid status, e.g. CHF patients, as many of these equations are generated from healthy populations. SFBIA operates at a single frequency (50 kHz), at which the measured bioimpedance is determined by some combination of the ECW and ICW conductivities and the cell membranes, rather than exclusively by one compartment or another. This does not allow the ECW and ICW to be measured independently. Finally, BIA measurements are also affected in uncontrollable ways by measurement conditions, such as posture, hydration status, food consumption, exercise, and so on.

Some of BIA’s limitations can be mitigated by performing multi-frequency measurements, or measuring body segments individually. However, because BIA uses regression techniques to estimate volumes, even with these improvements the measurement is still dependent on the population used to generate the regression coefficients.
2.3.2 Bioimpedance Spectroscopy

The second commonly used bioimpedance volume estimation method is called bioimpedance spectroscopy (BIS). BIS, as the name suggests, measures bioimpedance over a range of frequencies, often 1 kHz to 1 MHz. Like BIA, BIS assumes the body is cylindrical. However, rather than assuming the body is a single homogeneous cylinder, BIS assumes the body consists of three conductive cylinders with different dimensions in series: one for the arm, one for the leg, and one for the trunk [31].

For the calculation of ECW, three series cylinders are assumed to be filled with conductive fluid and suspended non-conductive spherical elements (i.e. cells). The apparent resistivity of such a suspension is:

\[ \rho_a = \frac{\rho}{(1 - c)^{3/2}} \]

(2.10)

where \( \rho \) is the resistivity of the conductive fluid and \( c \) is a dimensionless volume fraction of the non-conducting spheres. If the non-conducting spheres have a volume equal to the ICW, \( c \) becomes:

\[ c = 1 - \frac{Vol_{ECW}}{Vol_B} \]

(2.11)

where \( Vol_{ECW} \) is the volume of ECW in the cylinder and \( Vol_B \) is the total volume of body (cylinder). Assuming the ECW has a resistivity \( \rho_e \), the apparent resistivity of the cylinder at low frequencies (cells non-conducting) is then:

\[ \rho_{ae} = \rho_e \left( \frac{Vol_B}{Vol_{ECW}} \right)^{3/2} \]

(2.12)

Now assume each of the cylinders has the same resistivity \( \rho_{ae} \) (which, by definition, requires a common \( \frac{Vol_B}{Vol_{ECW}} \) ratio for each cylinder). The “total body” resistance is then the sum of the resistance of each of the three cylinders:

\[ R_{total} = \rho_{ae} 4\pi \left( \frac{L_a}{C_a^2} + \frac{L_l}{C_l^2} + \frac{L_t}{C_t^2} \right) \]

(2.13)

where \( L_a \) and \( C_a \) are the length and circumference of the arm, respectively, \( L_l \) and
\(C_L\) are the length and circumference of the leg, respectively, and \(L_L\) and \(C_L\) are the length and circumference of the trunk, respectively. In practice and for simplicity’s sake, however, standard BIS measurements use the height of the individual, and not the lengths and circumferences of an arm, trunk, and leg. Instead, it is assumed that human anthropometrics can be accounted for with a “shape factor” \(K_b\). Then the whole body resistance can be related to the volume as in Equation 2.8 multiplied by \(K_b\):

\[
R = \frac{K_b \rho_{ae} H^2}{Vol_B}
\]

(2.14)

where \(K_b\) is a constant derived from anthropometric ratios usually assumed to be 4.3 for all individuals \[35\], \(H\) is the individual’s height, and \(Vol_B\) is the total body volume. Plugging the expression of \(\rho_{ae}\) into Equation 2.14, the resistance of the volume at low frequencies then becomes:

\[
R_e = K_b H^2 Vol_B^{1/2} \rho_e Vol_{ECW}^{-3/2}
\]

(2.15)

and then the volume of ECW can be calculated as:

\[
Vol_{ECW} = k_e \left( \frac{H^2 W^{1/2}}{R_e} \right)^{2/3}
\]

(2.16)

with:

\[
k_e = 10^{-2} \left( \frac{K_b \rho_e}{D_b^{1/2}} \right)^{2/3}
\]

(2.17)

where \(W\) is body weight (kg), \(H\) is height (cm), \(\rho_e\) is the \(\rho\) of ECW (\(\Omega \cdot \text{cm}\)), and \(D_b\) is body density (kg/l).

For calculation of TBW, one could follow a procedure analogous to what has been described for ECW, and obtain:

\[
Vol_{TBW} = k_t \left( \frac{H^2 W^{1/2}}{R_\infty} \right)^{2/3}
\]

(2.18)
with:

\[ k_t = 10^{-2} \left( \frac{K_b \rho_\infty}{D_b^{1/2}} \right)^{2/3} \]  

(2.19)

where \( \rho_{ICW} = 3 - 6 \rho_{ECW} \) \[36].

This method requires estimation of TBW resistivity \( \rho_\infty \). There are multiple approaches to estimate this resistivity. One method is to assume it is linearly related to ECW and ICW resistivities in proportion to their respective volumes \[35,37\]. Another method is to assume \( \rho_\infty \) is non-linearly related to the ECW and ICW resistivities, and also related to the measured resistances \( R_0 \) and \( R_\infty \) (from \[37,38\]):

\[ \rho_\infty = \rho_{ICW} - (\rho_{ICW} - \rho_{ECW}) \left( \frac{R_\infty}{R_0} \right)^{2/3} \]  

(2.20)

In practice, it can be very difficult to determine the mean resistivity of ICW as it varies depending on the type of cells. It may be most appropriate to determine \( k_t \) empirically.

ICW is the most difficult compartment to estimate independently. It is represented by both the intracellular resistance \( R_i \) and the membrane capacitance \( C_m \), so one cannot solve the analogous equations for ECW and TBW with the \( R_i \) term. Additionally, because the relationship of TBW resistivity and ECW/ICW ratio is non-linear, these equations will not account for those effects. It appears that the best way to calculate ICW is to subtract ECW from TBW (ICW = TBW - ECW) \[37\].

Like BIA, BIS relies on a number of assumptions. Some variables in the above equations are measured, and others are assumed (see Table 2.1). Assumptions include 1) that the anthropometric factor \( K_b \) is accurate for the patient, 2) that tissue behaves like a mixture of non-conducting spheres in a conducting medium, 3) that the \( R_e \) and \( R_i \) extrapolated from measured bioimpedance data do in fact correspond to resistances at DC and infinity frequency, 4) that the ECW and ICW are electrically homogeneous fluids on a macroscopic scale, and 5) that the resistivities of the ECW and ICW are known and constant.

BIS measurements tend to perform well in aggregate, though there are limitations
Table 2.1: Variables in BIS measurements.

<table>
<thead>
<tr>
<th>Var.</th>
<th>Descr.</th>
<th>Units</th>
<th>Meas.?</th>
<th>Male</th>
<th>Female</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_b$</td>
<td>Shape Factor</td>
<td>unitless</td>
<td>No</td>
<td>4.3</td>
<td>4.3</td>
<td>35</td>
</tr>
<tr>
<td>$\rho_e$</td>
<td>ECW Resistivity</td>
<td>$\Omega$ cm</td>
<td>No</td>
<td>40.3</td>
<td>42.3, 39.0</td>
<td>37</td>
</tr>
<tr>
<td>$\rho_\infty$</td>
<td>TBW Resistivity</td>
<td>$\Omega$ cm</td>
<td>No</td>
<td>see Eq. 2.20</td>
<td>see Eq. 2.20</td>
<td>38</td>
</tr>
<tr>
<td>$H$</td>
<td>Height</td>
<td>cm</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>$D_b$</td>
<td>Body Density</td>
<td>kg/L</td>
<td>No</td>
<td>1.05</td>
<td>1.05</td>
<td>37</td>
</tr>
<tr>
<td>$R_0$</td>
<td>R @ DC</td>
<td>$\Omega$</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>$R_\infty$</td>
<td>R @ $\infty$</td>
<td>$\Omega$</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>$W$</td>
<td>Weight</td>
<td>kg</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

$$k_e = 10^{-2} \left( \frac{K_b \rho_e}{D_b^{1/2}} \right)^{2/3}$$

unitless, No, 0.306, 0.316 or 0.299

$$k_t = 10^{-2} \left( \frac{K_b \rho_\infty}{D_b^{1/2}} \right)^{2/3}$$

unitless, No, see Eq. 2.20, see Eq. 2.20

in how well these measurements perform in any one individual [37]. Factors that limit accuracy include similar factors that limit BIA accuracy (hydration, eating, posture, etc.) and also the assumptions of the BIS models. BIS measurements may be improved by performing segmental measurements, or by modifying the equations presented in this section. However, even with a robust estimation of key BIS parameters from over 170 patients, there are fundamental limitations to the BIS method [37]. Additionally, the effort of this estimation does not produce significantly better volume estimates. According to Buendia et al., ECW estimation appears to be most limited by the anisotropy inherent in actual tissue and TBW due to the uncertainty of $\rho_e$. ICW estimated independently is limited by the issues described in a previous paragraph in this section. Improvements to BIS do not seem likely without developing entirely new models or techniques.

BIS may be good enough at estimating ECW, TBW, and ICW for CHF applications. However, a limitation of using standard BIS is the lack of a reference in order to classify hydration status. Knowing an individual’s compartment volumes (i.e. ECW, ICW, and TBW) does not make a statement as to whether that patient has excess fluid or not, and so classification is necessary.
2.4 Classifying Patients Based on Bioimpedance Data

In the previous section, two methods of relating measured bioimpedance data to volume were presented: bioelectrical impedance analysis (BIA) and bioimpedance spectroscopy (BIS). The challenge with using BIA and BIS for management of CHF is that even with knowledge of an individual’s fluid volumes (ECW/ICW/TBW), it is challenging to determine whether that patient has excess fluid or not [39]. Ideally, such a method would both determine whether a patient is fluid overloaded or not, and if they are, by how much. In this section, methods for classifying patients based on bioimpedance data will be presented. Some of these methods can be combined with BIA/BIS, and others are standalone.

2.4.1 Bioelectrical Impedance Vector Analysis

Bioelectrical Impedance Vector Analysis is a single frequency measurement (usually 50 kHz) performed from hand-to-foot or on a body segment. BIVA measures bioimpedance and compares a conductor length (i.e. height or segment length) normalized bioimpedance value with a probabilistic distribution of fluid status to determine whether a patient has fluid overload [40]. Patients with bioimpedance measurements outside the 75% percentile are considered dehydrated or fluid overloaded depending on the direction of the deviation.

BIVA assumes that an individual’s hydration state can be determined with respect to a population with similar demographics. It also assumes that the phase angle is accurate enough for proper characterization. BIVA suffers from some similar limitations to that of standard BIA, including lack of differentiation between ECW and ICW. Though BIVA allows for categorization with respect to a population, it does not provide any estimate of how much fluid overload a patient has.

2.4.2 ECW/TBW ratio

The ECW/TBW ratio can be to classify patients as fluid-overloaded vs. normally hydrated. It has been shown that CHF patients tend to have higher ECW/TBW ratio
than healthy participants \[41\]. A patient’s ECW/TBW ratio could be measured, for example, using BIS techniques, and compared with a threshold determined from healthy participants of a similar demographic.

The ECW/TBW ratio is independent of geometry. When calculating ECW and TBW as indicated in Equations 2.16 and 2.18, the ratio reduces to a function of resistivities and measured resistances:

\[
\frac{Vol_{ECW}}{Vol_{TBW}} = \left( \frac{\rho_{ECW}R_{\infty}}{\rho_{\infty}R_e} \right)^{2/3}
\] (2.21)

Unfortunately, in practice, there are a wide range of “healthy” ECW/TBW ratios \[42\]. This makes it difficult to use ECW/TBW ratio to determine any individual person’s normal hydration status. ECW/TBW ratio can distinctly determine that an individual is fluid overloaded if their ECW/TBW ratio is sufficiently high, but not what a healthy number for that patient should be. ECW/TBW ratio seems like a metric that may be useful to use in combination with other metrics, but not as a sole classifier of fluid status.

### 2.4.3 Body Composition Monitor

One investigatory method to classify fluid overloaded patients is a technique that has been integrated into a device called the Body Composition Monitor. This technique uses regression methods to estimate the amount of fluid overload directly (i.e. the equations are empirical from the patient population). It takes ECW and ICW volume estimates from BIS measurements and the patient’s current weight, applies a regression based on data from a similar patient population, and outputs a fluid overload estimate in liters. The fluid overload volume can then inform the ultrafiltration rate or diuretic dosage for overloaded patients. One BCM equation used in the literature is:

\[
FO = 1.136 \times Vol_{ECW} - 0.43 \times Vol_{ICW} - 0.114 \times W_{pre-HD}
\] (2.22)

where \( FO \) is the total fluid overload, \( Vol_{ECW} \) and \( Vol_{ICW} \) are patient-specific
measured ECW and ICW volumes, and \( W_{\text{pre-HD}} \) is the weight pre-hemodialysis. The BCM assumes that the fluid overload state of a patient can be determined from a regression of similar patients. In practice, this appears to be performing well in trials [43][44], though more data from diverse populations is required. As with all regression techniques, BCM is limited in its efficacy to the population used to generate said regressions and the patient’s relationship to that population.

2.4.4 Healthy CNR Range

Figure 2-5: Electrode placement for the calf measurement used in [45].

The last method to be discussed in this section is a method introduced by Zhu et al [45]. Unlike previous methods that measure complex bioimpedance at 50 kHz and from hand-to-foot, this method measures 5 kHz resistance at the calf. The method was developed for use with hemodialysis patients to determine their dry weight toward the end of a session. The authors compare the calf normalized resistivity (CNR, calf resistivity divided by body mass index) with measurements of healthy individuals’ CNR to verify the patient is in a healthy range (\( 18.3 \cdot 10^{-2} \Omega M^3 kg^{-1} \) for male patients and \( 20 \cdot 10^{-2} \Omega M^3 kg^{-1} \) for female patients).

Electrodes are placed in the middle of the calf with an inter-electrode distance for the voltage electrodes of 10 cm (see Figure 2-5). The average calf circumference is measured at the beginning and end of the hemodialysis session and used in combination with the inter-electrode distance (10 cm) and the resistance at 5 kHz to calculate the resistivity of the calf. Because the circumference of the calf will change
continuously throughout the course of the hemodialysis sessions, the authors derived an equation to calculate the circumference during hemodialysis:

\[
C(t) = \sqrt{C(0)^2 - \frac{4\pi \rho(0)L}{R(0)}} \left(1 - \frac{R(0)}{R(t)}\right) \tag{2.23}
\]

where \(C(0)\) and \(R(0)\) are the circumference and the low frequency resistance at the start of the hemodialysis session, \(\rho(0)\) is a experimentally calibrated initial resistivity of the calf, \(L\) is the inter-electrode distance (10 cm), and \(C(t)\) and \(R(t)\) are the circumference and the low frequency resistance at time \(t\).

The resistivity as a function of time is then:

\[
\rho(t) = \frac{C(t)^2 \cdot R(t)}{4\pi L} \Omega \text{ cm} \tag{2.24}
\]

The instantaneous calf resistivity \(\rho(t)\) can be normalized by BMI \((\text{Weight} / H^2)\) to obtain the calf normalized resistivity” (CNR). Resistivity is normalized by BMI because body fat can impact the measurement, especially with a short inter-electrode distance. A typical measurement is pictured in Figure 2-6.

This method assumes that the calf can be modeled as a cylinder with a uniform resistivity. The method also assumes that fluid in the calf is the last segment to lose its excess fluid, and so when the calf is in a healthy range, so is the rest of the body.

Zhu et al.’s method has been developed specifically for determining dry weight in real-time during a hemodialysis session. In this sense, it has an advantage over methods standard BIA, BIS, and BIVA in that those methods have been developed for body composition in general, whereas this method was developed specifically for determining fluid overload. Additionally, Zhu et al. argue that their method is more robust than using the ECW/TBW ratio, as the ECW/TBW ratio has greater variability. Placement at the calf does require the patient to keep one leg still for the course of the session, but this is preferable compared to keeping an entire side still as in the hand to foot cases.

One of the limitations of this method is that it cannot not estimate fluid overload before the start of the hemodialysis session; it can only tell when a patient reaches a
Figure 2-6: Changes in calf normalized resistivity as a function of time during a hemodialysis session (pink curve) [26]. The blue curve represents the current measured resistance divided by the initial measured resistance.

healthy CNR range. In this sense, the Body Composition Monitor has an advantage over this method. However, a recent paper suggests that it may be possible to use CNR measurements to estimate fluid overload before the start of a hemodialysis session [42].

2.5 Discussion

Two methods of volume estimation (Section 2.3) and four methods for classifying patients and/or estimating dry weight (Section 2.4) have been presented. In this section, the functional requirements of the BIS system to be developed in this thesis will be re-examined, and the methods presented evaluated.

Recall the function requirements first outlined in Section 1.4. For translation to a wearable form factor, it is important that a particular method satisfies the following:

1. Distinguish between ECW and ICW.

2. Accurately determine changes in ECW or its correlates.

3. Classify a patient’s hydration status.
4. Perform robustly in an every day setting.

5. Integrate with a wearable system.


An evaluation of each of the methods presented in this thesis thus far, including the two volume estimation methods (BIA and BIS), and the four classification methods (BIVA, ECW/TBW ratio, BCM, and CNR), is presented in Table 2.2.

<table>
<thead>
<tr>
<th>Functional Requirement</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distinguish ECW and ICW</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Accurately track ECW changes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>Hydration classification</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Robust Measurement</td>
<td>Least</td>
<td>Middle</td>
<td>Least</td>
<td>Middle</td>
<td>Middle</td>
<td>Most</td>
</tr>
<tr>
<td>Integration into wearable</td>
<td>Least</td>
<td>Least</td>
<td>Least</td>
<td>Least</td>
<td>Least</td>
<td>Most</td>
</tr>
<tr>
<td>Patient compliance</td>
<td>Least</td>
<td>Least</td>
<td>Least</td>
<td>Least</td>
<td>Least</td>
<td>Most</td>
</tr>
</tbody>
</table>

Table 2.2: Functional Requirements of the evaluated methodologies. Methods: 1 - BIA, 2 - BIS, 3 - BIVA, 4 - ECW/TBW ratio, 5 - BCM, 6 - CNR. * Method 6 tracks ECW indirectly.

2.5.1 Distinguish ECW and ICW

Four out of the six methods (BIS, ECW/TBW ratio, BCM, and CNR) are capable of distinguishing between ECW and ICW. This is particularly important because fluid overload involves the expansion of the extracellular space. BIS, ECW/TBW ratio, and BCM distinguish between ECW and ICW by measuring bioimpedance at multiple frequencies. The CNR method distinguishes ECW by only measuring ECW. It measures resistance at 5 kHz, which is a frequency at which most if not all of current driven through the body flows through the extracellular space and around cells. BIA and BIVA cannot distinguish between ECW because they typically only measure bioimpedance at 50 kHz. Multiple and/or low frequency implementations of these methods would be able to distinguish ECW.
2.5.2 Accurately Track ECW Changes

The same four methods that can distinguish between ECW and ICW can also track ECW over time. In the case of BIS and its derivatives, this is achieved by performing subsequent measurements and comparing the volume estimates to that of previous estimates. The CNR estimate method measures ECW indirectly by comparing the resistivity over time. It is not yet understood how well these technologies will be able to track ECW changes over time in an ambulatory environment.

2.5.3 Hydration Classification

As described in Section 2.4, one requires more than volume alone to classify a patient as fluid overloaded. BIA and BIS both cannot classify hydration status without additional information. The other methods (BIVA, ECW/TBW ratio, BCM, CNR) are all intended to classify patients and/or estimate fluid overload. BIVA classifies patients based on population data from similar individuals. ECW/TBW ratio uses a threshold to determine whether a patient is fluid-overloaded or not. BCM uses equations derived from a similar patient population to estimate fluid overload in an individual patient. Finally, the CNR method does not classify patients directly; rather it determines when the patient has returned to healthy fluid status with real-time monitoring of calf bioimpedance during a hemodialysis session.

2.5.4 Robust Measurement

In order for bioimpedance measurements to be practical in an ambulatory environment, the methods used have to be robust to changing conditions such as motion, eating, temperature, etc. Unfortunately, all bioimpedance methods will be affected somewhat by conditions such as food intake and exercise. However, methods that are hand-to-foot are likely more affected than the CNR method, as it is only on the calf, and most vital organs that influence bioimpedance measurements are in the trunk.

As for noise considerations, BIA and BIVA are both single frequency measurements and can be considered the “least” robust. It seems it will be the most challeng-
ing to ensure robust measurements with only one data point. BIS and its derivatives (ECW/TBW ratio and BCM) involve multiple frequency measurements. The data are fitted, minimizing the impact of a small number of noisy data points. Additionally, with an entire frequency spectrum, it is easier to determine whether the measurement is “valid” or needs to be repeated.

Electrode placement presents another problem. In this case, the CNR is considered to be the most robust, because the geometry of the calf in the region of measurement is relatively uniform. It has been shown that the measurement is minimally sensitive to electrode placement [45], and correlates well with gold standard hydration markers such as the ECW volume (derived using sodium bromide dilution) divided by the fat-free mass (derived from MRI) [42].

2.5.5 Integration into Wearable

Integrating a hand-to-foot measurement into a wearable appears to be the most challenging. It would require something like a suit that covered both the wrist and ankle, or a way to complete the circuit to perform a measurement (such as touching the hand or wrist to a contact on the leg). Calf measurements appear best suited for integration into a wearable, as electrodes for measuring bioimpedance to derive CNR and calf volumes could be integrated into a sock or a band.

2.5.6 Patient Compliance

The last functional requirement is patient compliance. It is difficult to assess patient compliance without speaking with patients directly. However, similar to the wearable functional requirement, it seems likely that integration into a sock or a band would be most comfortable for the patient, and integrate into their daily life. Many CHF patients already wear compression socks, and one could imagine them wearing a sock with sensors inside.
2.5.7 Measurements in this Thesis

Given the discussion above, measurements in this thesis will be at the calf. A multi-frequency measurement at the calf can measure calf extracellular water, calf intracellular water, and calf total water, track volume changes over time, and afford a robust measurement in a hopefully compliant form factor. Methods such as the BCM method or the CNR method could be incorporated with these measurements to classify patients according to fluid status, and alert patients and physicians of decompensation, ideally preventing hospitalization.

2.6 Chapter Summary

Bioimpedance measures the electrical properties of tissue, which can in turn be related to compartment volumes. Bioimpedance measurement spectra can be modeled as a three element circuit with two resistors and a constant phase element. Fluid volume can be estimated using regression techniques (Bioimpedance Analysis) or by using the high and low frequency resistances with equations for resistivity of a suspension of cells (Bioimpedance Spectroscopy). Fluid volumes alone are not sufficient to determine whether a patient has fluid overload and classification is needed. Classification can be achieved using probabilistic diagrams (Bioimpedance Vector Analysis), regression (Body Composition Monitor), compartment ratios (ECW/TBW), and/or by tracking normalized calf resistivity over time (Healthy CNR range). Measurements can be performed from wrist-to-ankle or on a specific body segment. It was determined that multi-frequency, calf based measurements are preferred for this thesis, as they are more robust to changes in electrode placement in a hopefully more compliant form factor.
Chapter 3

Fluid Status Changes in the Calf During Hemodialysis

This Chapter addresses Aim 1 of the thesis: how are calf bioimpedance changes measured during hemodialysis related to fluid removed during hemodialysis?

3.1 Introduction to Hemodialysis

3.1.1 The Process of Hemodialysis

Hemodialysis is a therapy used when patients have impaired renal function. A filter known as a dialyzer acts as an artificial kidney that removes waste products and fluid from the blood (see Figure 3-1). The dialyzer is a semipermeable membrane that is filled with a solution called dialysate. Standard hemodialysis today consists of two processes: diffusive hemodialysis for the removal of solutes, and ultrafiltration for the removal of fluid and solutes using a pressure gradient. Blood is removed from the body, filtered, and then returned back to the body, plus/minus solutes diffused across the dialyzer membrane, and minus fluid and solutes removed by ultrafiltration. This section will provide an overview for the fluid and solute shifts that occur during hemodialysis.
3.1.2 At Rest

As discussed in Section 1.2.3, the human body is composed of three fluid compartments: intracellular fluid, interstitial fluid and plasma. The sum of the interstitial fluid and plasma is called extracellular fluid. These compartments have concentrations of solutes such as sodium and potassium as listed in Table 3.1. Cells use active transport of solutes to maintain the listed concentration gradients between intracellular fluid and extracellular fluid (i.e. low sodium and calcium concentrations, and high potassium concentration).

In addition to active transport of certain solutes, water can flow across the cell membrane to equalize osmolarity on both sides by a process called osmosis. Osmosis works to equalize the osmotic pressure in each compartment, where the osmotic
Table 3.1: Major solutes in ECW and ICW. * The major anions of ICW are proteins and organic phosphates not included in the table. Table adapted from [47]. Solute concentrations are expressed in milliequivalents per liter (mEq/L). A milliequivalent (mEq) is $10^{-3}$ times the number of moles of the solute multiplied by its valence. For example, one mole of NaCl in solution dissociates into one equivalent of Na$^+$ and one equivalent of Cl$^-$. An osmole (osm) is the number of particles into which a solute dissociates in solution. For the case of NaCl, the osmolarity for 1 mmol/L NaCl is 2 mOsm/L.

Pressure ($\pi$) is defined as:

$$\pi = CRT$$  \hspace{1cm} (3.1)

where $C$ is the concentration of solutes in osmoles per liter, $R$ is the ideal gas constant, and $T$ is the absolute temperature in kelvin.

**Permeant vs. Impermeant Solutes**

The properties of different solutes within each compartment affect how they change compartment volumes. Solutes in the body can be permeant or impermeant. Permeant solutes move across the cell membrane by a process called diffusion, which is a function of the concentration gradient across the membrane. Permeant solute concentrations will eventually settle to their equilibrium values with time and therefore increasing or decreasing the number of permeant solutes will not cause changes in fluid shifts at equilibrium. However, permeant solutes may cause transient fluid shifts as water flows more quickly than the concentration of most solutes equilibrate. Impermeant solutes, on the other hand, do not move freely across membranes. Addition or subtraction of an impermeant solute will result in changes in compartment
volumes at equilibrium.

In cells, proteins are impermeant. Additionally, because the concentration of solutes like sodium, potassium, and calcium are controlled by active processes, one can consider these solutes impermeant as well. The waste product urea is permeant. In extracellular fluid, the interstitial fluid contains sodium, potassium, calcium, and urea (all permeant), and the plasma contains sodium, potassium, calcium, and urea as permeant solutes and proteins as impermeant solutes.

### 3.1.3 Diffusive Hemodialysis

Diffusive hemodialysis involves the removal of waste products such as urea and the adjustment of plasma sodium and potassium concentrations as needed. Sodium and potassium will move in or out of the plasma depending on the concentration gradient between the dialysate and the plasma (see Figure 3-2). There is also a large gradient to move urea and creatinine out of the plasma.

During diffusive hemodialysis, permeant solutes begin to diffuse across the various membranes. If the concentration of dialysate sodium and potassium are in equilibrium with plasma concentrations, there will be no changes in compartment volumes at equilibrium. However, the diffusion of permeant solutes such as urea can transiently shift fluid into and out of cells. Consider for example, the simplified case of a system with only sodium and urea. The concentration of sodium is at equilibrium across all membranes (see Figure 3-3). As urea is cleared by the dialyzer, the osmolarity of the extracellular space decreases. Urea will begin diffusing across the cell membranes to increase the osmolarity of the extracellular fluid, but water will begin to flow first and faster, leading to a transient fluid shift from the extracellular space to the intracellular space. This fluid shift causes an increase in extracellular osmolarity, which induces a fluid shift back out of cells. The net effect can be a small increase in intracellular fluid that dissipates over the course of the session and is completely eliminated after the session.

Mismatched solute concentrations such as that of sodium, for example, can result in increases or decreases in solute concentrations that can influence compartment vol-
umes. Because the concentration of sodium is “pinned” inside cells, it is effectively an impermeant solute. Using a high sodium dialysate compared to plasma concentrations, for example, would result in decreased intracellular fluid and increased extracellular fluid at equilibrium as water is pulled out of cells to decrease the extracellular sodium concentration.

### 3.1.4 Ultrafiltration

Ultrafiltration involves the removal of fluid and solutes by a pressure gradient. A negative pressure is applied to the dialysate that creates a pressure gradient for water to flow into the dialyzer. As water flows across the dialyzer membrane, solutes are dragged with it. Small particles such as sodium move readily through the dialyzer membrane pores, and so ultrafiltration results in the removal of fluid and solutes that leaves the concentration of the solutes in plasma unchanged (see Figure 3-4). When fluid is removed from the plasma by ultrafiltration, fluid from the interstitial space “refills” the plasma via the capillaries. This refill rate is governed by the hydrostatic and oncotic pressure differences (known as Starling Forces) between the plasma...
Figure 3-3: Fluid flow during diffusive hemodialysis.

\[ J = L_p S ([P_c - P_i] - \sigma [\pi_c - \pi_i]) \]  

(3.2)

where \( J \) is the net flow with positive \( J \) indicating flow out of capillaries, \( L_p \) is the hydraulic conductivity of the membrane, \( S \) is the surface area for filtration, \( P_c - P_i \) is the hydrostatic pressure gradient between the capillaries and the interstitial space, \( \sigma \) is the reflection coefficient, and \( \pi_c - \pi_i \) is the oncotic pressure gradient between the capillaries and the interstitial space. Hydrostatic pressure is the pressure of blood against the vessel walls, and oncotic pressure is a form of osmotic pressure exerted specifically by proteins.

Fluid removal from the plasma reduces plasma hydrostatic pressure and increases plasma oncotic pressure (proteins are too large to pass through the dialyzer), which induces fluid flow into plasma at a rate called the “plasma refill rate.” As fluid leaves the interstitial space, the interstitial osmolarity increases. With time, solutes will diffuse from the interstitial space to the plasma to reduce the osmolarity gradient.
However, if the ultrafiltration rate is sufficiently fast, fluid will temporarily flow out from cells in order to reduce the interstitial osmolarity.

### 3.1.5 Combined Hemodialysis

Combined hemodialysis involves both diffusion and ultrafiltration. The resulting compartment volume shifts will depend on fluid and solute shifts induced by each process. Fluid flow in or out of cells, for example, will be determined by a combination of three mechanisms: 1) Urea that freely diffuses across the cell membrane, which induces a small transient fluid shift into cells, 2) dialysate concentrations that induce fluid shifts in or out of cells depending on the concentration gradient with respect to the dialyzer, and 3) transient fluid shifts out of cells that occur at sufficiently high ultrafiltration rates. Fluid flow in or out of the interstitial space will be governed by a combination of the Starling forces and the intracellular fluid shifts. Finally, fluid flow in or out of the plasma will be governed by ultrafiltration and the Starling Forces.
3.1.6 Calf Bioimpedance Changes During Hemodialysis

Previous literature measuring changes in bioimpedance during hemodialysis have found that the leg is disproportionately recruited for fluid removal as compared with the trunk and arms in routine hemodialysis patients [49–53]. Additionally, Zhu et al. have documented that the leg tends to empty last, making the calf an ideal measurement location for determining a patient has reached a healthy fluid status [26,51]. These studies cite one or both of two hypotheses to explain this presentation: 1) differences in regional blood flow and 2) a greater amount of fluid overload in the leg relative to other parts of the body. It has also been hypothesized that the fluid from the calf is recruited to refill the trunk [51].

3.2 Clinical Testing Methods

The goal of clinical testing was to relate changes in calf bioimpedance to fluid removed during hemodialysis. Calf bioimpedance measurements were performed with patients presenting to the Massachusetts General Hospital (MGH) Inpatient Units undergoing hemodialysis using a commercial measurement system (Impedimed SFB7). Patient vital signs, calf circumference, relevant hemodialysis parameters, and relevant patient information were also recorded. All patients received standard clinical care, including routine clinical assessments, laboratory testing, and diagnostic imaging.

3.2.1 Inclusion / Exclusion Criteria

Inclusion criteria:

1. Age > 18 years
2. Inpatients undergoing hemodialysis

Exclusion criteria:

1. Pregnant women
2. Inability to consent
3. Amputations

4. Metal in body (in current path and/or active device)

5. Inability to place electrodes at test location (calf)

Inclusion criteria were intentionally broad to increase the rate of patient recruitment, which at times even with these criteria could be less than one scheduled patient every two weeks. Exclusion criteria were driven by concerns for patient safety/ethics (pregnant women, inability to consent), or concerns about an influence on the bioimpedance measurements (metal in body, inability to place electrodes) or patient circulation (amputations).

3.2.2 Study Procedures

After the patient gave informed consent, the researcher attended the patient’s next hemodialysis session. Upon patient arrival, nursing staff assisted the patient in performing a standing weight (referred to as the patient’s “Initial Weight”). The patient then laid back down on a bed in a “semi-supine” position with their legs at the same level as their buttocks and their torso slightly elevated on pillows. Four Ag/AgCl electrodes were placed on the side of the patient’s calf (see Figure 3-5). The researcher measured the distance between the middle of the patella (knee) and lateral malleolus (ankle) and placed the voltage electrodes 5 cm on either side of the midpoint of this distance. Current electrodes were placed 5 cm outside each voltage electrode.

The patient was allowed to choose which leg the electrodes were placed on. After electrodes were placed on the patient, the calf circumference was measured at the location of each voltage electrode. The mean of these two measurements was used in subsequent analyses. After the calf circumference was measured, five measurements were performed with a commercial bioimpedance spectroscopy measurement system (Impedimed SFB7). All inputs / outputs (blood draws, eating/drinking) and relevant vital signs (blood pressure, and heart rate and blood oxygenation when available) were recorded throughout the session. At the end of the session, the experimental
Figure 3-5: Electrodes are placed along the side of the calf. The inner electrodes are voltage electrodes spaced 5 cm on either side of the “center” of the calf, defined as half the distance between the center of the patella and the center of the fibular protrusion at the ankle. The outer electrodes are current electrodes that are spaced 5 cm apart from the inner electrodes. The positive current and voltage electrodes are the more proximal pair of electrodes and the negative current and voltage electrodes are the more distal pair.

system was removed from the patient and an additional five measurements were performed with the commercial system. The calf circumference was measured again and the patient performed another standing weight (referred to as the patient’s “Final Weight”).

3.2.3 Calculating Bioimpedance Parameters

Bioimpedance parameters were extracted using MATLAB’s \textit{lsqcurvefit} algorithm, which performed a non-linear least squares fit to the Cole model (see Section 2.2.2). The magnitude of the impedance was selected as input data and fitted to the Cole
model with the parameters $R_0, R_\infty, \tau,$ and $\alpha$. The *lsqcurvefit* algorithm implementation allows the user to specify lower/upper bounds and starting values for each parameter. The lower/upper bounds were configured as follows:

\[
15 \leq R_0 \leq 100 \, \Omega \\
15 \leq R_\infty \leq 100 \, \Omega \\
\frac{1}{80 \, kHz \ast \frac{2\pi}{s}} \leq \tau \leq \frac{1}{20 \, kHz \ast \frac{2\pi}{s}} \, s \\
0.65 \leq \alpha \leq 1
\]  

with starting values of:

\[
R_0 = 60 \, \Omega \\
R_\infty = 20 \, \Omega \\
\tau = \frac{1}{50 \, kHz \ast \frac{2\pi}{s}} \, s \\
\alpha = 0.8
\]

These bounds were selected both to constrain parameters to their possible physical values (in this case, all parameters must be positive), and to constrain parameters to an empirically determined “physiological range.” For example, the $\alpha$ parameter bounds were originally set to $0 \leq \alpha \leq 1$, but in some cases this resulted in $\alpha$ parameters outside a physiological range, so the lower bound was increased to 0.65. The resistive upper bounds were set assuming all fitted bioimpedance data was measured at the calf, which in the measured patient population did not result in an $R_0$ value greater than 80 Ω. The bounds of both $R_0$ and $R_\infty$ were set to be the same, though technically $R_\infty$ should be strictly less than $R_0$. The $\tau$ parameter was set assuming that the time constant associated with $\tau$ must be in the range of 20 kHz and 80 kHz, which allows for a 30 kHz deviation around the nominal value of 50 kHz. The starting
values were selected based on an actual bioimpedance measurement performed at the calf in a healthy participant.

### 3.2.4 Calculating Calf Volumes

**Calf Volume Abbreviations**

As described in Section 1.2.3, the body is divided into extra- and intracellular fluid (abbreviated ECW and ICW, respectively), the sum of which equals the total body water (abbreviated TBW). When measuring bioimpedance in the calf, compartment volumes will also consist of extra- and intracellular fluid for that measured volume. For clarity, any reference to calf volumes will have a small c in front: calf extracellular water is abbreviated cECW, calf intracellular water is abbreviated cICW, and calf total water is abbreviated cTW.

**Calculating cECW**

The main difference between calculation of compartment volumes in the calf versus the whole body (see Section 2.3) is that the calf is a single cylinder of known length rather than three cylinders with a total length equal to the patient’s height. To calculate cECW it is assumed that the cECW is the only contributing factor to the resistance at low frequencies (i.e. $R_0$), and that the measured volume is a single conductive cylinder with homogeneous composition and constant geometry. In this case the resistance of such a cylinder is:

$$R_0 = \frac{\rho L}{A}$$  \hspace{1cm} (3.11)

where $\rho$ is the resistivity of the cylinder, L is the length of the segment, and A is the cross sectional area. By multiplying the right half of the equation by $L/L$, this equation can relate the resistance of the cylinder to its volume:
\[ R_0 = \frac{\rho L}{A} \]  \hspace{1cm} (3.12)

\[ R_0 = \frac{\rho L}{A} * \frac{L}{L} \]  \hspace{1cm} (3.13)

\[ R_0 = \frac{\rho L^2}{Vol_{calf}} \]  \hspace{1cm} (3.14)

\[ Vol_{calf} = \frac{\rho L^2}{R_0} \]  \hspace{1cm} (3.15)

where \( Vol_{calf} = L * A \). Calculating the resistivity of the cylinder will allow the measured resistance to be related specifically to the cECW volume.

The apparent resistivity of a medium filled with conductive fluid and suspended non-conductive spherical elements is:

\[ \rho = \frac{\rho_{ECW}}{(1 - c)^{3/2}} \]  \hspace{1cm} (3.16)

where \( \rho_{ECW} \) is the resistivity of the conductive fluid and \( c \) is a dimensionless volume fraction of the nonconducting spheres \(^{54}\). A typical value for \( \rho_{ECW} \) is 40.5 $\Omega \ cm$ \(^{36, 1} \). If one assumes only the cECW is conducting at low frequencies, \( c \) becomes:

\[ c = 1 - \frac{Vol_{cECW}}{Vol_{calf}} \]  \hspace{1cm} (3.17)

where \( Vol_{cECW} \) is the volume of the cECW in the cylinder. Plugging in Equation \(^{3.17} \) to Equation \(^{3.16} \) the resistivity of the cylinder becomes:

\[ \rho = \rho_{ECW} \left( \frac{Vol_{calf}}{Vol_{cECW}} \right)^{3/2} \]  \hspace{1cm} (3.18)

By plugging in the resistivity to Equation \(^{3.11} \), \( Vol_{cECW} \) can be solved for:

\[ Vol_{cECW} = \left( \frac{L^2 \rho_{ECW} \sqrt{Vol_{calf}}}{R_0} \right)^{2/3} \]  \hspace{1cm} (3.19)

\(^{1}\)There may be small changes in $\rho_{ECW}$ over the course of the hemodialysis session. See Appendix A for an analysis of how these changes affect measured results.
Calculating cTW

An analogous approach can be used to solve for cTW. The resistance at high frequencies $R_\infty$ can be related to the volume by:

$$R_\infty = \frac{\rho L^2}{V_{\text{ol \_ calf}}}$$  \hspace{1cm} (3.20)

with

$$\rho = \frac{\rho_\infty}{(1 - c)^{3/2}}$$  \hspace{1cm} (3.21)

If $c = 1 - \frac{V_{\text{ol \_ cTW}}}{V_{\text{ol \_ calf}}}$, the cTW volume is:

$$V_{\text{ol \_ cTW}} = \left( \frac{L^2 \rho_\infty \sqrt{V_{\text{ol \_ calf}}}}{R_0} \right)^{2/3}$$  \hspace{1cm} (3.22)

where $\rho_\infty$ has been shown by Matthie et al. to be \[38\]:

$$\rho_\infty = \rho_{ICW} - (\rho_{ICW} - \rho_{ECW}) \left( \frac{R_\infty}{R_0} \right)^{2/3}$$  \hspace{1cm} (3.23)

where $\rho_{ICW} = 4.5\rho_{ECW}$. The value of $4.5\rho_{ECW}$ was selected because results from different studies range between 3 to 6 times $\rho_{ECW}$ \[36\]. A change of $\rho_{ICW}$ to 3$\rho_{ECW}$ or 6$\rho_{ECW}$ would change $V_{\text{ol \_ cTW}}$ by -10% and 10%, respectively. It would change $V_{\text{ol \_ cICW}}$ by -25% and 25%, respectively.

Calculating cICW

It is assumed that:

$$cICW = cTW - cECW$$  \hspace{1cm} (3.24)

A change of $\rho_{ICW}$ to 3$\rho_{ECW}$ or 6$\rho_{ECW}$ would change $V_{\text{ol \_ cICW}}$ by -25% and 25%, respectively.
Measuring the “Total Volume” of the Calf

The compartment calculations in the previous sections use a volume \( V_{\text{calf}} = L \times A \). In the present measurements, \( L \) is assumed to be 10 cm, which is the inter-electrode distance of the voltage pickup electrodes placed on the calf (see Figure 3-5). If one assumes the calf is a cylinder, the cross-sectional area can be related to the circumference by:

\[
A = \frac{\text{circ}^2}{4\pi} \tag{3.25}
\]

For this testing, the circumference \( \text{circ} \) is the average of the circumference measurement at each voltage electrode.

3.2.5 Evaluation of Fluid Status

Three different metrics were used to assess patient fluid status: total body fluid overload, pedal edema, and calf normalized resistivity. Total fluid overload was calculated as the difference between the patient’s weight at the start of the hemodialysis session and a clinician’s assessment of a patient’s estimated dry weight (EDW) as obtained from patient medical records. The clinician performs this assessment using a combination of vital signs, physical exam, symptoms, labs and/or imaging. The fluid overload can be calculated using the patient’s weight and their EDW as:

\[
\text{Fluid Overload (kg)} = \text{Initial Weight (kg)} - \text{Estimated Dry Weight (kg)} \tag{3.26}
\]

Pedal edema was scored on a scale of 0 to 3 by clinicians (also as obtained from patient medical records), where: 0 = no visible edema, 1 = trace edema, 2 = significant edema, and 3 = pitting edema. The assessment was made based on a combination of visual inspection and palpation.

Finally, the calf normalized resistivity (CNR) was calculated as a metric of hy-
dration in the calf: 

\[ CNR = \frac{\rho}{BMI} \]  

(3.27)

where

\[ \rho = \frac{R_e A}{L} = \frac{R_{e \text{circ}}^2}{4\pi L} \]  

(3.28)

and

\[ BMI = \frac{W}{H^2} \]  

(3.29)

where \( R_e \) is the mean extracellular resistance, \( \text{circ} \) is the average of the calf circumference measured at the voltage electrodes, \( L \) is the inter-electrode distance between the two voltage electrodes, \( W \) is the patient’s weight, and \( H \) is the patient’s height.

### 3.3 Results

#### 3.3.1 Patient Demographics

A table of all the patients in the research study is presented in Table 3.2. There were 5 women and 12 men who participated in the study. There were 4 Black participants, 1 Asian participant and 12 White participants. Nine patients had diabetes and 9 patients had CHF (4 patients had both). All patients were on chronic hemodialysis treatment and participated in the study for one session, with the exception of patient 9, who had acute kidney injury and participated in the study for two consecutive hemodialysis sessions two days apart.

#### 3.3.2 Data Overview

A table summarizing the main measurements from this study are presented in Figure 3-6. The subsequent sections will review different aspects of these measurements.
Patients undergoing hemodialysis have fluid removed from the vasculature by a hemodialysis machine. The hemodialysis machine displays the rate of fluid removal (ultrafiltration rate or UFR) and the total amount of fluid removed during the session (ultrafiltration volume or UFV). It is important to determine the reliability of the recorded ultrafiltration measurements before they are used as a metric of fluid status changes. Two comparisons are performed in this section: 1) the predicted UFV removed as determined by UFRs is compared with the recorded UFV from the hemodialysis machine at the end of the session, and 2) the predicted weight change estimated from recorded inputs/outputs is compared with the measured weight change over the course of the hemodialysis session.

### 3.3.3 Ultrafiltration Measurement Reliability
Predicted vs. Recorded Ultrafiltration Volume

The UFR is set at the beginning of the session and may change throughout the course of the session. It is displayed in real-time on the hemodialysis machine, along with the total UFV. For example, one patient started the session with a UFR of 940 ml/h, and the UFR was increased an hour before the end of the session to 1160 ml/h (see Table 3.3 and Figure 3-7). The predicted UFV is obtained by discrete integration of the UFR over time at one second intervals. The recorded and predicted UFV for each patient was consistent within ±5% for 16/18 patient runs, and within ±10% for the other two patients (see Table 3.4). The larger % difference for the latter two patients appears to be due to an incorrect recording of the time of a UFR change.

Predicted vs. Recorded Weight

A patient’s weight change between the beginning and end of the hemodialysis session can be predicted using the UFV and other inputs and outputs that occur over
<table>
<thead>
<tr>
<th>Time</th>
<th>Rate (ml/h)</th>
<th>Predicted (ml)</th>
<th>Recorded (ml)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:34:49</td>
<td>940</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10:01:11</td>
<td>1160</td>
<td>2293</td>
<td>2300</td>
<td>-0.30</td>
</tr>
<tr>
<td>11:03:54</td>
<td>0</td>
<td>3506</td>
<td>3500</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Table 3.3: An example UFR table used to determine the researcher’s accuracy in recording UFR and UFV during the session.

Figure 3-7: An example graph showing the consistency of the predicted vs. recorded UFV during a hemodialysis session.
Table 3.4: Predicted vs. Recorded UFV measurements for each patient.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Predicted (ml)</th>
<th>Recorded (ml)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3671</td>
<td>3645</td>
<td>0.71</td>
</tr>
<tr>
<td>2</td>
<td>1392</td>
<td>1384</td>
<td>0.58</td>
</tr>
<tr>
<td>3</td>
<td>2773</td>
<td>2801</td>
<td>-1.00</td>
</tr>
<tr>
<td>4</td>
<td>2782</td>
<td>2711</td>
<td>2.62</td>
</tr>
<tr>
<td>5</td>
<td>3241</td>
<td>3288</td>
<td>-1.43</td>
</tr>
<tr>
<td>6</td>
<td>1322</td>
<td>1288</td>
<td>2.64</td>
</tr>
<tr>
<td>7</td>
<td>3523</td>
<td>3513</td>
<td>0.28</td>
</tr>
<tr>
<td>8</td>
<td>3506</td>
<td>3500</td>
<td>0.17</td>
</tr>
<tr>
<td>9 run 1</td>
<td>619</td>
<td>609</td>
<td>1.64</td>
</tr>
<tr>
<td>9 run 2</td>
<td>609</td>
<td>611</td>
<td>-0.33</td>
</tr>
<tr>
<td>10</td>
<td>2316</td>
<td>2301</td>
<td>0.65</td>
</tr>
<tr>
<td>11</td>
<td>1266</td>
<td>1301</td>
<td>-2.69</td>
</tr>
<tr>
<td>12</td>
<td>2859</td>
<td>2810</td>
<td>1.74</td>
</tr>
<tr>
<td>13</td>
<td>1323</td>
<td>1290</td>
<td>2.56</td>
</tr>
<tr>
<td>14</td>
<td>2206</td>
<td>2137</td>
<td>3.23</td>
</tr>
<tr>
<td>15</td>
<td>3042</td>
<td>2992</td>
<td>1.67</td>
</tr>
<tr>
<td>16</td>
<td>2527</td>
<td>2800</td>
<td>-9.75</td>
</tr>
<tr>
<td>17</td>
<td>1713</td>
<td>1602</td>
<td>6.93</td>
</tr>
<tr>
<td><strong>Total Mean (STD)</strong></td>
<td><strong>2261 (997)</strong></td>
<td><strong>2255 (1005)</strong></td>
<td><strong>0.57 (3.33)</strong></td>
</tr>
</tbody>
</table>

The course of the session. Inputs include ingestion of food/drink/medications, saline injections, and/or IV drips. Outputs include the UFV, blood draws, and in the case of one patient, urination. For each patient, records of the time and amount of these inputs and outputs were recorded. In the case of food or drink, the weight of the intake was measured using a portable food scale. In other cases, the density of the fluid was estimated (see Table 3.5). An example patient input/output table can be found in Table 3.6. The inputs/output volumes were converted to weights and used to calculate the net predicted weight change (Initial Weight − Final Weight, fluid loss = positive change).

The error of the predicted weight difference varied from within 2 g to 716 g (see Table 3.7 and Figure 3-8). Patients consistently lost more weight than predicted. This discrepancy is likely due to the hemodialysis machine removing more fluid than reported. Other possibilities include an underestimation of the density of the dialysate, or an overestimation of saline injection volumes.
### Table 3.5: Densities of input/output fluids used to estimate each patient’s weight change between the beginning and end of the hemodialysis session.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Density (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFV</td>
<td>Hemodialysis Machine Screen</td>
<td>1.008</td>
</tr>
<tr>
<td>Blood draw</td>
<td>Vial volume</td>
<td>1.06</td>
</tr>
<tr>
<td>Food/drink</td>
<td>Weight scale</td>
<td>n/a</td>
</tr>
<tr>
<td>Urine</td>
<td>Container volume</td>
<td>1.03</td>
</tr>
<tr>
<td>Saline Drips</td>
<td>Saline bag or syringe</td>
<td>1.0046</td>
</tr>
<tr>
<td>Medication Drips</td>
<td>IV drip</td>
<td>1.0046</td>
</tr>
</tbody>
</table>

1 Based on spent dialysate density from [56].
2 Assumes average blood density as reported in Physics, Fourth Edition.
3 Assumes high end of normal urine specific gravity.
4 Assumes saline is “normal saline” (0.90% NaCl).
5 Assumes equivalent density to “normal saline” (0.90% NaCl).

Table 3.6: An example input/output table for a patient.

<table>
<thead>
<tr>
<th>Time</th>
<th>In (ml)</th>
<th>Out (ml)</th>
<th>Density (g/ml)</th>
<th>In (g)</th>
<th>Out (g)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:33:00</td>
<td>0</td>
<td>30</td>
<td>1.06</td>
<td>0</td>
<td>31.8</td>
<td>blood draws</td>
</tr>
<tr>
<td>7:34:00</td>
<td>10</td>
<td>0</td>
<td>1.0046</td>
<td>10.0</td>
<td>0</td>
<td>small saline bolus</td>
</tr>
<tr>
<td>8:04:48</td>
<td>0</td>
<td>10</td>
<td>1.06</td>
<td>0</td>
<td>10.6</td>
<td>more labs</td>
</tr>
<tr>
<td>8:08:49</td>
<td>7</td>
<td>0</td>
<td>1.0046</td>
<td>7.0</td>
<td>0</td>
<td>medication</td>
</tr>
<tr>
<td>9:05:30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>muffin</td>
</tr>
<tr>
<td>10:07:37</td>
<td>118.3</td>
<td>0</td>
<td>1</td>
<td>118.3</td>
<td>0</td>
<td>water, meds</td>
</tr>
<tr>
<td>11:12:00</td>
<td>5</td>
<td>0</td>
<td>1.0046</td>
<td>5.0</td>
<td>0</td>
<td>saline for meds</td>
</tr>
<tr>
<td>11:12:00</td>
<td>0</td>
<td>2711</td>
<td>1.008</td>
<td>0</td>
<td>2732.7</td>
<td>UFV</td>
</tr>
<tr>
<td>11:12:00</td>
<td>44.032</td>
<td>0</td>
<td>1.0046</td>
<td>44.2</td>
<td>0</td>
<td>heparin drip</td>
</tr>
<tr>
<td>11:12:00</td>
<td>157.75</td>
<td>0</td>
<td>1.0046</td>
<td>158.5</td>
<td>0</td>
<td>nitroglycerin drip</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td>342.08</td>
<td>2751</td>
<td></td>
<td>427.1</td>
<td>2775.1</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.6: An example input/output table for a patient.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Weight (kg)</th>
<th>Measured Weight Diff. (g)</th>
<th>Predicted Weight Diff. (g)</th>
<th>Absolute Difference (g)</th>
<th>Percent Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>113.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>93.7</td>
<td>1300</td>
<td>1021.0</td>
<td>-279.0</td>
<td>-21.46</td>
</tr>
<tr>
<td>3</td>
<td>85.0</td>
<td>2500</td>
<td>2358.1</td>
<td>-141.9</td>
<td>-5.67</td>
</tr>
<tr>
<td>4</td>
<td>74.1</td>
<td>2400</td>
<td>2348.0</td>
<td>-52.0</td>
<td>-2.17</td>
</tr>
<tr>
<td>5</td>
<td>99.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>59.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>127.4</td>
<td>3900</td>
<td>3231.8</td>
<td>-668.2</td>
<td>-17.13</td>
</tr>
<tr>
<td>8</td>
<td>83.6</td>
<td>3400</td>
<td>3349.7</td>
<td>-50.3</td>
<td>-1.48</td>
</tr>
<tr>
<td>9 run 1</td>
<td>80.2</td>
<td>-400</td>
<td>-579.2</td>
<td>-179.2</td>
<td>44.81</td>
</tr>
<tr>
<td>10 run 2</td>
<td>80.5</td>
<td>-100</td>
<td>-233.2</td>
<td>-133.2</td>
<td>133.22</td>
</tr>
<tr>
<td>11</td>
<td>56.3</td>
<td>2100</td>
<td>1943.7</td>
<td>-156.3</td>
<td>-7.4</td>
</tr>
<tr>
<td>12</td>
<td>57.9</td>
<td>800</td>
<td>660.7</td>
<td>-139.3</td>
<td>-17.4</td>
</tr>
<tr>
<td>13</td>
<td>104.9</td>
<td>2400</td>
<td>1683.4</td>
<td>-716.6</td>
<td>-29.9</td>
</tr>
<tr>
<td>14</td>
<td>73.3</td>
<td>800</td>
<td>727.8</td>
<td>-72.2</td>
<td>-9.0</td>
</tr>
<tr>
<td>15</td>
<td>71.1</td>
<td>1700</td>
<td>1536.9</td>
<td>-163.1</td>
<td>-9.6</td>
</tr>
<tr>
<td>16</td>
<td>103.7</td>
<td>2300</td>
<td>2298.1</td>
<td>-1.9</td>
<td>-0.1</td>
</tr>
<tr>
<td>17</td>
<td>53.3</td>
<td>2400</td>
<td>2153.3</td>
<td>-246.7</td>
<td>-10.3</td>
</tr>
<tr>
<td>18</td>
<td>72.7</td>
<td>1100</td>
<td>1074.4</td>
<td>-25.6</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

Table 3.7: A table summarizing the accuracy of the predicted weight changes during the hemodialysis sessions vs. the measured weight changes. The Absolute Difference and Percent Difference columns present the absolute and percent difference between the predicted and measured weight differences. Final Weights for three patients were not available.
Figure 3-8: Predicted vs. Measured Weight Differences (Initial Weight – Final Weight, positive change = weight loss) across all patient runs with available Initial and Final Weights. The red line is the identity (Predicted Weight Difference = Measured Weight Difference).

Reliability of UFV

Estimation of UFV based on recorded UFR were all consistent within less than 10% error, with most patients consistent within less than 5% error. Estimated weight changes were consistently lower than actual weight changes, with errors up to 716 g. Most errors were within 200 g, which is within the ±0.1 kg resolution of the weight scale. Net UFV measurements should be suitable to use, with knowledge that UFV may be underestimating actual weight loss, particularly in those patients with differences larger than 200 g.

3.3.4 Calf Circumference Measurements

Methods

Calf circumference measurements were performed at the beginning and end of the hemodialysis session at each voltage electrode and averaged to produce a single calf circumference value in centimeters. The individual measurement sites will be referred to as V+ and V-. For the first 11 patient runs, a single measurement was taken before
and after the session, for a total of two measurements. For the last 7 patient runs, three measurements were performed before and after, for a total of six measurements.

There is no gold standard to measure the accuracy of the calf circumference measurements. However, Zhu et al. developed a method to at least compare measured calf circumference changes over the course of hemodialysis with estimated calf circumference changes using bioimpedance data \[57\]. This method assumes that changes in bioimpedance during hemodialysis are solely due to changes in fluid, and so the final calf circumference can be predicted from the starting calf circumference and the measured resistances.

Assume a cylinder that is a model of the calf and starts with a radius \(r(0)\) at time \(t=0\) and changes to \(r(t)\) at time \(t=t\). The change in volume from time \(t=0\) to time \(t=t\) is:

\[
\Delta V_{ol} = \pi L (r(0)^2 - r(t)^2) = \pi L (2r(0) \Delta r - \Delta r^2)
\] (3.30)

where \(\Delta r = r(0) - r(t)\). If the change in circumference \(\Delta C = 2\pi \Delta r\), the change in volume can be expressed in terms of the circumference as:

\[
\Delta V_{ol} = L \left( \frac{2C(0) \Delta C - \Delta C^2}{4\pi} \right)
\] (3.31)

The circumference at a given time \(C(t) = C - \Delta C\) is then equal to:

\[
C(t) = \sqrt{C(0)^2 - \frac{4\pi}{L} \Delta V_{ol}}
\] (3.32)

The change in volume \(\Delta V_{ol}\) can also be expressed as a function of the measured resistance of the cylinder:

\[
\Delta V_{ol} = \rho L^2 \left( \frac{1}{R(0)} - \frac{1}{R(t)} \right) = \frac{\rho L^2}{R(0)} \left( 1 - \frac{R(0)}{R(t)} \right)
\] (3.33)

where \(\rho\) is the resistivity of the cylinder, \(R(0)\) is the resistance at time \(t = 0\) and \(R(t)\) is the resistance at time \(t\).

Combining these two equations, the circumference as a function of time can be ex-
pressed in terms of the initial measured circumference, the initial measured resistivity, and the measured resistances at time \( t = 0 \) and time \( t \):

\[
C(t) = \sqrt{C(0)^2 - \frac{4\pi \rho L}{R(0)}} \left(1 - \frac{R(0)}{R(t)}\right)
\]  
(3.34)

Results

A comparison of the measured calf circumference using measuring tape and the estimated calf circumference measurements using Equation 3.34 is presented in Figure 3-9. The data were highly correlated \((r^2 = 0.94)\). However, there was a statistically significant error of \(-0.55 \text{ cm} \pm 1.18 \text{ (p < 0.001)}\) between the two measurements, with the estimated calf circumference underestimating the measured calf circumference.²

The average measured change in calf circumference was \(-0.4 \text{ cm}\), which is on the same order as the difference between the measured and estimated circumference. This high error suggests that calf circumference measurements may not be sufficiently reliable for assessing changes in fluid status (such as calculations of changes in compartment volumes), and should be used for the purpose of determining an “operating point” of calf circumference only. One possible explanation for these results could be that the calf circumference measurement was performed around the electrode after the electrode had been placed, which could alter the results.

Measurement Repeatability

Calf circumference data for patients who had their calf circumference measured more than once at the beginning and end of the hemodialysis session can be found in Table 3.8. The mean standard deviation across all measurements was 0.16 cm. Standard deviations for individual measurement sessions (i.e. \( V^+ \) in a patient) varied between 0.00 cm and 0.47 cm. Based on these data, one can infer that the repeatability of calf measurements is about 0.2 cm in most cases, which is repeatable to less than 1% at a calf circumference of 30 cm.

²By comparison, Zhu et al. found a much smaller deviation of 0.07 ± 0.56 cm.
Figure 3-9: Measured calf circumference vs. estimated calf circumference based on bioimpedance data.

<table>
<thead>
<tr>
<th>Patient</th>
<th>V- Before</th>
<th>V+ Before</th>
<th>V- After</th>
<th>V+ After</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>29.90 ± 0.26</td>
<td>36.17 ± 0.31</td>
<td>28.63 ± 0.47</td>
<td>35.60 ± 0.10</td>
</tr>
<tr>
<td>12</td>
<td>33.33 ± 0.15</td>
<td>41.77 ± 0.06</td>
<td>33.67 ± 0.31</td>
<td>41.43 ± 0.06</td>
</tr>
<tr>
<td>13</td>
<td>25.53 ± 0.06</td>
<td>32.50 ± 0.10</td>
<td>24.13 ± 0.06</td>
<td>31.67 ± 0.15</td>
</tr>
<tr>
<td>14</td>
<td>26.53 ± 0.15</td>
<td>29.90 ± 0.10</td>
<td>25.67 ± 0.21</td>
<td>32.10 ± 0.00</td>
</tr>
<tr>
<td>15</td>
<td>35.47 ± 0.23</td>
<td>39.90 ± 0.00</td>
<td>33.73 ± 0.35</td>
<td>40.47 ± 0.06</td>
</tr>
<tr>
<td>16</td>
<td>24.73 ± 0.15</td>
<td>32.20 ± 0.17</td>
<td>24.00 ± 0.10</td>
<td>30.67 ± 0.32</td>
</tr>
<tr>
<td>17</td>
<td>34.37 ± 0.15</td>
<td>41.97 ± 0.12</td>
<td>32.77 ± 0.12</td>
<td>40.80 ± 0.26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>29.98 ± 4.47</strong></td>
<td><strong>36.34 ± 4.95</strong></td>
<td><strong>28.94 ± 4.44</strong></td>
<td><strong>36.10 ± 4.74</strong></td>
</tr>
</tbody>
</table>

Table 3.8: Calf circumference measurements (cm) in patients with three measurements at the beginning and end of each session. Each measurement is the mean of three measurements plus/minus the standard deviation of the measurements. V+ measurements are measurements performed at the positive voltage electrode and V- measurements are measurements performed at the negative voltage electrode.
3.3.5 Fluid Overload Measurement Reliability

Patient fluid overload in kilograms was calculated using a clinician’s assessment of patient dry weight (see Section 3.2.5). Dry weight, by definition, is the weight at which a patient becomes hypotensive during hemodialysis in the absence of antihypertensive drugs [58]. In the present study, there were four patients who had “negative” fluid overload estimates, despite fluid removal during hemodialysis (see Figure 3-6). These patients were excluded from any analysis involving estimated fluid overload in kilograms.

3.3.6 Bioimpedance Changes During Hemodialysis

Patient bioimpedance changes over the course of hemodialysis are presented in Table 3-6. While there were average increases in the bioimpedance parameters $R_e$, $R_i$, and $R_\infty$ of 5-6%, some patients experienced decreases in one or more bioimpedance parameters, indicating an increase of fluid in that compartment. This heterogeneous presentation will be explored further in Section 3.3.10.

3.3.7 Volume Changes During Hemodialysis

Calf extracellular and intracellular compartment volumes estimated using the methods described in Section 3.2.4 are presented in Figure 3-10. Measured calf total water varied between 250 mL and 600 mL. There were a range of ECW / TBW ratios between 0.33 and 0.84. Because of the inaccuracies of the calf circumference measurements, the changes in calf compartment volumes from the beginning to the end of the session should be considered with caution. Resistance measurements will be used in lieu of volume measurements in subsequent sections.

3.3.8 Comparison of Fluid Assessment Metrics

Three methods of fluid status assessment were used in the present study: estimated fluid overload, pedal edema scores, and calf normalized resistivity / CNR (see Section
There was a weak correlation between clinician assessed fluid overload (expressed as % of body weight) and CNR ($r = 0.50$). Other researchers have observed correlations between CNR and gold standard assessments of whole body ECW [42]. These results could be due to inaccurate clinical assessments of dry weight, or imply that calf edema does not correlate with overall fluid status. A lack of correlation between clinician assessed FO and CNR would not be entirely surprising, as fluid buildup in the calf vs. rest of the body likely depends on a variety of factors such as posture, etiology of a patient’s fluid overload, and individual patient factors.

There was a strong correlation between pedal edema scores and CNR ($r = -0.75$). Pedal edema scores at higher CNR tend to be either one or zero, and increase as CNR lowers (see Figure 3-11). There can be 10% changes in body weight without perceptible changes in edema, which could explain the variable pedal edema scores at higher CNR [59].

### 3.3.9 Changes in Total Calf Water

Patients with the highest ultrafiltration rates (8 mL/h/kg and above) tended to have the largest changes in $R_\infty$, with patients with lower ultrafiltration rates having a
smaller change (see Figure 3-12). One might expect a linear relationship between ultrafiltration rate and fluid removal from the calf, as other researchers have suggested that fluid is recruited from the calf to refill the trunk (see Section 3.1.6). These data support this hypothesis. The resistance $R_\infty$ is inversely proportional to the total calf water, and therefore one would expect to see a curve like these patient data show.

There are some outliers in this present graph; these patients and more will be explored in the subsequent sections.

### 3.3.10 Heterogeneity of Calf Fluid Status Changes

As discussed in Section 3.3.6, there were heterogeneous changes in calf bioimpedance parameters over the course of hemodialysis. These patients can be grouped based on changes in $R_e$ and $R_i$ into three distinct presentations denoted by the colors blue, red and yellow (see Figure A-1).
Figure 3-12: Changes in $R_\infty$ vs mean UFR.

Figure 3-13: Percent changes in $R_e$ vs. percent changes in $R_i$. 
Blue patients

Patients in the blue group had increases in $R_e$ and $R_i$, which implies fluid removal from both cECW and cICW. They had initial cECW/cTW ratios of $0.48 \pm 0.07$, which suggests moderate calf edema (an ECW/TBW ratio of 0.33 is considered normal [60]). Figure 3-14a provides a visual representation of the fluid status changes. Blue patients present as one might expect during standard hemodialysis: as fluid is removed from plasma, it is partially refilled by the interstitial space, which in turn is partially refilled by the intracellular space. This results in a decrease in both cECW and cICW.

Red patients

Patients in the red group have increases in $R_e$, but decreases in $R_i$, implying a shift of fluid from cECW to cICW. They had initial cECW/cTW ratios of $0.48 \pm 0.11$, which suggests moderate calf edema that was not statistically different from patients in the blue group ($p = 0.96$). Figure 3-14b provides a visual representation of the fluid status changes. Half the red patients also had an increase in $R_\infty$, implying that cECW was moved both to cICW and out of the calf. Red patients tended to have lower ultrafiltration rates than blue patients, but similar CNR in addition to cECW/cTBW ratios (for CNR data, see Figure 3-15).

Other researchers have shown that overall ICW can increase over the course of hemodialysis, particularly in patients with low ultrafiltration rates or diffusive hemodialysis (see Section 3.1.3) [60, 61]. Additionally, simulations performed by Akcahaveyin et al. suggest that these fluid shifts into cells tend to be more pronounced in low perfusion areas like the legs [60]. These data corroborate these findings as there were fluid shifts into cells at low ultrafiltration rates and fluid shifts out of cells at higher ultrafiltration rates for patients with similar CNR values.

One exception to the ultrafiltration rate relationship was a blue patient that had a much lower ultrafiltration rate and lower CNR than other blue patients; this patient’s ultrafiltration rate was in the same range as the red patients (see Figure 3-15). It is possible that in this patient, a lower ultrafiltration rate was required to “prevent”
shifts into cICW due to higher plasma refill rates due to fluid overload.

Yellow patients

Yellow patients all had decreases in $R_e$, which implies increases in cECW. They had cECW/cTW ratios of $0.65 \pm 0.13$, which suggests high calf fluid overload that is statistically significantly higher than patients in the blue group ($p = 0.02$) and in the red group ($p = 0.03$). Figure 3-14b provides a visual representation of the fluid status changes. Two patients had no net change in $R_i$ as represented in the figure (see error bars in Figure 3-16b), and two patients had increases in $R_i$. This means that while all patients had increases in cECW, in two cases this increase appears to come from elsewhere in the body, and in the other two cases it appears to come from cICW in addition to the body. Yellow patients were also characterized by lower CNR compared with patients in other groups (see Figure 3-15b), although there were two red patients and one blue patient that had similar fluid overload levels.

Increases in cECW with no change in cICW could be due to posture / gravity. Changes in posture result in fluid shifts in extracellular fluid via plasma, with shifts into and out of the interstitial spaces in different segments of the body [62]. When sitting or standing, fluid pools in the legs, which reverses when lying in a supine or “semi-supine” position (i.e. legs and buttocks at same level, torso supported by
pillows or bed frame).

The patients in this study were all in a “semi-supine” position. While it is generally assumed that patients in the “semi-supine” position will experience fluid shifts from the calf to the trunk, this is the opposite of what was observed here. One study did find that there was fluid pooling in the leg in a subset of patients when those patients sat up in bed during their hemodialysis session [63], which suggests that postural changes that result in pooling in the leg are possible. However, the present study did not monitor posture. Additionally, it is not clear whether increases in cECW due to posture only happen with low CNR, or could happen with a patient with higher CNR. Future research should examine the role of posture and calf hydration in fluid accumulation in the calf during hemodialysis.

The last two patients had increases in cECW and decreases in cICW, which implies fluid flow into the extracellular space from cells. One of these patients had net zero cTW change, whereas the other patient had a decrease in cTW. These two patients had the lowest CNR of all patients, with moderate/low UFR. Fluid flows out of cells when the interstitial fluid has higher osmotic pressure, which in this case could occur due to the dialysate sodium concentration gradient and/or plasma refill (see Section 3.1.3). Sodium is the main solute that could pull fluid out of cells. This
Figure 3-16: (b) Percent changes in $R_e$ vs. percent changes in $R_i$; (a) changes in calf volume in the yellow group. Dashed lines represent the original compartment volumes before hemodialysis.

would occur if the dialysate sodium concentration is higher than the plasma sodium concentration. However, both patients had dialysate sodium concentrations lower than equilibrium, which would imply flow into cells rather than out of them. Another possibility is that interstitial osmolarity is increased due to high plasma refill rates due to low CNR. Other researchers have documented increases in plasma volume at the end of hemodialysis [64]. However, this effect was documented several hours after hemodialysis, so further research is needed to determine the mechanism behind this effect.

### 3.4 Chapter Summary

In this study, calf bioimpedance measurements from hemodialysis patients were recorded before and after each session. Total fluid removal from the calf was related to the mean ultrafiltration rate, with higher ultrafiltration rates resulting in larger changes in total calf water.

Changes in calf extracellular and calf intracellular volumes were heterogeneous and were grouped into three different categories. The first group of patients had decreases in both calf extracellular and intracellular fluid. This was in line with what
was originally expected. The second group of patients had fluid shifts from the calf intracellular space to the calf extracellular space. This appears to be due to low ultrafiltration rates compared to the patients in the previous group. The final group of patients had increases in calf extracellular fluid. These patients had the most fluid overload in the calf.

These findings suggest that fluid from the calf is recruited more readily at higher ultrafiltration rates for patients with low to moderate edema levels in the calf. Patients with high calf edema have less fluid recruitment, or even fluid increases, in the calf. These findings are contrary to what one might expect from the literature, in that patients with the most overload had the lowest fluid removal from the calf.

The ultrafiltration relationship here support the hypothesis that fluid from the calf is recruited to replenish fluid lost in the trunk. Higher ultrafiltration rates mean more fluid removed from the trunk, which in this study led to larger decreases in calf total water. The dependence of fluid recruitment on calf edema supports the hypothesis that regional blood flow may play a role in fluid changes in the calf. If fluid was removed from everywhere at the same rate, one would not expect any increases in calf fluid to occur, which is what was observed here.

Some caution must be taken when considering the fluid shifts into and out of cells presented here. Because compartment volumes can take hours to equilibrate after hemodialysis, measurements performed immediately after the hemodialysis session may not be at equilibrium. It is therefore likely that some portion of the fluid shifts into and out of cells observed here would not persist at equilibrium (see Section 3.1). Additionally, changes in fluid conductivity could account for some fraction of the measured bioimpedance changes (see Appendix A).
Chapter 4

Determining Ideal Calf Electrode Placement to Measure Fluid Status Changes

The aim of this chapter is to determine the ideal electrode placement at the calf to measure changes in fluid status. Calf impedance measurements during hemodialysis range from 10–70\(\Omega\) and change by single digit \(\Omega\) values in most patients over the course of their sessions. Because these changes are small, it is important to place electrodes on the calf in a way that will maximize the impedance change due to fluid status changes. The purpose of this section is to 1) determine an ideal electrode placement topology and spacing for fluid status measurements at the calf and 2) determine an ideal electrode placement around the calf.

4.1 Topology Simulations

There are two main functional requirements for a successful electrode configuration: to maximize resistance changes due to fluid overload, and to maximize uniformity of current distribution in the tissue. Finite element simulations were performed using commercial software (COMSOL) to evaluate these requirements.
4.1.1 Methods - Simulation Configuration

The calf was modeled as a cylinder with a bone of constant radius at the center. The default parameters for the calf measurement model can be found in Table 4.1. The toroid surrounding the bone has resistivity determined by the fluid status of the patient and is anisotropic to mimic the properties of muscle tissue. The tissue has a value $\rho_{\text{longitudinal}}$ down the length of the calf with resistivities seven times that in other dimensions [65]. Electrodes are simulated as small spheres with centers on the surface of the calf (a three-dimensional adaptation of the electrodes in [66]).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf length</td>
<td>35 cm</td>
<td>length of experimenter calf (height: 5’1”)</td>
</tr>
<tr>
<td>Electrode radius</td>
<td>0.5 cm</td>
<td>approx. size of real electrode</td>
</tr>
<tr>
<td>Bone radius</td>
<td>1.375 cm</td>
<td>[67]</td>
</tr>
<tr>
<td>Calf radius</td>
<td>5 cm</td>
<td>average patient calf radius</td>
</tr>
<tr>
<td>Bone resistivity</td>
<td>20 $\Omega$ m</td>
<td>[68]</td>
</tr>
<tr>
<td>ECW resistivity</td>
<td>40.5 $\Omega$ cm</td>
<td>[36] (may change, see Appendix A)</td>
</tr>
</tbody>
</table>

Table 4.1: Default values for parameters in the calf measurement model.

Two electrode topologies called “longitudinal” and “transverse” were investigated. For each topology, an “optimal” configuration was selected that minimized the error between the measured and expected resistance (i.e. $R = \frac{\rho L}{A}$). Both topologies consist of two current carrying electrodes and two voltage sensing electrodes.

The longitudinal topology is the standard bioimpedance topology, with all four electrodes placed in a line along the side of the cylinder (see Figure 4-1a) [69]. The voltage electrodes are spaced a distance of 11 cm on either side of the midpoint of the calf, and the current carrying electrodes are spaced 5 cm outside each voltage electrode; 5 cm current and voltage spacing is considered standard for bioimpedance measurements [69]. In the transverse case, the current electrodes are placed on opposite sides of the calf midpoint. The voltage electrodes are placed 1.1 cm below each current electrode (see Figure 4-1b). In both cases, the calf is oriented such that the X-axis is in the lateral-medial (left-right) axis of the calf, the Y-axis is the superior-inferior (up-down) axis of the calf, and the Z-axis is the dorsal-ventral (back-front) direction of the calf.
4.1.2 Methods - Fluid Overload

To simulate the tissue undergoing increasing fluid overload, it was assumed that in the presence of edema, the length of the calf and the calf intracellular volume $V_{cICW}$ stay constant, and that increasing fluid in the calf causes an outward expansion of the calf (i.e. increase in cross-sectional area). For an increase in edema $\Delta$, the calf volume $V_{calf}$ and cECW volume $V_{cECW}$ change as:

\[
V_{calf,new} = V_{calf,orig} + \Delta \tag{4.1}
\]
\[
V_{cECW,new} = V_{cECW,orig} + \Delta \tag{4.2}
\]

As edema increases, the calf resistivity decreases. Recall that the apparent resistivity $\rho$ (i.e. the $\rho$ used to calculate the resistance of the calf $R = \frac{\rho L}{A}$) of tissue
is:

\[ \rho = \frac{\rho_{ECW}}{(1 - c)^{3/2}} \]  

(4.3)

where \( \rho_{ECW} \) is the resistivity of the extracellular fluid and \( c \) is the volume fraction of non-conducting tissue. In this case, \( c = 1 - \frac{Vol_{cECW}}{Vol_{calf}} \), so the resistivity \( \rho \) before and after edema are:

\[ \rho_{orig} = \frac{\rho_{ECW}Vol_{calf}^{3/2}}{Vol_{cECW}^{3/2}} \]  

(4.4)

\[ \rho_{new} = \frac{\rho_{ECW}(Vol_{calf} + \Delta)^{3/2}}{(Vol_{cECW} + \Delta)^{3/2}} \]  

(4.5)

As both the volume of the cECW and the total volume of the calf increase at the same rate, \( \rho \) decreases. For the simulations, the initial radius of the calf was 5 cm, and fluid was added or removed in increments of 1 cm of calf radius.

### 4.1.3 Methods - Current Uniformity

The second requirement to choose between the two electrode topologies is the uniformity of current distribution in the tissue. This is important to ensure that current penetrates into the tissue and as little preference is given to the surface of the skin (which can be affected by non-fluid related parameters such as body temperature or sweat) as possible.

Bioimpedance measurements performed in this thesis are four-point measurements. Current is driven between two electrodes, and the resulting voltage is picked up by a separate pair of electrodes. Both the distribution of driven current through the tissue and the “pickup” of the voltage electrodes must be considered to determine the uniformity of the measurement. Sensitivity is a measure of how much a volume of tissue contributes to the overall measured resistance. The sensitivity \( S \) is defined
as [66]:

\[
S = \frac{J_{cc}J_{reci}}{I^2}
\]  

(4.6)

where \(J_{cc}\) is the current density that results from a current \(I\) driven between the two current electrodes and \(J_{reci}\) is the current density that results from a current \(I\) driven between the two voltage electrodes. The measured resistance \(R\) for sensitivity \(S\) is the integration in volume of the sensitivity times the resistivity:

\[
R = \int \rho S dv = \int \frac{\rho J_{cc}J_{reci}}{I^2} dv
\]  

(4.7)

See Figure 4-2 for an example.

Current must be driven through both pairs of electrodes to calculate sensitivity. One electrode of each pair is assigned to be a current source of 100\(\mu\)A in COMSOL and the other electrode is assigned to be ground. Then the sensitivity is calculated as the normalized dot product of the resulting current densities in the calf. The resistance is calculated as the integration of the sensitivity over the volume of the calf, minus the space occupied by the electrodes. All simulations are performed at DC, which corresponds to the low frequency bioimpedance case used to calculate cECW.

To compare the two topologies, the sensitivity was analyzed at the midpoint of the calf \((L_{calf}/2)\) in both the X (left/right) direction and in the Z (front/back) direction. The uniformity was calculated as the percent change between the maximum sensitivity value in tissue and the minimum sensitivity value in tissue.
(a) Current density distribution of the current driving electrodes (i.e. \( J_{cc} \) in Equation 4.7).

(b) Current density distribution of the voltage sensing electrodes (i.e. \( J_{reci} \) in Equation 4.7).

(c) Sensitivity distribution (log scale) that is the dot product of subfigures a and b multiplied by the resistivity \( \rho \) and normalized by the squared current \( I^2 \).

Figure 4-2: An example sensitivity distribution for a scenario with four electrodes placed along the length of a rectangle. The current density of a constant current driven through the current electrodes (subfigure a) is multiplied by the current density of a constant current driven through the voltage electrodes (subfigure b) to produce the sensitivity distribution in subfigure c.
4.1.4 Results

The longitudinal topology consistently had larger changes in resistance as a function of edema (see Figure 4-3). For example, the change between 5 cm and 6 cm was -36.7% in the longitudinal configuration and -16.0% in the transverse configuration.

There was poor sensitivity uniformity in both topologies. The best case in the X direction was a change of -92% from the maximum sensitivity value in tissue to the minimum value in the longitudinal configuration and -99% in the transverse configuration (see Figure 4-4). The best case in the Z direction was -23% in the longitudinal configuration and -87% in the transverse configuration (see Figure 4-5).

4.1.5 Discussion

The measured resistance in the longitudinal configuration changed about two times more with edema than the transverse configuration (-36.7% vs. -16.0%). The absolute change between the different configurations was less pronounced (-8.2 Ω vs. -6.0 Ω). The larger percent change is due both to a larger starting resistance and a larger absolute change in resistance.

Both configurations had poor sensitivity uniformity at maximum depth in the
Figure 4-4: A comparison of the longitudinal and transverse topologies in the X Direction (left to right) for $Y = \frac{L_{\text{calf}}}{2}$ and $Z = 0$. 

(a) graph of log sensitivity for both topologies; 

(b) Current distribution for the driving electrode pair for the longitudinal topology; 

(c) Current distribution for the driving electrode pair for the transverse topology.

Figure 4-5: A comparison of the longitudinal and transverse topologies in the Z Direction (back-front) for $Y = \frac{L_{\text{calf}}}{2}$ and $X = 0$. 

(a) graph of log sensitivity for both topologies; 

(b) Current distribution for the driving electrode pair for the longitudinal topology; 

(c) Current distribution for the driving electrode pair for the transverse topology.
X-direction (-92% for longitudinal, -99% for transverse), with improvement in the Z-direction for both configurations (-22.1% and -82.84% values, respectively). The large decreases over the calf were due to both the anisotropy of the muscle tissue (which causes current to prefer to flow down the leg rather than across it), and due to the relatively short length of the calf. The calf length of 35 cm was chosen as a conservative value, and the sensitivity should improve for longer calf lengths in the longitudinal case (but will not affect the results in the transverse case).

Overall, the longitudinal configuration is more suitable for the impedance measurement in hemodialysis than the transverse configuration. The measured resistance changes more as cECW is added and the current is less concentrated in any one particular region.

4.1.6 Improving Current Uniformity With Ring Electrodes

Placing electrodes in a longitudinal configuration increases expected changes in bioimpedance during a simulated hemodialysis session. The main limitation of this method is poor sensitivity uniformity due to the use of point electrodes.

One method to improve sensitivity is to use ring electrodes rather than point electrodes. Previously, point electrodes were simulated as spheres with radii equal to the electrode radius \( R_{elec} \). The center of each sphere was located on the calf surface. If the electrodes are instead simulated as toroids with outer radii equal to the calf radius \( R_{calf} \) and inner radii equal to the electrode radius \( R_{elec} \) (see Figure 4-6), the sensitivity uniformity in both directions improves substantially to a change of -10% in both the X-direction and the Z-direction compared with -92% and -23% in the longitudinal configuration, respectively (see Figure 4-7).

Point electrodes are used for bioimpedance measurements primarily for convenience. Ring electrodes can be more difficult to work with due to the need for gel and adhesive around the whole leg. In patients with hair, it also means shaving more of the leg. Ring electrodes should be more feasible to implement in the wearable implementation using fabrics.
Figure 4-6: (a) COMSOL model for the ring electrode configuration. The electrodes are spaced the same as in the longitudinal case, but with rings instead of point electrodes. (b) A top down schematic view of a ring electrode. The lightest gray is calf muscle, the middle gray is bone, and the darkest gray is the electrode. The dashed line indicates the calf surface, with the ring electrode on either side of it.

Figure 4-7: (a) Comparison of sensitivity distribution in the longitudinal configuration with and without the use of ring electrodes. (b) Current distribution for the driving electrode pair in the longitudinal configuration using ring electrodes.
4.2 Placement Measurements

In this section, electrode placement is investigated through measurements with patients undergoing hemodialysis and COMSOL simulations.

4.2.1 Study Procedures - Electrode Placement

It was hypothesized that placing electrodes at the back of the calf instead of on the side of the calf would result in higher impedance changes over the course of hemodialysis. To evaluate this hypothesis, a variation of the protocol in Section 3.2.2 was implemented. Eight electrodes were placed on the body, with four in the same locations as the previous protocol and four along the back of the calf. The electrodes on the back of the calf were spaced the same as the four electrodes on the side and at equivalent locations along the leg. Measurements with the side electrodes were performed, followed by measurements with the back electrodes.

4.2.2 Results - Changes in $R_e$

Changes in $R_e$ between the beginning and end of the hemodialysis session for patients enrolled in this part of the study is shown in Figure 4-8. There were larger changes in $R_e$ in the back of the calf vs. the side of the calf in 4/7 patients. Of those patients with larger changes at the back, two of those patients had a decrease in $R_e$ at the side of the calf and an increase in $R_e$ at the back of the calf. The other two had increasing $R_e$ in both positions. One patient had equal changes in both locations, and the final two patients had greater changes in the side of the calf than the back of the calf.

4.2.3 Results - Changes in $R_\infty$

Changes in $R_\infty$ between the beginning and end of the hemodialysis session for patients enrolled in this part of the study is shown in Figure 4-9. There were larger changes in $R_\infty$ in the back of the calf vs. the side of the calf in 5/7 patients. Two of those patients had $R_\infty$ moving in opposite directions, with a decrease at the side and an
Figure 4-8: $R_e$ changes at the side and back of the calf over the course of the hemodialysis session.

increase at the back in patient 11, and an increase at the side and a decrease at the back in patient 15. One patient had greater $R_\infty$ changes at the side of the leg, and the last patient had about equal changes but in opposite directions (increase at the side, decrease at the back).

4.2.4 Discussion

There appears to be a benefit in measuring at the back of the leg versus the side of the leg in some patients, with higher impedance changes of up to 4% at the back of the leg than at the side of the leg. However, in other patients there is a larger change at the side of the leg. There were three patients that had bioimpedance values move in different directions depending on the calf location. These patients all had high calf fluid overload, and hence small calf bioimpedance values. It is not known whether the difference in presentation at the side vs. back is a reflection of a physiological difference in these patients or whether these differences are due to systematic measurement error.
Figure 4-9: $R_\infty$ changes recorded at the side and back of the calf over the course of the hemodialysis session.

### 4.3 Placement - Simulations

Heterogeneity in patient presentation has been observed when measuring bioimpedance at the side and the back of the calf. COMSOL simulations were conducted to elucidate the patterns observed. In particular, the effect of bone location and size on impedance measurements and changes in impedance were investigated.

#### 4.3.1 Methods

For these simulations, the calf was simulated as a cylinder with up to two bones (the tibia and the fibula). Both bones were assumed to be cylinders with radii listed in Table 4.3. Bone resistivity was assumed to be constant. Muscle resistivity was set to the average calf resistivity calculated from all patients before and after the hemodialysis session (see Table 4.2).

Voltage electrodes were placed in a longitudinal configuration (see Section 4.1) spaced 10 cm apart. The current electrodes were spaced 5 cm from the voltage electrodes. The location of the electrodes on the surface was moved along the circumference of the calf in 20 degree increments from $\theta = 0^\circ$ to $\theta = 360^\circ$, where $\theta = 0^\circ$ is located on the calf as indicated in Figure 4-10.
Figure 4-10: Location and dimensions of COMSOL simulation setup for determining the influence of electrode placement and bone location on changes in bioimpedance.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Final</th>
<th>Absolute Change</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Resistivity (Ω cm)</td>
<td>335</td>
<td>353</td>
<td>18</td>
<td>5.37</td>
</tr>
<tr>
<td>Calf radius (cm)</td>
<td>5.07</td>
<td>5.03</td>
<td>-0.04</td>
<td>-0.79</td>
</tr>
</tbody>
</table>

Table 4.2: Parameters simulating changing hydration status in the calf due to fluid removal during hemodialysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf length</td>
<td>40 cm</td>
<td>length of experimenter calf (height: 5'1&quot;)</td>
</tr>
<tr>
<td>Electrode radius</td>
<td>0.5 cm</td>
<td>approx. size of real electrode</td>
</tr>
<tr>
<td>Tibia radius</td>
<td>1.375 cm</td>
<td>[67]</td>
</tr>
<tr>
<td>Fibula radius</td>
<td>0.7 cm</td>
<td>[70]</td>
</tr>
<tr>
<td>Calf radius</td>
<td>5 cm</td>
<td>average patient calf radius</td>
</tr>
<tr>
<td>Bone resistivity</td>
<td>20 Ωm</td>
<td>[68]</td>
</tr>
<tr>
<td>Muscle resistivity</td>
<td>335 Ωcm</td>
<td>average calculated from patients</td>
</tr>
</tbody>
</table>

Table 4.3: Default values for parameters in the calf measurement model with both bones.
Figure 4-11: Simulated resistance for different combinations of bones in the calf.

### 4.3.2 Results

Simulations for the calf with different combinations of bone/no bone are presented in Figure 4-11. When no bones are present in the calf, the resistance is flat as a function of $\theta$ with a resistance of $47 \, \Omega$. With the tibia only, the impedance peaks at $74 \, \Omega$ at $\theta = 0^\circ$ and the baseline resistance increases from $47 \, \Omega$ in the no bone case to $50 \, \Omega$.

With the fibula only, the baseline resistance increases to $48 \, \Omega$ with a peak of $51\Omega$ at $\theta = 120^\circ$. With both bones, there are multiple peaks in resistance, with the tibia peaking at $81 \, \Omega$ at $\theta = 0^\circ$ and the fibula peaking at $54 \, \Omega$ at $\theta = 120^\circ$.

Simulated changes in resistance due to simulated hemodialysis were consistently around $7\%$ across all theta (see Figure 4-12). The percent changes near the tibia were slightly larger than those near the fibula ($7.4\%$ at $\theta = 0^\circ$ vs. $6.9\%$ at $\theta = 100^\circ$), and there was no difference between percent changes near the fibula and changes on the opposite side of the leg ($6.9\%$ at $\theta = 100^\circ$ vs. $6.9\%$ at $\theta = 260^\circ$). The changing resistivity dominated the total resistance change, accounting for about $70\%$ of the total change in resistance.
4.3.3 Discussion

In this section, results from longitudinal measurements performed at the side of the calf and at the back of the calf were presented. It was hypothesized that placement of the electrodes in the back of the leg would result in higher changes in calf resistance during hemodialysis because the back of the leg is further from the bones in the calf. However, results from patients were mixed, with some patients having higher changes at the back of the calf, and others having higher changes at the side.

Simulations were conducted to understand the influence of bone on the bioimpedance measurement. Electrode placement was varied around the leg in 20° increments and the resistance was measured in a simulated before and after hemodialysis state. There were higher absolute resistance values closer to calf bones than away from them. Percent changes in calf resistance were consistent around the leg, with only slightly larger changes (0.5% out of a total change of 7.5%) occurring near the tibia. The changes in calf resistance were dominated by changing resistivity, which accounted for 70% of the measured change, with area accounting for the other 30%.

There is a discrepancy between measured changes in bioimpedance during hemodial-
ysis, in which there were higher resistance changes at the back in some patients, and
the simulations, which suggest that there should be minimal influence of bone in gen-
eral, and the fibula in particular. The most likely explanation for these discrepancies
is that the resistivity of the calf is not uniform. This could be due to a number of
factors, such as resistivity differences in different muscle groups and fluid pooling in
different locations.

In practice, it is likely that the ideal electrode placement will depend on each
patient, with the ideal location somewhere between $90^\circ$ and $270^\circ$. Although there
were slightly larger percentage changes near the front of the leg, it is hypothesized that
these changes would be smaller when accounting for regional resistivity differences,
as more fluid is expected to pool in the back of the leg due to gravity.

4.4 Chapter Summary

In this Chapter, electrode topologies and placement for measurements of calf fluid
status via bioimpedance have been evaluated. Simulations were conducted to compare
the changes in resistance and the sensitivity in longitudinal and transverse topologies.
It was found that the longitudinal topology has greater changes in resistance due to
fluid status changes and improved current uniformity throughout the calf muscle
compared with the transverse topology. However, the current uniformity was limited
in both topologies. This can be substantially improved with ring electrodes in a
longitudinal topology using fabrics in the eventual wearable implementation.

Measurements were performed using the longitudinal topology and point elec-
trodes at the side and back of the leg. It was hypothesized that there would be
larger changes in the back of the leg than the side of the leg, but experimental results
were mixed. Simulations showed that when simulated with uniform resistivity in the
calf, there are larger changes in impedance near bone, not away from it. In practice,
ideal electrode placement will depend on that patient’s individual resistivity and fluid
distribution throughout the calf.
Chapter 5

Portable BIS System

This chapter will review the results of the final two thesis aims: to design and verify a portable bioimpedance spectroscopy system on the bench (Thesis Aim 3) and in a clinical setting (Thesis Aim 4).

5.1 Portable Bioimpedance System

A portable bioimpedance system that measures body impedance from 1 kHz to 1 MHz was designed and fabricated to the specifications shown in Table 5.1. It drives an AC current of $100 \mu A$ through two Ag/Ag-Cl electrodes placed on the body and measures the resulting voltage between two neighboring Ag/Ag-Cl electrodes. The device consists of the following components:

1. Custom-Designed Impedance Measurement PCB “Daughter Board”
2. ADI Bluetooth Low Energy (BTLE) and Microcontroller (MCU) PCB “Mother Board”
3. Metal Enclosure
4. BNC cables w/ snap button attachments

Components 1 and 2 are mounted within a metal enclosure (Component 3). The daughter board impedance measurement PCB (Component 1) is an analog front end (AFE) designed by the author, and the mother board BTLE/MCU PCB (Component 2) is manufactured by Analog Devices. The device is connected to the Ag/Ag-Cl
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
<th>Actual</th>
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<tr>
<td>Frequency range</td>
<td>1 kHz to 1 MHz</td>
<td>1 kHz to 1 MHz</td>
</tr>
<tr>
<td>Current</td>
<td>$100 \mu A_{rms}$</td>
<td>$100 \mu A_{rms}$</td>
</tr>
<tr>
<td># Frequencies</td>
<td>10 / decade</td>
<td>10 / decade</td>
</tr>
<tr>
<td>Magnitude range</td>
<td>100 – 1000 $\Omega$</td>
<td>35.1 – 3510 $\Omega$</td>
</tr>
<tr>
<td>Phase range</td>
<td>0 – -$90^\circ$</td>
<td>0 – -$90^\circ$</td>
</tr>
<tr>
<td>Battery Life</td>
<td>Several hours</td>
<td>4+ hrs</td>
</tr>
</tbody>
</table>

Table 5.1: Specifications for the portable bioimpedance spectroscopy system.

electrodes by BNC cables with snap-button connectors on the end (Component 4).

5.1.1 System Design

The Analog Front End drives current through the body and measures the resulting voltage using the magnitude-ratio and phase-difference detection method (see Figure 5-2). A direct digital synthesizer (AD9833, ADI) is used to generate a sinusoidal voltage that is converted to a sinusoidal current by an op-amp placed in the inverting configuration (ADA4891, ADI). The resulting current is driven through the body by a set of two electrodes. The current is in series with a known, non-inductive resistance (350 $\Omega$). The voltage across the body and the reference resistance are both amplified by instrumentation amplifiers and converted to single-ended voltages (AD8231, ADI). The resulting single ended voltages are then placed through a Gain-Phase Detector (AD8302, ADI). The Gain-Phase Detector outputs a voltage proportional to the ratio of the magnitudes and phase difference between the two signals. These two outputs are sampled by two ADC input lines on the ADI mother board and sent to an iOS device using Bluetooth Low Energy.

Power for the device is provided by a single-cell 3.7V Lithium-Ion battery with 600 mAH nominal charge capacity. A 3V analog and 3V digital supply are generated from this voltage using an ADP3301-3 (ADI) voltage regulator for the analog supply and a REF193 (ADI) voltage regulator for the digital supply. Power to the analog front end and to the Bluetooth module can be toggled on and off by the microcontroller.

The voltages corresponding to the magnitude ratio and phase difference are sampled by an ADC on the Analog Devices mother board. These data are then trans-
mitted to a modified version of an Analog Devices iOS app. The iOS app visualizes the magnitude and phase data and transmits them over Bluetooth Low Energy to an MIT server using SFTP.

Four BNC cables with snap button attachments are used to connect the electrodes to the participant (see Figure 5-3). The BNC cable shields are connected to battery ground and the BNC conductor is connected directly to the electrode. Two different electrode connectors were used during the experiments (see Figure 5-4). The custom-designed electrode connectors were used during the first round of clinical testing. The connectors were switched to using extensions of standard snap button connectors for the second round of clinical testing due to concern for patient comfort when the patient rested on the comparatively bulky connectors.
5.1.2 Calibration

The system is calibrated with three RC networks using quadratic Lagrange interpolation prior to each measurement session [71]. Each RC network is configured with three circuit elements to mimic the electrical properties of the body (see Figure 5-5a). Circuit parameters for each RC network are listed in Table 5-5b and a bode plot of the calibration impedances can be found in Figure 5-6. All resistors in the RC networks had at least ± 1% tolerance and all capacitors had at least ± 10% tolerance. Additionally, the impedance of each RC network was independently verified using an Agilent 4294A precision impedance analyzer.

5.1.3 Data Processing

Data from the bioimpedance spectroscopy system are analyzed in MATLAB to extract circuit parameters according to the Cole model (see Section 2.2.2). MATLAB’s \texttt{lsqcurvefit} algorithm was selected to achieve a non-linear least squares fit (see Section 3.2.3).
5.2 Device Validation

A distinct set of four RC networks (Test 1 – 4 in Figure 5-5b) were used to validate the experimental bioimpedance measurement system. For each network, bioimpedance spectroscopy data from 1 kHz to 1 MHz was collected and the circuit parameters for each model were extracted assuming a three element circuit model (see Sections 5.1.3 and 2.2.1). The percent error of the extracted parameters for each test RC network is presented in Table 5.2. The error of the two resistances \( R_e \) and \( R_i \) were all less than 1%, and the error for the capacitance \( C_m \) was less than 3% with the exception of Test 3, which was about 7%.

<table>
<thead>
<tr>
<th>RC Network</th>
<th>( R_e ) Error (%)</th>
<th>( R_i ) Error (%)</th>
<th>( C_m ) Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>-0.02</td>
<td>-0.02</td>
<td>0.54</td>
</tr>
<tr>
<td>Test 2</td>
<td>-0.11</td>
<td>0.37</td>
<td>2.7</td>
</tr>
<tr>
<td>Test 3</td>
<td>0.56</td>
<td>-0.41</td>
<td>7.04</td>
</tr>
<tr>
<td>Test 4</td>
<td>0.33</td>
<td>0.7</td>
<td>1.79</td>
</tr>
</tbody>
</table>

Table 5.2: The percent error of the experimental bioimpedance spectroscopy system measuring four different test RC networks (parameter values in Table 5-5b).
(a) The custom designed electrode connectors and the 3M-2560 Ag/Ag-Cl electrodes used during the first round of clinical testing.

(b) The re-purposed standard electrode connectors used during the second round of clinical testing.

Figure 5-4: The two types of electrode connectors used during the hemodialysis studies.

5.3 Device Repeatability

Human subjects testing with two healthy volunteers was performed to evaluate the repeatability of the bioimpedance spectroscopy system and compare BIS measurements from opposite sides of the body. All testing took place at MIT’s Clinical Research Center under the supervision of a trained nurse and informed consent was obtained from all participants. After obtaining appropriate consent, 20 Ag/AgCl electrodes (3M-2560) were placed in pairs on five different parts of both sides of the body. In all cases, effort was made to place the electrodes in identical locations on both sides of the body.

- **Wrist/Hand**: Two electrodes were placed on the palmar side of each arm (the side with the palm of the hand on it). For each side, one electrode was at least 2 cm proximal from the process of the radial and ulna bones; the other electrode was placed at least 5 cm proximal from the first electrode.

- **Neck**: Two electrodes were placed on the lateral sides of the neck and shoulder. For each side, one electrode was placed on the lateral side of the neck 5-10 cm below the hair line. The other electrode was placed superior to the clavicle,
(a) The three element circuit model used for the RC calibration networks.

(b) Values for each of the RC networks used for calibration and testing.

<table>
<thead>
<tr>
<th>RC Network</th>
<th>$R_e$ (Ω)</th>
<th>$R_i$ (Ω)</th>
<th>$C_m$ (nF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibration 1</td>
<td>60.4</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>Calibration 2</td>
<td>316</td>
<td>1620</td>
<td>1.8</td>
</tr>
<tr>
<td>Calibration 3</td>
<td>1000</td>
<td>953</td>
<td>2.2</td>
</tr>
<tr>
<td>Test 1</td>
<td>402</td>
<td>402</td>
<td>5.6</td>
</tr>
<tr>
<td>Test 2</td>
<td>464</td>
<td>499</td>
<td>2.3</td>
</tr>
<tr>
<td>Test 3</td>
<td>300</td>
<td>300</td>
<td>2.7</td>
</tr>
<tr>
<td>Test 4</td>
<td>60</td>
<td>100</td>
<td>11.2</td>
</tr>
</tbody>
</table>

Figure 5-5: The RC networks used to calibrate the system (topology in Figure 5-5a) with component values in Figure 5-5b.

- **Hips:** Two electrodes were placed on the left and right side of the anterior side of the trunk. For each side, one electrode was placed at least 5 cm superior to the midpoint of the iliac crest. The other electrode was placed at least 5 cm proximal from the first electrode.

- **Knee:** Two electrodes were placed on the anterior side around both knees. For each side, one electrode was placed on the proximal side of the knee, at least 2 cm proximal to the patella (kneecap) and 2-5 cm lateral. The other electrode was placed 2-5 cm distal and 2-5 cm lateral to the knee.

- **Ankle/Foot:** Two electrodes were placed on the medial surface of each leg. One electrode was placed at least 2 cm proximal to the ankle. The other electrode was placed at least 5 cm proximal from the first electrode.

After all the electrodes were placed on the participant, the participant laid down on a hospital bed in the supine position for 5 minutes. After 5 minutes has elapsed, the experimenter began taking bioimpedance measurements. Each frequency sweep consists of 10 points per decade from 1 kHz to 1 MHz for a total of 31 points. Each bioimpedance run consists of 5 continuous frequency sweeps, and runs are repeated
Figure 5-6: Bode plot of the RCs used to calibrate the experimental system. Component values are listed in Table 5-5b.

3 times per measurement type (see Figure 5-7). The BNC cables are removed and replaced between measurements.

A total of 10 different types of measurements are made in the order shown below.

1. Hand (+) to foot (-) (left side)
2. Neck (+) to foot (-) (left side)
3. Hip (+) to foot (-) (left side)
4. Knee (+) to foot (-) (left side)
5. Hand (+) to foot (-) (right side)
6. Neck (+) to foot (-) (right side)
7. Hip (+) to foot (-) (right side)
8. Knee (+) to foot (-) (right side)
9. Foot (L/+ to foot (R/-)
10. Knee (L/+ to foot (R/-)
Figure 5-7: A schematic overview of repeatability measurements performed for each measurement type. This method was repeated 10 times, once for each of the different measurement types.

Repeatability is determined separately for magnitude and phase at each frequency of interest. It is determined both “within run” (i.e. between the 5 different sweeps), “across runs” (i.e. between the 3 different runs, which are each the average of 5 sweeps), and “across sides” (i.e. between the two different sides, if applicable). To calculate the magnitude repeatability, the standard deviation of the measured magnitude at the frequency of interest is calculated (this will be 5 points for “within run” calculations and 3 points for “across run” calculations). The resulting standard deviation is divided by the mean magnitude at that frequency and multiplied by 100. This calculation is repeated for all frequencies, and the maximum (worst case) percent error is reported. The repeatability calculation for the phase is the same, with the exception that the absolute standard deviation is reported, not the percentage error.

Results for the two participants are shown in Figure 5.3. In BIS001, deviations were smallest within runs and increased both across runs and across sides of the body. BIS002 had a single run with high error (Neck to foot (left) 3) that skews the within run results. Without this run the worst case within run repeatability was 2.45 % for magnitude and $4.96^\circ$ for phase. Error between runs was comparable between BIS001 and BIS002. Repeatability between sides was slightly higher between sides for BIS002 compared with BIS001.
Table 5.3: Standard Deviations of the worst case error within runs, across runs, and across sides. The worst case magnitude error is expressed in percentage points and the worst case phase error is expressed in degrees.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Within Runs</th>
<th></th>
<th>B/W Runs</th>
<th></th>
<th>Across Sides</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (%)</td>
<td>P (°)</td>
<td>M (%)</td>
<td>P (°)</td>
<td>M (%)</td>
<td>P (°)</td>
</tr>
<tr>
<td>BIS001</td>
<td>2.65</td>
<td>1.42</td>
<td>3.09</td>
<td>1.48</td>
<td>5.01</td>
<td>4.94</td>
</tr>
<tr>
<td>BIS002</td>
<td>10.57</td>
<td>7.15</td>
<td>3.18</td>
<td>4.93</td>
<td>6.94</td>
<td>6.41</td>
</tr>
</tbody>
</table>

5.4 Comparing Commercial and Experimental Measurement System

The experimental system has been verified on the bench (Thesis Aim 3). The final aim is to verify the system in a clinical setting (Thesis Aim 4). Bioimpedance measurements with patients undergoing hemodialysis were performed with a commercial measurement system (Impedimed SFB7) and the experimental measurement system described here. Measurements were performed with the same set of electrodes for each system, with a configuration as shown in Figure 3-5. As described in Section 3.2, five bioimpedance measurements were performed with the commercial system before and after hemodialysis. In addition, continuous measurements were performed with the experimental measurement system throughout the session. Five bioimpedance measurements at the beginning and end of these continuous measurements were selected for comparison with the commercial measurement system. To compare the two devices, circuit parameters $R_e$ and $R_\infty$ were extracted from the bioimpedance spectra using MATLAB (see Section 5.1.3).

5.4.1 Evaluation Criteria for Experimental System

The most important requirement for the experimental system is to be able to track changes in bioimpedance consistently over an extended period of time. In this thesis, the time period of evaluation is about 4 hours over the course of a hemodialysis session. Bioimpedance measurements from the experimental system were compared with measurements from a commercial measurement system. While the commercial
system may have errors of its own, for the sake of this work it is assumed to be the “gold standard.”

The requirements for the experimental system in comparison with the commercial measurement system are listed in Table 5.4. Because these measurements cannot be readily compared with physiology, the specifications were selected based on the actual impedance values and changes that need to be measured, namely impedances between 12 and 70 Ω with changes of single digit Ω values. The absolute difference specification is present to evaluate the system’s ability to calculate absolute impedance values for calculating the ECW/TBW ratio and calf resistivity (see Sections 2.4.2 and 2.4.4), which depend on absolute bioimpedance values. The specification of 3 Ω represents a much higher % error at low impedances than at high impedances. However, the accuracy of calf bioimpedance at very low bioimpedances is less important as patients with sufficiently low impedance values are almost certainly fluid overloaded.

Absolute differences between measurements do not include systematic error between systems. If, for example, there is a bias of 1 Ω between the two devices, this will not count toward the absolute difference as it is a bias that can be calibrated out.

When relevant, Bland-Altman plots will be presented. A Bland-Altman plot is commonly used in clinical testing to compare an experimental measurement with a gold standard. In this case, this would be the experimental system and the commercial measurement system. The measured data are plotted against each other on the left side of the graph, with the unity line of Experimental = Commercial indicated in dashed gray line and a solid line indicating the line of best fit based on linear regression. Relevant equations and statistics are listed in the top left-hand corner of the graph. The mean of the commercial and experimental systems is plotted on the X access of the right side of each figure, with the difference Experimental - Commercial presented on the Y-axis. In this case, the dashed black lines correspond to the limits of agreement for the data set, which is defined as a 95% confidence interval or 1.96 times the standard deviation of the points on the graph. The reproducibility coefficient discussed in the text is 1.96 times the standard deviation.
5.4.2 Electrode Connectors

Two different electrode connectors were used for the measurements (see Figure 5-4). The electrode connectors were switched after the first 10 patient runs both to perform measurements at the back of the leg and because there were large absolute differences in bioimpedance measurements between the two devices, particularly at high frequencies after the run (see Figure 5-8). It was hypothesized that the electrode connectors were contributing to loose electrode connections that were affecting measurements with the experimental system. The electrodes were adjusted at the end of the hemodialysis session and before performing measurements with the commercial system, which appears to have artificially degraded the performance of the experimental system. As such, graphs will present data with all or just the 7 patients with new connectors as is relevant.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute difference between measurements</td>
<td>≤ 3 Ω</td>
</tr>
<tr>
<td>Difference in change</td>
<td>≤ 2 Ω</td>
</tr>
<tr>
<td>Direction of change</td>
<td>same direction (positive/negative)</td>
</tr>
</tbody>
</table>

Table 5.4: Specifications to compare the experimental measurement system with the commercial measurement system.

5.4.3 Absolute Data

There were strong correlations between $R_e$ data as measured by the two devices ($r = 1.00$ before the hemodialysis session, $r = 0.99$ after the hemodialysis session). There was an offset of 1.6 Ω between the two devices before the hemodialysis session and 1.2 Ω between the two devices after the hemodialysis session. The reproducibility coefficients were 2.8 Ω and 4.3 Ω, respectively. Data from all but one patient was within the limits of agreement (i.e. 1.96 SD) both before and after the session. The repeatability coefficient of $R_e$ final data improved to 3.2 Ω after switching electrode connectors.

$R_e$ data from before the hemodialysis session satisfied the absolute difference functional requirement (i.e. difference ≤ 3 Ω) with the exception of a single patient (16/17
who had the lowest bioimpedance values measured. Although there does not appear to be consistently higher errors at lower resistance values, it is likely that this difference is due to limitations of both measurement systems resolving impedances below 20 Ω.

$R_e$ data from after the hemodialysis session satisfied the absolute difference functional requirement for 14/17 (82%) of patients. Values that did not satisfy the functional requirement included $R_e$ data from the patient that did not satisfy the functional requirement with data from before the hemodialysis as well. The other two patients were patients measured before the switch to the new connectors.

There were greater differences between the two devices for $R_\infty$ compared with $R_e$. The correlations between the two devices before and after the session were $r=0.94$ and $r=0.46$, respectively. $R_\infty$ was underestimated both before the session by 3.4 Ω and after the session by 5.6 Ω. The reproducibility coefficients were 6.6 Ω and 13.4 Ω. Data from all but one patient after the dialysis session was within the limits of agreement.

$R_\infty$ can be more difficult to estimate because of poor electrode connection and/or stray capacitance. This may explain why there was both greater variation and absolute differences between measurements from the two devices (as compared with $R_e$ data) both before and after the session. The differences between the two devices after the hemodialysis session were much greater than before the session. This is most likely due to loose electrodes toward the end of the hemodialysis session. After the first round of testing, the type of electrode connectors were switched and the final measurements were taken after the electrodes had been adjusted. Data using only these patients is much improved (compare Figures 5-8 and 5-9). The offset reduced from 5.6 Ω to 2.1 Ω ($p = 0.07$), with a new reproducibility coefficient of 4.8 Ω (down from 13.4 Ω).

$R_\infty$ data before the hemodialysis session satisfied the absolute difference requirement with 13/17 patients (76%). Of those not satisfying the requirements, three patients were measured before transitioning to the new electrode connectors. $R_\infty$ data after the hemodialysis session satisfied the absolute difference requirement with
10/17 (58 \%) with both sets of electrode connectors and 5/7 (71 \%) with only the new electrode connectors.

Figure 5-8: $R_\infty$ **Final Data:** a Bland-Altman plot comparing measured $R_\infty$ data acquired at the end of the dialysis session.
Figure 5-9: $R_\infty$ Final Data (second round of patients only): a Bland-Altman plot comparing measured $R_\infty$ data acquired at the end of the dialysis session for only the patients with the new electrode connectors and improved protocol.
5.4.4 Changes Data

There was a strong correlation between changes in $R_e$ between both devices ($r = 0.85$, see Figure 5-10). There was a small offset not significantly different from zero between the two devices (-0.53 Ω, $p = 0.32$). The reproducibility coefficient was 4.17 Ω, and measurements from two patients were outside this range. The correlation increases to $r = 0.99$ and a reproducibility coefficient of 1.12 Ω with the new electrode connectors.

The changes in bioimpedance functional requirement for $R_e$ data was satisfied in 13/17 (76 %) patients with both sets of electrode connectors, and with all 7/7 (100 %) patients with the new electrode connectors. Bioimpedance changes were in the same direction using both sets of connectors in 13/17 (76 %) patients; 6/7 (85%) patients had changes in the same direction using only the new set of connectors.

Figure 5-10: Changes in $R_e$ over course of the hemodialysis session: a bland-altman plot comparing changes in bioimpedance from the beginning of the dialysis session to the end of the dialysis session for both devices.

There was a negative correlation ($r = -0.45$) for $R_\infty$ changes measured by the two devices and an offset of -2.4 Ω that was not statistically significant ($p = 0.13$, see Figure 5-11). The reproducibility coefficient was 12.6 Ω. All measured data points fall within this range. Results improved to a correlation of $r = 0.97$, with an offset of -0.39 Ω ($p = 0.11$) and a reproducibility coefficient of 1.11 Ω with the new electrode connectors (see Figure 5-12).
Changes in $R_\infty$ were within the functional requirement for 9/17 (53 %) patients using both connectors, and for 7/7 patients (100 %) using the new connector. 7/17 (41 %) changes in $R_\infty$ were in the same direction using both sets of connectors; 4/7 (57 %) were in the same direction using the new connectors only. The changes in $R_\infty$ were small overall, which could explain why there are discrepancies between the direction of changes even with the new connectors.

Figure 5-11: Changes in $R_\infty$ over course of the hemodialysis session: a bland-altman plot comparing changes in bioimpedance from the beginning of the dialysis session to the end of the dialysis session for both devices.

<table>
<thead>
<tr>
<th>Specification</th>
<th>$R_e$ % Met</th>
<th>$R_\infty$ % Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute difference between measurements (3 $\Omega$)</td>
<td>Initial: 94 (86)</td>
<td>Initial: 76 (86)</td>
</tr>
<tr>
<td></td>
<td>Final: 82 (86)</td>
<td>Final: 58 (71)</td>
</tr>
<tr>
<td>Difference in change (2 $\Omega$)</td>
<td>76 (100)</td>
<td>53 (100)</td>
</tr>
<tr>
<td>Direction of change (same)</td>
<td>76 (85)</td>
<td>41 (57)</td>
</tr>
</tbody>
</table>

Table 5.5: Percentage satisfaction of the functional requirements comparing the experimental measurement system with the commercial measurement system. Each percentage is the total percentage ($N = 17$) with the percentage from using the new connectors only ($N = 7$).
Figure 5-12: Changes in $R_\infty$ over course of the hemodialysis session (second round of patients only): a bland-altman plot comparing changes in bioimpedance from the beginning of the dialysis session to the end of the dialysis session for both devices.
5.5 Chapter Summary

A portable bioimpedance spectroscopy system that measured bioimpedance in the range of 1 kHz to 1 MHz was developed and verified both on the bench and in a clinical setting (hemodialysis). Resistance and capacitance values extracted from experimental system data were within 2% and 1.1 nF of the actual values, respectively. The device repeatability for magnitude measurements was within 3% between consecutive sweeps.

Calf bioimpedance measurements were performed before and after hemodialysis patients using a commercial device and the experimental device developed in this thesis. Ten patients were measured with a custom made electrode connector and the final seven patients were measured using a standard button connector (see Figure 5-4). Functional requirements for such a comparison were presented in Table 5.4.

$R_e$ absolute bioimpedance values and changes from beginning to end of hemodialysis more closely satisfied the functional requirements than $R_\infty$ measurements. This is not unexpected as stray capacitance and electrode contact disproportionately affect $R_\infty$ measurements compared with $R_e$ measurements. The implementation of the new electrode connectors improved the satisfaction of all functional requirements for both measurement types both before and after the hemodialysis session. Because the new connectors improved results both before and after, it’s likely that the connectors themselves contributed to discrepancies between the measurements, in addition to electrode contact issues at the end of the hemodialysis session. Ultimately, results between the two devices were comparable, especially when the changes were greater than 2 $\Omega$. 
Chapter 6

Conclusion

6.1 Summary of Contributions

This thesis had four aims:

1. Determine how changes in calf impedance are related to fluid removed during hemodialysis
2. Determine the best electrode placement to perform the calf bioimpedance measurement
3. Develop and verify a portable bioimpedance measurement system on the bench
4. Evaluate experimental system against a commercial system in a clinical setting

This work presents several contributions that addressed each of these aims:

1. A clinical test was conducted with 17 patients undergoing hemodialysis that demonstrated that changes in the calf bioimpedance parameters $R_e$, $R_i$ and $R_\infty$ between the beginning and end of the hemodialysis session depend on calf hydration and ultrafiltration rate (Thesis Aim 1).

2. Simulations were conducted that support using a longitudinal electrode topology with ring electrodes for performing calf bioimpedance measurements (Thesis Aim 2).
3. A clinical test was conducted with 7 patients undergoing hemodialysis that demonstrated that changes in the calf bioimpedance parameter $R_e$ during hemodialysis depends on electrode location along the calf (Thesis Aim 2).

4. A discrete, portable bioimpedance spectroscopy system was designed, built, and verified on both the bench and in a clinical setting (Thesis Aims 3 and 4).

6.2 Progress Toward Wearable Bioimpedance Vision and Future Work

The ultimate goal of this research project is to develop a wearable bioimpedance measurement system to reduce heart failure readmissions in patients with Congestive Heart Failure. This thesis focused on measuring calf bioimpedance in a controlled environment (hemodialysis) and on improving the electrode placement for fluid status monitoring. In this section, a summary of the findings of this thesis will be presented, along with a discussion of how these results could be translated to an ambulatory CHF setting and future work to achieve this vision.

6.2.1 Summary of Findings

Changes in the bioimpedance parameters $R_e$ and $R_\infty$ between the beginning of hemodialysis and the end of hemodialysis were heterogeneous and categorized into three distinct groups (see Section 3.3.6). There were two main findings relating to different patient presentation: 1) that calf fluid overload affects changes in calf compartment volumes, and 2) that fluid flow in or out of cells is dependent on the mean ultrafiltration rate in patients with lower calf fluid overload. In particular, patients with lower fluid overload in the calf had fluid removal from the calf that was proportional to the mean ultrafiltration rate. This was consistent with what was expected. However, patients with higher fluid overload in the calf displayed greater heterogeneity, and a subset of these patients actually retained fluid in the calf despite a decrease in Total Body Water.
Fluid shifts into or out of cells depended on the mean ultrafiltration rate for patients with lower calf fluid overload. Fluid shifted out of cells at higher mean ultrafiltration rates, and into cells at lower mean ultrafiltration rates. A portion of these fluid shifts are transient and will not persist at equilibrium.

A combination of simulations and measurements were performed to determine the ideal electrode placement for calf bioimpedance measurements. Simulation results showed that measuring in a longitudinal topology (i.e. up and down the leg) resulted in larger changes in calf bioimpedance and improved current uniformity compared with measuring in a transverse topology (i.e. across the leg). Simulations also showed that point electrodes have poor uniformity, but that that uniformity can be improved almost ten times by using ring electrodes. Longitudinal measurements at the side of the leg and the back of the leg revealed that electrode placement around the calf depends on the individual patient. This is likely due to regional resistivity differences. Measurements with ring electrodes would eliminate the need for evaluating the best placement.

6.2.2 Translation to Ambulatory CHF

Findings from this thesis suggest that changes in calf bioimpedance will depend on calf fluid overload and on the fluid removal rate (i.e. ultrafiltration rate). Patients with high fluid overload had a heterogeneous and less predictable presentation than those with lower levels of fluid overload. In an eventual ambulatory setting, patients would have the wearable bioimpedance monitor placed when a clinician assesses a patient to be at their “dry weight” (i.e. no fluid overload). This means that patients should be at lower calf fluid overload levels, which had a more clear relationship with changes in fluid status than patients with higher levels of fluid overload. Additionally, the wearable implementation will involve a feedback loop and intervention to help minimize fluid overload in the calf. Should a patient reach sufficiently high levels of fluid overload as observed in a subset of the hemodialysis patients, medical intervention (i.e. hospitalization) would be necessary.

In a hemodialysis setting, fluid is removed rapidly from the body, resulting in
transient fluid shifts into and out of cells that do not persist at equilibrium. The rate of fluid accumulation and removal in an ambulatory CHF setting will be an order of magnitude slower than fluid accumulation/removal in hemodialysis (0 to 1 L / hour in hemodialysis vs. 0 to 1 L / day in ambulatory CHF); this means that the system should effectively be at equilibrium at all times and any changes in fluid status should reflect longer lasting changes rather than transient ones.

Another consideration in translation to an ambulatory CHF setting is the expected volume changes in that setting. In hemodialysis, patients have up to 0-4 kg of fluid removed every other day. In ambulatory CHF, patients are instructed to consult a physician when their weight increases by more than 2 kg over the course of a few days. Because these changes are on the same order, the calf bioimpedance system should be able to detect these changes so long as the device can consistently measure bioimpedance over a period of several days. Ideally, the calf bioimpedance system would measure bioimpedance over the period of a year without recalibration.

6.2.3 Future Work

Future work should integrate the measurements performed here in a wearable form factor and determine the relationship between posture and fluid accumulation. In particular, results from this thesis show that such a system should use ring electrodes placed in a longitudinal configuration to perform calf bioimpedance measurements from 1 kHz to 1 MHz. Using ring electrodes will ensure current uniformity throughout the entire measurement volume and average out any regional resistivity differences in the calf.

Additionally, future research should consider integration of strain gauges into the wearable system. Strain gauges could allow for continuous assessment of calf circumference, which can be used for calf resistivity measurements (one metric of fluid overload used in this thesis).

Fluid accumulation is affected by patient posture, so future research should consider how different postures affect fluid accumulation in the calf. Accelerometers could be integrated into the wearable system to enable correction for changes in pa-
tient posture.
Appendices
Appendix A

Conductivity Changes During Hemodialysis

A.1 Motivation

Changes in bioimpedance were measured in patients in a hemodialysis unit. There was a heterogeneous patient presentation in changes of the extracellular resistor $R_e$ and the intracellular resistor $R_i$ (see Figure A-1). These changes were presumed to be due to fluid volume changes in the calf. However, there are other possible explanations for these changes, such as a change in the extracellular conductivity. This appendix will evaluate the possible influence of changes in fluid conductivity on the measurements.

A.2 Relationship of Measured Resistance to Fluid Conductivity

Assuming the calf is a cylinder, the measured low frequency resistance $R_e$ is a function of the resistivity of the calf $\rho$ and the cross-sectional area $A$:

$$R_e = \frac{\rho L}{A}$$ (A.1)
Equation A.1 can also be expressed as a function of the calf volume $V_{calf}$:

\[
R_e = \frac{\rho L}{A} \quad (A.2)
\]
\[
R_e = \frac{\rho L}{A} * \frac{L}{L} \quad (A.3)
\]
\[
R_e = \frac{\rho L^2}{V_{Vol_{calf}}} \quad (A.4)
\]

If one assumes tissue is a conductive fluid with suspended non-conductive spherical elements (i.e. cells), the resistivity $\rho$ is related to the volume fraction of the non-conducting spheres $c$ and the resistivity of the conductive medium $\rho_{ECW}$:

\[
\rho = \frac{\rho_{ECW}}{(1 - c)^{3/2}} \quad (A.5)
\]

Assuming the non-conductive spheres have a volume equal to the total calf volume $Vol_{calf}$ minus the extracellular volume $Vol_{cECW}$, the volume fraction $c$ is:

\[
c = 1 - \frac{Vol_{cECW}}{Vol_{calf}} \quad (A.6)
\]
The resistivity $\rho$ can then be expressed as:

$$\rho = \rho_{ECW} \left( \frac{Vol_{calf}}{Vol_{cECW}} \right)^{3/2}$$  \hspace{1cm} (A.7)

The equation for $R_e$ can then be expressed as:

$$R_e = \frac{\rho_{ECW} \frac{Vol_{calf}}{Vol_{cECW}}^{3/2} L^2}{Vol_{calf}}$$  \hspace{1cm} (A.8)

$$R_e = \rho_{ECW} \sqrt{Vol_{calf} Vol_{cECW}^{3/2} L^2}$$  \hspace{1cm} (A.9)

The conductivity of extracellular fluid $\sigma_{ECW}$ is the inverse of the extracellular resistivity $\rho_{ECW}$, and so the final equation is:

$$R_e = \frac{\sqrt{Vol_{calf} Vol_{cECW}^{3/2} L^2}}{\sigma_{ECW}}$$  \hspace{1cm} (A.10)

### A.3 Determinants of Extracellular Conductivity

The extracellular conductivity is a function of the ionic content of the extracellular fluid:

$$\sigma_{ECW} = \sum_i = \lambda_i c_i$$  \hspace{1cm} (A.11)

where $\lambda_i$s are the ionic conductivities of extracellular solutes and $c_i$s are the concentration of those solutes. It is assumed that sodium is the dominant solute that will dictate the conductivity, and any changes in conductivity are attributed to changes in sodium concentration. The resistivity of extracellular fluid is assumed to be around $41 \ \Omega cm$ [37]. This translates to a conductivity of $0.02 \ S/cm$. 

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A.4 Changes in Extracellular Conductivity During Hemodialysis

There are two main ways the extracellular conductivity could potentially change during hemodialysis: changing solute concentration due to fluid removal, and changing solute concentration due to diffusion of solute across the dialyzer membrane. Because the relevant question here is how the concentration could change without changes in volume, emphasis will be on the later mechanism.

Sodium can diffuse across the dialyzer membrane in either direction, which would alter the concentration of sodium in the plasma. For example, if the dialyzer concentration is higher than equilibrium, sodium concentration in the plasma would increase. This would increase the concentration of all extracellular fluid by a fraction of the plasma volume change, as the plasma volume accounts for only one portion of the extracellular space (around 20%). With sufficient time, the sodium concentration of the entire space would increase to reach equilibrium with the dialysate sodium concentration. This would depend on the length of the hemodialysis session.

In this cohort of patients, dialysate sodium was fixed to 140 mEq/L, with plasma sodium concentrations that ranged from 130 mEq/L to 141 mEq/L (see Figure A-2). The equilibrium value at which no sodium will flow occurs when plasma sodium concentrations are equal to 135.8 mEq/L due to the Donnan effect (red line in Figure A-2). Patients with sodium gradients lower than this threshold should have decreasing sodium concentrations, and patients higher than this threshold should have increasing sodium concentrations.

Because sodium is the dominant ion, an X% change in extracellular sodium concentration should change the extracellular resistance by -X% (see dashed black line on graph). If one assumes the plasma volume fully equilibrates, but the interstitial space does not change at all, there would be a -.2X% change (see solid black line on graph). Many patients change in an opposite direction from what the sodium gradient would predict, which suggests a change due to volume in addition to some possible change in conductivity. There are some patients that change in a direction consistent with
Figure A-2: Percent changes in $R_e$ as a function of $\Delta Na^+$ (Dialysate Sodium - Serum Sodium). The red line represents the equilibrium difference due to the Donnan effect. The solid black line represents the expected change in resistance due to changes in sodium conductivity when only the plasma equilibrates (assumed 20% of cECW). The dashed black line represents the expected change in resistance when the entire cECW equilibrates.

the sodium gradient. In all of these patients, the change in resistance exceeds the predicted change, even if the entire extracellular space has reached equilibrium. In two patients, the difference is only slightly larger than the change predicted by plasma equilibration. Therefore, it is reasonable to conclude that resistance changes measured over the course of hemodialysis are a combination of conductivity and volume changes, as conductivity alone cannot explain the measured changes in resistance.

A.5 Conclusion

Changes in calf bioimpedance were heterogeneous. It was hypothesized that these differences were due to different changes in calf compartment volumes. This assumption did not consider the possible effect of changing extracellular conductivity on the
measurements. Here it was shown that the changes measured during hemodialysis exceed that which would be expected to be due to changes in extracellular conductivity, supporting the previous hypothesis that these changes are due to changes in volume status.
Chapter 7

Bibliography


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