Bioimpedance as a tool in cardiac resynchronisation therapy

Fred-Johan Pettersen

*Department of Clinical and Biomedical Engineering,
Oslo Hospital Services,
Oslo University Hospital*

UiO : University of Oslo

*Department of Physics,
University of Oslo*

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Part I

Introduction

Chapter 1

Introduction

This thesis is meant for readers with medical background as well as electrical bioimpedance or physics background. To enable both groups to get the most out of it, a short introduction for both worlds is given. For a more thorough coverage, these three books are recommended: *Bioimpedance & Bioelectricity Basics* [1] which covers the field of electrical bioimpedance, *Cardiac pacing, defibrillation and resynchronization: a clinical approach* [2] which covers the details of cardiac resynchronisation therapy (CRT), and *Comprehensive Electrocardiology* [3] which covers most aspects of electrocardiology.

1.1 Biomedical background: On the heart

1.1.1 Myocytes and myocardium

Understanding the tissues of the heart is a key to understand some of the heart diseases and their treatments. For this work, the myocytes, or muscle cells, are of special interest. A myocyte is an excitable cell, which means that it can be stimulated to do an action. This action can be divided into an electrical part and a mechanical part. The electrical part is where the cell's ion balance is involved, and the mechanical part is where the mechanical contraction of the cell is involved. There are several types of myocytes in the body, but only cardiac myocytes are considered here. Tissue consisting of contractile myocytes is called *myocardium*.

Starting with the electrical part, a myocyte, as all cells, has a cell membrane a few nanometer thick. This membrane is not permeable for ions, which means that it is electrically isolating since ions are the charge carriers in a biological system. To allow ions to cross the membrane, there are three types of transport mechanisms available.

The first is the *ion channel* which may open an ion channel through the cell membrane. This channel may be highly selective and allow only certain ions, or it may be more generic and differentiate on ion charge polarity. The movement of ions through the ion channels is driven by the electric field present across the cell membrane and by any lack of concentration equilibrium for the ion or ions the channel is open for. This means that if a myocyte potential is negative relative to the outside, there is a force to move positively charged ions into the myocyte. If the extra- and intracellular concentrations of are different, there will also be a force to drive the ions in the direction of

the lowest concentration.

Secondly, a special type of ion channels called *voltage gated ion channels* are sensitive to the voltage across the cell membrane. If this voltage reaches a given level, the ion channel opens and stay open for a limited amount of time. Different types of voltage gated ion channels have different thresholds for opening, and different timing. There are two important voltage gated ion channels in the myocyte, namely a Sodium (Na^+) channel that turns on in less than a millisecond, and stay open about one millisecond, and the Potassium (K^+) channel that turns on in around 3 ms, and stays on for around 20 ms. The Na^+ channel is triggered by a +20 mV change of potential across the cell membrane, and is of particular interest since the resulting inrush of Na^+ is the start of the excitation process.

The last transport mechanism through the cell membrane is the *ion pump* where selected ions are transported across the cell membrane by spending metabolic energy. The pumps may also be seen as ion exchangers since they always move one type of ions in one direction, and another type in the other direction. An ion pump can move charges against the electric field and against the concentration gradient.

Hodgkin and Huxley presented a mathematical model of an excitable cell where the cell membrane is modelled as a capacitor and the ion channels as ionic conductances in 1952 [4]. This model has been replaced by many models since then, but one important feature of the model remains: The cell membrane is modelled as a capacitor and flow of ions through the membrane is modelled as electric current sources in parallel to the capacitor. Since this model is based on an electrical circuit model, it is the electric currents and not the number of ions through the ion channels and pumps that are used. This implies that the current for an ion pump can be zero if an active pump sends equally many and equally charged ions each way through the membrane. It is common to combine several ion currents into one electrical model current. For example, the model presented by Hodgkin and Huxley in 1952 had only three currents.

Figure 1.1 illustrates the ion transport processes in a myocyte. Each of the ion channels and pumps moves ions through the cell membrane. The current through each of the ion channels and pumps are dependent on a number of factors, but in steady state the myocytes responsible for contraction are at an equilibrium where the net currents are zero, and the potential on the inside is approximately -90 mV relative to the outside. Figure 1.1 is not showing all current flows involved in the creating of the action potential. A full model has more compartments with additional currents, and ions are involved in other processes within the cell.

In medicine, the term *action potential* is used as a name of the potential across the cell membrane during one excitation cycle. For contractile myocytes, the action potential is divided into five phases, and starts from phase 4, the resting phase. The phases are, along with typical durations:

Phase 0: Rapid depolarisation, 2 ms This phase is initiated by a positive cell membrane potential change of approximately +20 mV which opens the voltage gated Na^+ ion channels for a large and short-lived (milliseconds) Na^+ inrush (I_{Na}) and a smaller and somewhat longer-lived Calcium (Ca^{2+}) inrush (I_{CaL}). The movement of positive charges into the cell causes the potential relative to the outside to increase rapidly as can be seen in figure 1.2.

Phase 1: Initial repolarisation, 25 ms A short-lived K^+ -current (I_{t0}) out of the cell is causing the initial repolarisation. Since this current is relatively high, the potential across the cell membrane is dropping sharply.

Phase 2: Plateau, 160 ms Phase 2 is dominated by slow-changing currents of Ca^{2+} into the cell (I_{CaL}) and K^+ out of the cell (I_{Kr} and I_{Ks}). The net current is close to zero, so there is little change in potential across the cell membrane. Due to the stable potential, this phase is called the plateau phase.

Phase 3: Repolarisation, 100 ms A steady outflow of K^+ out of the cell (I_{Kr} and I_{K1}) causes the cell membrane potential to fall back to its resting level.

Phase 4: Resting stage The cell is in an equilibrium. The Na^+/K^+ ion pumps are moving Na^+ out of the cell and K^+ into the cell (I_{NaK}) and thus prepares for the next action potential.

Figure 1.1: Myocyte ion currents. The figure shows the main contributors to the action potential. The ion channels are drawn with a single arrow and the ion pumps are drawn with two arrows.

Precise timing of the various stages is dependent on several factors such as density of ion channels, density of ion pumps, availability of relevant ions, and myocyte morbidity.

When an action potential is initiated, there is a period where a new stimulus cannot re-excite the myocyte called the *refractory period*. After depolarisation (phase 0) has started, there is an *absolute refractory period* that lasts through phases 0 through 2 where it is impossible to re-excite the cell. During the *relative refractory period* which lasts through phase 3, it is possible to trigger an excitation, but it requires a stronger than normal stimulus.

The description above is giving a short introduction to the action potential. It is possible to model the process mathematically using several models from the first model of an excitable cell presented by Hodgkin and Huxley in 1952 [4] to a much more comprehensive model of a cardiac ventricular cell as presented by O'hara et al. [5].

A myocyte action potential can be transmitted to the neighbouring myocytes via gap junctions which essentially are small structures creating tunnels between myocytes. This way, the action potential in one myocyte will spread from the first myocyte that got excited as illustrated in figure 1.3 to create an action potential wavefront. The wavefront is also called a depolarisation wavefront since depolarisation is the initial

Figure 1.2: Action potential of ventricular myocyte and associated cell membrane currents. All plots are generated by a mathematical model presented in *Simulation of the un-diseased human cardiac ventricular action potential: model formulation and experimental validation* [5]. The top plot shows the potential across the cell membrane in mV. The middle plot shows most of the electric currents. Since the rapid inflow of Na^+ in Phase 0 is not comparable to the other currents on either time nor magnitude scales, this current is shown in the bottom plot using different scales.

event for an action potential. Since the action potential wavefront carries information (it tells the neighbour to get excited), it can be considered to be a signal.

In addition to the contractile myocytes already mentioned, there are three other types. These have almost no contractile material, and are as such only a part of the electrical system of the heart. The myocytes in the sinoatrial (SA) node are not stable, which means that the cells do not need an external impulse to start an action potential. The function of the SA node is to act as the pacemaker that initiates each heart beat. The SA node is located in the right atrium (RA). The atrioventricular (AV) node has myocytes that are similar in function to those in the SA node, but the natural oscillation frequency is much lower, which means that action potentials are normally triggered by extracellular stimuli. The final type of cells are those of the His-Purkinje system. These myocytes are specialised conduction cells that are relatively long and are well connected to cells in each end. As with the AV node myocytes, these cells may start

Figure 1.3: Myocardial excitation. The cells are numbered in order of excitation. The excitation pattern creates an excitation wavefront that is moving away from the first cell to excite.

an action potential without external stimuli, but it rarely happens.

The contractile myocytes in the atria and ventricles are responsible for the contraction of the heart. Contraction is coupled to the influx of Ca^{2+} during phases 0 through 2 of the action potential. The resulting contractile force has a bell-shaped form with the peak at phase 3 of the action potential. Which means that there is a delay of around 100 to 150 ms after the depolarisation of the myocyte.

1.1.2 The conduction system

The non-contracting myocytes is forming what we call the *conduction system* of the heart. A normally functioning conduction system is a one-way system where the signal to start a heart-beat is starting in the SA node and propagates out to the rest of the heart before the signal dies out, and the heart is ready for another heart-beat. At the cellular level, the signal is the depolarisation wavefront, but it is called a signal for simplicity.

The myocytes in the SA node is starting the heart-beat, and the signal is spreading slowly out through the atria through normal contractile myocytes. Parts of the atria have anisotropic properties that makes it look like there are specialised conduction paths that ensures synchronous contraction of the atria. When the signal reaches the AV node, it is transferred slowly, typically around 100 ms, through the isolating layer of connective tissue separating the atria and ventricles. This slow conduction is responsible for the delay between atrial and ventricular contraction. After the signal has passed through the AV node, it enters a fast conduction system consisting of the bundle of His, left bundle branch (LBB), right bundle branch (RBB), and a network of Purkinje fibres that is in contact with the contractile myocytes. The His-Purkinje system is isolated from the contractile myocytes by a collagenous sheet. Figure 1.4 shows a simplified conduction system.

1.1.3 Conduction system heart diseases and Cardiac Resynchronisation Therapy

There are a large number of diseases that affect the heart. This work, however, is directed towards diseases in the conduction system where the disease causes non-synchronous contraction of the contractile myocytes in the LV. Strictly spoken, the

Figure 1.4: The conduction system. The signal for a hear-beat starts in the SA node (red), then propagates atrial myocardium (grey) to the isolating layer (white). The signal is delayed in the AV node (green), and then distributed rapidly via the HIS node, right bundle branch (RBB), left bundle branch (LBB), and finally to the myocardium via Purkinje fibers. The yellow lines in the atria is not Purkinje fibers, but pathways with higher conduction rate than the surrounding myocardium due to anisotropies in the tissue.

contraction is not fully synchronous, since a normal contraction start in apex (the bottom tip of the heart) and propagates towards the aortic valve where the blood is exiting the left ventricle. This group of diseases might qualify the patient to receive Cardiac Resynchronisation Therapy (CRT) where the patient get electrodes implanted in the heart as shown in figure 1.5a. Figures 1.5b, 1.5c and 1.5d show examples of leads and connectors. These electrodes are then used to deliver an electric pulse that causes the nearby myocytes to excite, and thereby start an action potential wavefront as shown in figure 1.3 which in turn causes the heart to contract.

The electric pulse is a potential of a given magnitude and duration. If the magnitude and duration is sufficient to excite enough cells to cause an action potential wavefront to spread out from the electrode, we have achieved *capture*. Delivering this pulse is called *pacing*. Both magnitude and duration of the pulse are controlled by the pacemaker. Given an infinite length pulse, the *rheobase* is the lowest potential of the pulse that causes capture. The *chronaxie* is the minimum time required for a pulse with a magnitude that is twice the rheobase to cause capture.

1.1.4 Cardiac Resynchronisation Therapy

There are a large number of diseases that affect the heart. This work, however, are directed towards diseases in the conduction system, or more specifically: diseases that qualify the patient to receive CRT. One example of such a disease is a left bundle branch block (LBBB) where the fast conduction of signals in the LBB are broken. This means that excitation of the LV cells is initiated through activation from the RBB, and is spreading slowly in myocardium without the efficacy of the specialised conduction system, resulting in an asynchronous delayed activation of the remote parts of the LV.

Figure 1.5: Examples of leads for CRT. Placement of RA leads are not shown.

1.2 Physics background: On electrical bioimpedance

For those not proficient in the art of electrical bioimpedance: To understand the work in this thesis, it is necessary to have a basic understanding of the theory, which will be presented here. However, since the theoretical background is large, only a small excerpt is presented.

If a steady-state electric potential, U , is applied across two electrodes connected to a material as shown in figure 1.7a, an electric current will flow through the resistor with resistance R . Ohm's law then states that the resistance follows from

$$U = RI. \quad (1.1)$$

If the steady-state electric potential is replaced by a sinusoidal potential, an expanded set of mathematical tools are required to describe the processes and signals involved. When looking at only a single signal, it is sufficient to describe the signal by its amplitude and frequency, but if more signals are involved, it is necessary to add information on relative timing. This is done by representing the signals by *complex numbers*¹. A complex number is written in the form $a + jb$ where a and b are real numbers, and j , the imaginary unit, is defined as $j^2 = -1$. The real part of the complex number is a , and the imaginary part is b . A complex number can be visualised as a vector in a 2-dimensional graph where the horizontal axis is representing the real part of the number and the vertical axis is representing the imaginary part of the number as shown in the examples in figure 1.6. A point in a plane can be described using either the cartesian coordinates (a , and b) or using polar notation using the vector length and angle. If we let the vector length represent the signal amplitude of a sinusoidal signal, and the phase angle the position in time relative to a given reference, a complex number can represent a signal of a particular frequency. In figure 1.6, two generic signals are presented as complex numbers in a complex plane and as waveforms in a time domain plot.

By replacing U , R , and I in equation 1.1 with their complex counterparts $\mathbf{U}$, $\mathbf{Z}$, and $\mathbf{I}$, a generalised version of Ohm's law is made:

$$\mathbf{U} = \mathbf{Z}\mathbf{I}, \quad (1.2)$$

where $\mathbf{Z}$ is called impedance. Note that if the imaginary components in the variables are zero, equation 1.1 and equation 1.2 are identical.

For a spectrum of several frequencies, 1.2 turns into

$$\mathbf{U}(f) = \mathbf{Z}(f)\mathbf{I}(f). \quad (1.3)$$

This is illustrated in figure 1.7b.

A generalised representation of an instrument that can utilise 1.3 to measure impedance at a given frequency is shown in figure 1.8, and consist of an AC source, together with a detector that can measure the magnitude and phase angle of the evoked potential at the given frequency. The AC source may be a controlled voltage or a controlled current, but in either case, the current magnitude and phase is measured internally in

¹Complex numbers are explained in more detail in textbooks on mathematics such as *Advanced Engineering Mathematics* [6] or in *Bioimpedance & Bioelectricity Basics* [1, Chapter 12]

Figure 1.6: Complex numbers plotted in a complex plane and in the corresponding signals in the time domain. The numbers $A = 3 + j1$ and $B = 2 - j2$ are drawn as points and vectors in the top plot and in the time domain in the bottom plot. The two numbers can also be described using vector lengths and angle, in which case we write $|A| = 2.83$, $\alpha = \angle A = 18.4^\circ$, and $|B| = 3.16$, $\beta = \angle B = 135^\circ$. A full period of a sine wave corresponds to 360 degrees, and the difference in phase angle of the two vectors is 117 degrees. Note that the complex number does not say anything about the frequency of the signals.

the instrument. The measured current and potential are the I and U in 1.2. The instrument can then calculate the resulting impedance calculate the impedance (Z) by using equation 1.2. If an instrument is set up to measure a sequence of frequencies, the result is called an impedance spectrum. Measuring the impedance spectrum by using single frequencies is called stepped sine excitation. Any time-limited time-domain signal can be represented by a sum of sine waves as shown by the French mathematician and physicist Joseph Fourier². A fast-changing signal is resulting in high frequencies and slow-changing signals is resulting in low frequencies. This means that if we use, for example, a square-wave for excitation, this can be seen as a large number of sine waves added together. In other word, we have a broadband excitation. The nice feature of this is that it is possible to do measurements on multiple frequencies simultaneously as

²A proper reference for the original work was hard to find, but the concept of Fourier transform can be found in any large number of books on mathematics, such as *Advanced Engineering Mathematics* [6].

Figure 1.7: Basic illustration of Ohm's law and the generalised law as specified in 1.1 and 1.2, respectively. Boldface is used for complex numbers.

opposed to the stepped sine approach. There are a number of methods for generating a good broadband excitation signal such as the sum of two or more sine waves [7], chirp signals where a continuous sine wave with time-dependent frequency are used [8, 9], or binary (digital) signals [10]. There are more types available, but the basic idea is the same; create a signal that has short duration with a frequency content that is high. Different signals will also have different features when it comes to noise, accuracy and frequency content, and there are a number of trade-offs to do when considering stepped-sine versus broadband excitation as shown by Schoukens et al. [11]. If an instrument is measuring a range of frequencies, either by using stepped sine or by using broadband excitation, the result is called an impedance spectrum, and the instrument is called an impedance spectrometer. Note that measuring the evoked potential at a given frequency may be challenging, and may involve quite complex processing of signals in the analogue and/or digital domain. Furthermore, the extraction of magnitude and phase information from a broadband evoked potential is a requiring a processing of a large amount of data. In figure 1.8, the two current-carrying (CC) connections are separated from the two used for voltage (or potential) pick-up (PU). This allows the instrument to be connected in several ways, which will be discussed later. The instrument may be programmed to measure at one or more frequencies.

Three basic electrode configurations for impedance measurements are shown in figure 1.9. The different configurations have properties that make them suitable for different tasks.

The most basic is the two-electrode configuration shown in figure 1.9a. This configuration is simple but suffers from undesired electrode effects. The most sensitive volume lies between the two electrodes, and there is no volume with negative sensitivity³. The three-electrode configuration shown in figure 1.9b is typically used to focus the sensitivity in a small volume. Finally, there is the four-electrode configuration in figure 1.9c, but even this suffers non-ideal effects [12].

One of the factors that determines the electrical impedance is the *electrical properties* of the measurand. There are two parameters that determine the electrical properties of a material; conductivity (σ) and permittivity (ϵ).

³Sensitivity is explained later in this section.

Figure 1.8: Basic illustration of how Ohm's law expanded for AC can be utilised in an instrument to make an impedance spectrometer. The processing unit of older instruments relies typically more on analog processing than newer instruments that relies more on digital processing. The instrument has a user interface and/or a data communication unit that is used to control the instrument and read out impedance data.

The conductivity is given by

$$\sigma = Fc\gamma(\mu_- + \mu_+) [\text{S/m}] \quad (1.4)$$

where F is the Faraday constant, c is the concentration of ions, γ is the activity coefficient which is indicating how much of the electrolyte that is available for conduction), and μ is the mobility of the ions [13]⁴. From this equation we see that conductivity is dependent on concentration of ions, and that high concentration means high conductivity. We can also see that the mobility plays an important role. Mobility is a function of friction or viscosity in the fluid where the ions are moving. In other words, a large ion has low mobility and a small ion has high mobility. Here, the size of ions is actually the size of a ion with all the water molecules that tends to be attached to it [1].

In a tissue, there are also a number of charges that are affected by an electric field, but does not migrate in the same way as free ions. For example, a water molecule has an electric charge of 0, but the molecule is a dipole where one end is positively charged and the other end is negatively charged. If an electric field is applied externally, this will cause the molecule to rotate so that it is oriented along the electric field lines. The parameter *permittivity* (ϵ) quantifies the material's ability to resist this rotation. How easy it is to rotate a dipole molecule is dependent on the medium it is contained in, the size/mass of dipoles, and whether it is engaged in a chemical process such as hydration of ions. If electric charges are uniformly oriented, it is called polarisation. Polarisation may apply to larger units such as molecules, which tends to have higher resistance to polarisation, or smaller units such as an the electron cloud and atom nucleus who tends to have less resistance to polarisation, which directly affects permittivity of the material the units are a part of. Permittivity is often expressed by *relative permittivity* (ϵ_r) given by $\epsilon = \epsilon_0\epsilon_r$, where ϵ_0 is the permittivity of vacuum.

⁴In all honesty, the book in the reference has not been read, but it seems, from *Bioimpedance and Bioelectricity Basics*, that this is the source of the knowledge.

Figure 1.9: The three basic electrode configurations for volume impedance measurements. Note that there are other possibilities too. The two center electrodes are partly greyed out to indicate that these may be placed inside the volume. In principle, all electrodes may be placed anywhere in or on the volume. Connections marked CC are current carrying, and connections marked PU are voltage Pick-Up connectors.

Both conductivity and permittivity are frequency dependent, and permittivity more so as shown in figure 1.10 where the parameters of a selection of tissues are shown. Figure 1.10 also illustrates the difference in parameters between tissues. This difference is caused by differences in ion types available, their concentrations, and geometrical features at cell level. Of particular interest for this work is the data for blood and heart tissue as shown in figure 1.10. We see that the conductivity for blood is significantly higher than that of other tissues. This means that, at least for low frequencies, that presence of blood, or rather variable presence of blood can be detected using impedance measurements.

Much data on electrical parameters exists [14], but due to the biological diversity and variability, one may argue that very little data exist.

It is possible to describe how conductivity and permittivity relates to the measured impedance of a material in several ways [1, Section 3.3], but only one method is presented here. For a given homogenous material with no edge effects and a pure sinusoidal excitation, the impedance of the material is given by

$$Z = \left(\frac{d}{A} \right) \left(\frac{1}{\sigma + j\omega\epsilon} \right) \quad (1.5)$$

where d is the length of the material, A is the area of the material, j is the imaginary unit, and ω is the frequency expressed in radians⁵.

Another factor that determine electrical impedance is the *geometry* of the measurand. With a two electrode set-up to measure the impedance between electrodes a and b in figure 1.11, the impedance will increase if the distance between electrodes a and b is increased. This follows from equation 1.5. If electrodes a and b are used for current injection only (CC electrodes), and two of the electrodes c through g for voltage pick-up (PU electrodes), one cannot directly measure the impedance of the measurand

⁵ $\omega = 2\pi f$ where f is the frequency in Hertz.

Figure 1.10: Permittivity and conductivity for selected materials [14]. The material *Average* is no real material, but the average of several materials. The data in this figure are used in finite element method analysis described in section 3.1.2.

since the different sections of the measurand will contribute differently to the measured impedance. To handle this situation, the term *transfer impedance* is used, which means that I and U in equation 1.2 come from two different electrode pairs [15, 16]. Where the PU electrodes are placed, or which pair is used, will affect the measurement as illustrated in figure 1.11 and table 1.1.

This example illustrates the importance of electrode placement, and due to its importance, electrode placement must always be a part of a transfer impedance measurement specification. There are several points worth noting in table 1.1:

- If the PU electrodes lie on the same iso-potential line, the result will always be 0Ω ($Z_{cd} = Z_{fg} = 0 \Omega$).
- The longer the distance (in terms of iso-potential lines crossed) is between two PU electrodes, the higher the transfer impedance is ($Z_{ce} < Z_{cf}$).
- If two electrodes are on the same iso-potential line, then they are interchangeable ($Z_{cf} = Z_{df} = Z_{cg} = Z_{dg}$).
- If two PU electrodes are swapped, the transfer impedance becomes negative ($Z_{ec} = -Z_{ce}$).

PU+	PU-	Symbol	Value / comment
<i>Two electrode measurement of impedance.</i>			
a	b	Z_{ab}	8Ω
<i>Four electrode measurement of transfer impedance where PU is on same iso-potential line.</i>			
c	d	Z_{cd}	0Ω , same iso-potential line.
f	g	Z_{fg}	0Ω , same iso-potential line.
<i>Four electrode measurement of transfer impedance where PU+ are placed nearest CC+.</i>			
c	e	Z_{ce}	2Ω
d	e	Z_{de}	$2 \Omega = Z_{ce}$
c	f	Z_{cf}	$3 \Omega > Z_{ce}$
c	g	Z_{cg}	$3 \Omega = Z_{cf}$
d	f	Z_{df}	$3 \Omega = Z_{cf} = Z_{cg}$
d	g	Z_{dg}	$3 \Omega = Z_{cf} = Z_{cg} = Z_{df}$
<i>Four electrode measurement of transfer impedance where PU+ are placed nearest CC-.</i>			
e	c	Z_{ec}	$-2 \Omega = -Z_{ce}$
g	d	Z_{gd}	$-3 \Omega = -Z_{dg}$

Table 1.1: Effects of choosing different PU electrodes in figure 1.11.

It is necessary to explain the concept of *negative* impedance. When measuring transfer impedance, the term negative impedance is allowed. For DC conditions, this may be somewhat disturbing, but when looking at AC conditions, it is suddenly less disturbing. For AC measurements, a negative sign simply means a phase shift of 180° .

Looking at figure 1.11, there are iso-potential lines and current paths. For this simple model with a homogenous material, both types of lines will look nice and smooth, but this will not be the case where the model or measurand is more complex and is made of several tissues with different electrical properties. Figure 3.3 is showing a more complex model. To make the image even more complex, the geometry and electrical properties may vary over time as is the case in a heart where each beat involves a geometry cycle caused by the contraction and a tissue property cycle caused by the intra- and extracellular ion balance cycle.

In figure 1.12, let the top two electrodes be CC electrodes. The red vectors are then the current densities at selected points. The iso-potential lines are drawn in red. By measuring the potential on the two lower electrodes, a transfer impedance can be calculated. If the situation is reversed, and the lower two electrodes are CC electrodes and the potential is measured on the two top electrodes, the exact same transfer impedance will be found. The corresponding current density vectors and iso-potential lines are drawn in blue. This is called *the principle of reciprocity*, and it tells us that the electrode pairs used for CC and PU are interchangeable. Figure 1.12 is created in an *in silico* experiment using a finite element model (FEM) ⁶.

Figure 1.12 illustrates another feature of transfer impedance of a volume. It can be shown that the dot product of the red and blue vector for a given point is the transfer impedance *sensitivity* for that point [17]. The dot product of two vectors are the product of the vector lengths multiplied with the cosine of the angle between them. Note that

⁶FEM models are explained in section 3.1.1.

Figure 1.11: Basic illustration of how geometry affects measured impedance. Red lines are current paths, and blue lines are iso-potential lines. For simplicity, we say that the iso-potential lines are 1 V apart from each other and that the injected current is 1 A.

this number may be negative if the angle between the vectors are more than 90° . The sensitivity multiplied with the resistivity in a given point is the contribution of that point to the total measured transfer impedance. The measured transfer impedance can be found by integrating the contributions from all points.

Impedance data can be presented in a variety of formats, such as Wessel plots, Cole plots, and Bode plots where impedance magnitude information, phase information, and frequency information are kept [1]. These plot types are primarily intended for static data, so most data in this work will be presented as plots of the impedance data versus time on the x-axis.

A given impedance is specified by a complex number in either cartesian or polar format, and a frequency. In some cases, the inverse of the impedance, admittance is used. The basic variants which are presented in table 1.2.

For some applications it may be beneficiary to use process the impedance values further or combine several measurements to extract the desired information [18, 19, 20].

Figure 1.12: Basic illustration of current density vectors. The red vectors are for the CC electrodes, and the blue vectors are for the PU electrodes. This is for a 2D situation, but the same principles apply for a 3D model such as the one shown in figure 3.3.

Name	Symbol	Mathematical representation
Impedance	$\mathbf{Z}$	$R + jX$
Resistance	R	R
Reactance	X	X
Impedance magnitude	$ \mathbf{Z} $	$\sqrt{R^2 + X^2}$
Impedance angle	$\angle \mathbf{Z}$	$\text{atan2}(R, X)$
Admittance	$\mathbf{Y}$	$\frac{1}{\mathbf{Z}} = G + jB$
Conductance	G	$\frac{R}{R^2 + X^2}$
Susceptance	B	$\frac{X}{R^2 + X^2}$
Admittance magnitude	$ \mathbf{Y} $	$\sqrt{G^2 + B^2}$
Admittance angle	$\angle \mathbf{Y}$	$\text{atan2}(G, B)$

Table 1.2: Impedance representations. The basis for the is the impedance as specified in the top row. The function $\text{atan2}()$ is a variant of $\text{atan}()$ commonly used in a number of programming languages that ensures that the sign is correct.

1.3 Motivation for work and current status

1.3.1 Motivation for work

Although much work has been done in the combined field of bioimpedance and cardiology, we felt that more could be done. The work presented here are motivated from both the bioimpedance field and the cardiology field.

From the bioimpedance side, we know that measured impedance is dependent on a number of factors such as geometry, tissue properties, electrode configurations, and excitation. This means that there is a potential of contributing with useful information to the medical field where variations in these factors are caused by diseases, injuries, or other health issues. Focusing on the heart, this is an organ where both geometry and tissue properties varies through a heart beat. The geometry changes through a heart beat of a diseased heart will in some cases diverge from that of a healthy heart, which means that the difference can show up in a bioimpedance measurement. Furthermore, different tissues have different electrical properties, and diseased hearts will in some cases have tissue properties that diverge from those of a healthy heart. It is in other words a potential to extract interesting and useful information from impedance measurements on hearts.

From the cardiology field, there is a need to improve the therapies of heart diseases that exist. One such therapy is CRT where pacemaker electrodes are placed on both sides of the LV and the heart receives stimuli on both sides simultaneously. To ensure optimal efficiency of the contraction of the left ventricle, the leads must be placed so that the contraction of the myocardium is as synchronous as possible. Since the reason for delivering CRT treatment is that parts of the heart is not functioning normally, it follows that there is a risk of placing the lead in a position where it is not contributing to improved synchronicity. Detection of optimal lead placement during the implantation of the CRT device could improve the response rate for receivers of CRT treatment, and it might be possible to identify non-responders before a CRT device is implanted. Detection of optimal lead placement could be based on information on ventricle volume during a heart beat, or on information on timing of events such as time to opening of aortic valve or duration of the systole.

It is crucial that the pacing is causing capture in myocardium. If pacing in LV and in RV is not delivered as intended, the evoked haemodynamic response will not be as intended, which means that the patient may not respond to the treatment.

We believe that it is possible to extract information that can aid or improve delivery of CRT treatment by using electric bioimpedance techniques during the implantation of CRT devices. This can ultimately lead to increased number of responders to treatment, decreased morbidity, and improved benefit/cost-ratio.

1.3.2 Bioimpedance in cardiology today

Use of electrical bioimpedance as a source of information of processes in the body is not new, but there are still many fields where electrical bioimpedance as a source of information is not fully exploited. One of these fields is in cardiology. Measurement of electrical activity in the heart dates back to 1913 [21], but it took around 50 years to

move into the start bioimpedance measurements on beating hearts [22, 23]. Some of the later applications of electrical bioimpedance are presented below.

Impedance Cardiography and Impedance Catheter measurements

Electrical bioimpedance can be used for hemodynamic measurements by measuring impedance through the thorax using skin electrodes. This technique is often referred to as Impedance Cardiography (ICG) or Thoracic Electrical Bioimpedance (TEB). The basic idea is to measure the impedance through the thorax using a four-electrode set-up. The measured transfer impedance will vary as the geometry of the thorax is varying, and in particular, organs related to hemodynamic function. The heart geometry, the vein diameters, and the amount of blood in the thorax will vary through the heart cycle and thus change the impedance. By placing electrodes in appropriate positions, and by using appropriate measurement frequency or frequencies, it is possible to extract information on several parameters such as cardiac output, stroke index, systemic vascular resistance, systemic vascular resistance index, heart rate, mean arterial pressure, thoracic fluid content, velocity index, left cardiac work, and systolic time ratio [24]. Some of these are calculated based on measurements. Even if the method is not considered to be as good as invasive methods [25, 26], it may still be useful in special cases such as cardiac output measurements on pediatric patients with congenital structural heart disease [27].

ICG measurements have also been used to extract timing information, and work in this area is ongoing [28].

It is possible to utilise bioimpedance measurements invasively to measure cardiac output and left ventricular volume by using a catheter with four or more electrodes using a technique presented by Baan et al. [18]. The basic idea is to place the catheter in the LV, and use the proximal and distal electrodes as CC electrodes, and the centre electrodes as PU electrodes. If the volume is high (diastole), the measured transfer impedance will be low due to the relatively high conductance of the blood compared to that of myocardium. The base method has been improved, and in particular, the work of Wei et al. is of importance since it takes into account both resistive and capacitive properties of the involved tissues as well as changes of the myocardium tissue during the cardiac cycle [19].

Navigation systems

Geometrical mapping of electrical activity in the heart is done as a part of ablation procedures. This mapping requires knowledge of where the particular electrodes are at a given time. One method to determine the position within the thorax is by measuring impedance between the electrode and one of three skin electrode pairs placed orthogonally to each other. One such system is the Ensite system from St Jude Medical [29].

Invasive tissue measurements

Since different tissues have different electrical properties and since these vary with tissue state [14, 30, 31], invasive tissue measurements are candidates for research. From

the early measurements by Gebhard et al. [31], Jorge et al. has presented measurements on pig hearts where they utilise bioimpedance measurements with very high temporal resolution to detect acute transmural myocardial ischemia [7]. In their article, the authors present a bioimpedance measurement system that can capture 1000 spectra per second where each spectra is ranging from 1 kHz to 1 MHz and contain 26 logarithmically distributed frequencies. Unfortunately, the equipment presented by Jorge et al. is not suitable to use on human subjects. The same instrumentation was used by Amorós-Figueras et al. in the work presented in *Recognition of Fibrotic Infarct Density by the Pattern of Local Systolic-Diastolic Myocardial Electrical Impedance* [32]. This work demonstrates that there are changes in the myocardial tissue after an infarct, and they suggest that it can be used in ablation procedures via a catheter to detect scar tissue.

Measurements using pacemaker leads

It is possible to use the pacemaker device itself to do impedance measurements with the aim of detecting fluid in the lungs [33, 34, 35]. While these measurements is possible and may give relevant information about patient status, they are not currently giving direct information on the heart itself. Fluid buildup in the lungs, or pulmonary edema, is an indicator of poor function of LV, and can as such be useful to monitor the severity of heart failure.

Another application of bioimpedance on pacemaker is capture detection, where work has been done since 1992 [36], but this method is not available in new devices today as far as we know.

There have been attempts on using pacemaker leads for long term monitoring of the heart itself, and in particular stroke volume [37, 38], but as far as we know, this is not an available feature on pacemakers or CRT devices today. Measurements using pacemaker leads in an acute situation has also been done [39], but all of these measurement are based on pulses being injected by a pacemaker, and simple measurement of the magnitude of the evoked potential. This method is only giving a limited amount of information since the frequency content is unknown, or at least not published. The measurements have all been done on animals, but the work has now been continued on human measurements [40]. It is somewhat unclear how the measurements were carried out, but a sort of intracardiac impedance measurement were performed with the aim of predicting worsening of heart failure for CRT patients [41].

The first attempts at using pacemaker leads to do volumetric measurements were presented by Porterfield et al. [42] in 2011. Their work were performed on animal models, and the heart were accessed via a thoracotomy. It is unknown if the thorax was closed during measurements. Although the excitation frequency or frequencies for the impedance measurements were not reported, they report use of instrumentation equipment capable of multi-frequency excitation and of measuring complex impedance, Z [43, 44]. The presented data shows that it is possible to extract impedance waveforms representing LV volume. The same group did also present similar use of pacemaker leads and bioimpedance measurements to detect alterations in LV stroke volume [45] on animal models. The same group has also been working on admittance catheters and the mathematics behind LV volume calculation [46]. In the latest work

form this group, a RV volume measurement method is presented where the RV lead has an extra electrode intended for use with a combined RV pacemaker and an implantable cardioverter defibrillator (ICD) [47]. The presented method is a development of the method presented by Baan et al [18].

Other systems

There are systems that does not fit into the categories above, which are presented here.

For patients with an implanted left ventricular assist device (LVAD), it is important to monitor the state of the heart. An attempt to do this using electrical bioimpedance has been done, and found to be more accurate than existing methods [48].

1.3.3 On particular relevance for the work presented in this thesis

On Finite Element Method analysis

A simple physics problem involving one object in a one-dimensional system can be described by a set of equations such as Newton's laws of motion [49]. If the problem grow in complexity, it is natural to increase the mathematical description to cover 3 dimensions by decomposing the vector variables along 3 orthogonal directions in space. If the problem involves a more complex geometry, it is possible to break the system down in smaller elements which are solved individually. If the system is broken down to elements of infinitesimal size, we will have a perfect mathematical description of the physics problem. Since such a system will be of infinite size, and thus not possible to handle, we have to settle for a finite number of elements. The analysis method where a model is described by a large, but finite, number of elements and analysed by applying associated laws or equations to the individual elements is called Finite Element Method (FEM). By applying laws governing electrical charges, potentials and currents, and by describing a measurement system such as the one shown in figure 1.11, it is possible to make a analyse a simple system using FEM. It is also possible to increase the complexity to make a model that describes thorax with internal organs. FEM models are especially suited for numerical analysis in computers, and as computers are becoming increasingly capable of analysing models, it is becoming more and more naturally to use FEM analyses initially in projects. This type of analyses or experiments are sometimes called *in silico* since the experiments are taking place in silicone processors in computers.

In silico experiments may be beneficiary in bioimpedance projects for several reasons:

- It is relatively simple to test ideas and concepts without having to make a physical model.
- It is possible to make models that cannot be made in real-life. An example is an electrode inside a volume without any cables.
- It is possible to extract data for all points in the model. An example is current density at any given point in the model.
- It is possible to extract secondary data such as sensitivity and volume impedance density [17, 50].

- It is possible to replace human experiments with *in silico* experiments to reduce risk of adverse situations and to reduce discomfort for patients.
- It is possible to replace animal experiments with *in silico* experiments in accordance with the three Rs of animal welfare [51].
- It is possible to see if an idea that is impossible to realise today due to imperfect instrumentation may be possible to realise when better instruments are available.

In the bioimpedance field, FEM analyses have been used to predict the outcome of a measurement and further to investigate sensitivity within the model. In its simplest form, a model is made, stimuli is applied, and resulting transfer impedance is extracted. In the case of a system that changes with time, two or more models can be made, and the differences over time can be extracted. This is particularly useful for a model that includes a heart because it makes it possible to evaluate whether our measurement set-up is capable of detecting what we want it to detect. Sensitivity is defined as [1]:

$$S = \frac{\overrightarrow{J_{CC}} \cdot \overrightarrow{J_{PU}}}{I_{CC} I_{PU}} \quad (1.6)$$

where S is sensitivity in a given point, $\overrightarrow{J_{CC}}$ is current density from current from CC electrodes, $\overrightarrow{J_{PU}}$ is current density from current from PU electrodes⁷, I_{CC} is excitation current in CC electrodes, and I_{PU} is excitation current in PU electrodes.

Although it is very common to publish plots of sensitivity, and to discuss it, sensitivity is a poor parameter. This is best illustrated by an example. Consider figure 1.13a where the regions marked I and II have a low conductivity (1 [Sm⁻¹]), and the region marked III has a high conductivity (100 [Sm⁻¹]). If we do an *in silico* four-electrode measurement we will find that the transfer impedance (Z) is 2.3164 Ω . The resulting current streamlines are shown in figure 1.13b and illustrates that the current prefer the high-conductivity region, and that the CC and PU currents are flowing the same way with high current density. This causes the sensitivity in this region to be high as is shown in figure 1.13c. Since the sensitivity is higher in region III than it is in region II, one could be led to believe that a 10% change in the conductivity in region III will affect the resulting Z more than a 10% change in the conductivity in region II. This is not the case. Volume impedance density, z , defined by

$$z = \rho S \quad (1.7)$$

where ρ is resistivity and S is sensitivity, for any given point of the model is shown in figure 1.13d. This quantifies the actual effect a variation in conductance has on the measured Z . This means that z is integrated over a given region, the result is this region's contribution to R . So if z is integrated over the whole model, the result is the measured Z . By comparing figures 1.13c and 1.13d, it is clear that the sensitivity plot and volume impedance density plots are representing two very different parameters. The numerical results are summarised in table 1.3 and 1.4.

The model contain three main parts that are equally important: The geometry and mesh which describes the system, the equations describing the behaviour of the system, and the parameters for each material or tissue in the model.

⁷See *Bioimpedance and Bioelectricity Basics* for more details [1].

Parameter	Region II	Region III	Unit
Mean S	0.2788	7.340	m^{-4}
Mean z	0.2788	0.0740	Ωm^{-3}
Contribution to Z	0.0697	0.0185	Ω

Table 1.3: Results from analysis of sensitivity and volume impedance density of the model in figure 1.13.

Description	Value [Ω]	Change in %	Z II contr. [Ω]	Z III contr. [Ω]
Base impedance	2.316	0	0.06971	0.01850
$\sigma_{II} + 10\%$	2.310	-0.29	0.07163	0.01821
$\sigma_{III} + 10\%$	2.315	-0.07	0.06944	0.01687

Table 1.4: Results from analysis of sensitivity and volume impedance density of the model in figure 1.13. σ_{II} and σ_{III} are the conductances for regions II and III, respectively.

The geometry of a FEM model can be made by construction using geometrical primitives and operations on these. This geometry is then broken down to a geometrical mesh of points in 3D-space. This is shown in figures 2 and 3 in the paper I – *Comparison of four different FIM configurations—a simulation study*. To achieve a good representation of a real-world system, the mesh has to be fine enough to represent important geometrical features of the real-world system. This normally means that the finer the mesh is, the more demanding it is on computing resources. The discipline of generating the meshes is huge as illustrated by *A Survey of Unstructured Mesh Generation Technology* already in 1998 [52]. For the work presented in this thesis, we are relying on the built-in meshing in the commercial tool we have used. The geometry of a simple model based on geometrical primitives can be very easy to make, and can be useful for analysis of concepts and simple real-world problems [53, 54]. On the other hand, it is possible to use data from imaging modalities such as Magnetic Resonance Imaging (MRI) to produce a mesh that can be used for FEM analysis [17]. This approach can be useful in many settings, but for a complex system such as a human thorax the mesh can easily be very big if one wish to include small structures. There have been done work on full body models based on the Visible Human Project, where the whole body was represented by 2.7 millions tetrahedra [55], but this resolution is not fine enough to model a heart accurately.

The equations that describe and electrical system are predefined in the software we used. These equations are only considering electrical parameters and variables such as potential, currents, conductivity, permittivity and so on [56]. For most bioimpedance purposes this will suffice, but if one is to do a detailed study, one should consider another set of equations. In particular, one could consider a model that takes into account the anisotropy of the tissues. For example, muscle cells have anisotropical electrical properties [14]. One could also take into account the different anisotropical electrical properties of the intra- and extracellular domains as it is done in a bi-domain model [57]. The individual myocytes as well as the whole heart change shape during the heart

Figure 1.13: Comparison of sensitivity and volume impedance density. For simplicity, only a DC (stationary) analysis is done, meaning that all imaginary values are zero, and that impedances are purely resistive.

cycle. This change the geometry of the heart, and this can be modelled in two ways: by analysing two or more geometries or by using a mesh that is dynamic. The dynamics of that mesh can again be coupled to the forces developed in the muscle tissue. Ultimately, such a model could be used to analyse several aspects of the processes in the heart, or even to create patient models [58]. So far, no work on combination of electrical activity, mechanical action, and bioimpedance have been published.

The material parameters that are used in FEM analysis essential to be able to create a model that gives useful output. The largest collection of tissue parameters is the work by Gabriel et al., *The dielectric properties of biological tissues: II. Measurements in the frequency range 10 Hz to 20 GHz* [14]. This work is important since it is the most comprehensive collection of tissue data available. The data are collected from measurements on tissues from freshly killed animals of different species, from human autopsies, and from *in vivo* measurements on humans. The measurements were done in the range of 0 hours (the *in vivo* measurements) to 48 hours after death, which means that parameters may have changed significantly as Martinsen et al. have showed [59].

On instrumentation and current sources

The gold standard instrument for impedance spectroscopy has been the Solartron 1260 together with the Solartron 1294 front-end or many years. The Solartron equipment is, however, not suitable for high speed spectroscopy measurements on human hearts since the 1260 is too slow (approximately three spectrums per second) and it is not safe nor approved to use on human hearts.

The requirements for an instrument suitable for impedance spectroscopy measurements will vary depending on type of measurements, electrode configuration and so

on. Some of the specification points which are of interest are listed below together with a brief explanation of the requirement.

Safety The instrument must be safe for use, which means that, ideally, an CE-marked instrument with a Cardiac Floating (CF) classified applied part (the part that is in contact with the patient).

Speed The instrument must be able to capture the changes that occurs in a heart during a heart-beat. To be able to capture the general shape of the time-dependent impedance waveform, 10 frequency spectrums per second may be enough, but if the goal is to capture the rapid changes happening around capture, a temporal resolution of around 200 frequency spectrums per second or more would be preferable. This is approximately the same rate as an ECG-monitor in a hospital uses for potentials.

Frequency spectrum To be useful as a research instrument, the instrument should be able to be able to work measure spectrums from near DC to 10 MHz as this will cover the much the frequencies where there are large differences in electric properties in tissues [14] as seen in figure 1.10. Doing measurements on high frequencies (above 1 MHz) on either humans or animals is becoming more and more challenging as frequencies goes up due to parasitic components in the measurement set-up as well as interference by other equipment in the operating room, so it can be debated if capability for very high frequencies is required for bioimpedance measurements in a cardiac setting. It is not necessary to be able to have very many frequency points in the spectrum since there are no sudden changes in the spectrum [30, 14].

Accuracy For measurements where waveform shape is the important, accuracy is not a very important parameter since an un-accurate instrument can still be capable of reproducing the waveform shape. Repeatability (or precision) is, on the other hand, very important since high precision allow us to be able to capture the small changes in impedance caused by heart activity as shown in table 3.1 in 3.1.1.

Size An instrument that is to be used in a clinical setting should be as small as possible to not get in the way for medical equipment present in the operating room.

Connectivity It must be possible to remotely control the instrument, as well as transfer measurements continuously in real-time. Some instruments have auxiliary features such as digital inputs and outputs, synchronisation connectors and so on, which can be useful for synchronisation and control of front-ends and other devices. In addition, there must be a well defined application programming interface.

Since there are no instruments that fulfil all of these requirements [60], it is natural to see what the current state of the art is. Starting with existing impedance spectrum analysers, table 1.5 from paper I *Bioimpedance measurements of temporal changes in beating hearts* gives a good overview of the instruments available. A full comparison is beyond the scope of this thesis, and deemed not necessary since the three instruments to the left in table 1.5 fulfilled our specifications short of one feature: sufficient safety rating for heart measurements. This means that these instruments can be used as a base for an instrument suitable for use in cardiology.

The Solartron 1294 front-end for the Solartron 1260 is supposedly making the system safe for use on humans [61], but this is not the case. The operating manual is *not*

Parameter	ISX 3v2	MFIA	HF2IS	WK	K. 90A	K. 91A	1260 + 1294	ImpTM SFB7
f_s range	+	+	+	-	-	?	-	-
f_Z range	+	+	+	+	+	-	+	+
Z range	+	+	+	+	+	+	+	-
GPIO	+	+	+	-	+	+	-	-
USB/Ethernet	U, E	U, E	U	U	U, E	U, E	-	E
Size**	Small	Med.	Med.	Large	Large	large	Large	Small
Calibration	+	+	+	+	+	+	+	-
API/Libraries	LV	Several	Several	Unkn.	Unkn.	Unkn.	No	Unkn.
Cost	€	€	€€	€€	€€	€€	€€	€€

Table 1.5: Commercially available instruments [60]. Manufacturer and model names: Sciospec ISX 3v2, Zürich Instruments MFIA, Zürich Instruments HF2IS, Wayne Kerr WK6500, Keysight E4990A, Keysight E4991A, Solartron 1260 + 1294, and Impedimed ImpTM SFB7. *) This is somewhat unclear from documentation, but according to sales representative, the sample rate is at least 200 samples per second. **) Sizes are $small < 5 \text{ kcm}^3 < medium < 20 \text{ kcm}^3 < large$.

declaring conformity to IEC 60601-1, but it states that the equipment has been tested to comply with leakage requirement for applied parts class B [62]. This means that if we want to use a commercial instrument as a base, we have to make our own front-end that provides necessary safety.

With the exception of the instruments from Zürich Instruments, the instruments in table 1.5 uses stepped sine excitation where a single sine wave is used as an excitation signal, and the frequency is stepped through all frequencies in the spectrum. The instruments from Zürich Instruments may use two or more frequencies [63].

Another possibility is to make an instrument without using existing instrument as a base. Since high temporal resolution is desired, it is relevant to consider both measurements based on sine wave(s) and broadband excitation. There advantages and difficulties of both systems have been debated for years [11, 9], but if both methods can be made fast and accurate enough, both systems are viable options. Currently, the measurements done using equipment published by Jorge et al. in 2016 [7, 32] and are the fastest multi-sine excitation measurements done on hearts. The system is capable of 1000 spectrums per second with a spectrum consisting of 26 logarithmically distributed frequencies ranging from 1 kHz to 1 MHz. The measurements are clearly capturing the waveforms, but the article is not discussing the accuracy of the equipment, also the equipment is also not safe to use on humans. Chirp-type broadband excitation has some popularity, and in *Broadband spectroscopy of dynamic impedances with short chirp pulses*, Min et al. is suggesting that impedance measurements based on chirp excitation is fast enough to capture data of interest in the heart cycle [8].

Implementation of the different system can be done in a number of ways, such as PXI and PC based instrumentation [7], it can be handled by circuits based on a micro-

controller or a Field Programmable Gate Array (FPGA), or combinations thereof. The FPGA solution is gaining popularity since it makes it possible to make a system with very high processing power relatively simple. Commercial instruments such as those from Sciospec Scientific Instruments GmbH, Germany, and Zurich Instruments AG, Switzerland, are said to be FPGA-based (this is according to conversations with company representatives). In principle, it is possible to make any excitation signal by using an FPGA-based instrument, but this has not yet been done. An example of a platform that has both micro-controller and FPGA is the Red Pitaya [64]. This device is a complete Linux-based computer, and it has an FPGA section that is user-programmable. What makes it especially useful is that it has two analogue inputs and two analogue outputs with 50 MHz sampling-rate in addition to a number of low-speed analogue and digital inputs and outputs, which makes the device capable of being the base of a rather advanced bioimpedance instruments. An instrument based on the Red Pitaya would still need a front-end.

What a front-end for a bioimpedance measurement system is comprised of varies from system to system, and will depend on a number of factors. One example of a front-end is the Solartron 1294 which accepts an analogue sine-wave excitation input, and returns two signals representing the I and the U in equation 1.2. On the measurand-side the front-end provides excitation currents or voltages which can be scaled, and there are amplifiers that buffers and amplifies the evoked signal. The front-end also add sophisticated shielding of the signals. As mentioned, this front-end is not making the equipment safe to use on humans, so other front-ends may add improved safety in the form of galvanically isolated signals and current limiting. Safety requirements for medical devices are specified in the standard IEC 60601-1 [65], but there are no particular sub-standard concerning bioimpedance measurements. The standard has limits on leakage currents from applied parts for equipment intended on being connected directly to a human heart. For equipment intended for delivering an electric current, such as nerve stimulators and bioimpedance CC electrodes, the limits for leakage does not apply [66, 8.4.1].

Electrical safety is important, and especially so for equipment intended to deliver electric currents into the heart. One requirement is isolation from ground and the mains. Another requirement is to limit the amount of potential harmful currents. There are several ways of achieving sufficiently isolation from the mains, and IEC 60601-1 specifies the approved isolation techniques well. The current limiting requirement is not specified, so this must be based on a risk assessment. Since both requirements are aimed at reducing risk of harmful electric energy to reach the heart, there are overlap in methods used to meet the requirements. For example, if the electronics that are in electrical contact with the heart is supplied with a galvanically isolated supply that has limited capacity, and there is no storage capacity for electric energy available, this could be used to meet both requirements. Galvanic isolation can be done on both power supply lines and on signal lines.

Further limiting of excitation currents can be done by inserting resistors in series with the signal. One may also look at which frequencies that are most troublesome [67], and use filters to reduce these.

On capture detection

CRT pacing require one pace lead attached to the septum in RV which separates RV from LV, and one lead placed on the outside of LV in CS or one of it's tributaries as shown in figure 1.5a. Pacing is then delivered to each side of the LV to make the LV myocytes contract synchronously. During implantation of the CRT device, the pacing thresholds are measured and the device is programmed to deliver a certain pacing voltage. In the case of loss of capture in one or both lead electrode positions, the intended therapy is not delivered, and the effect of the treatment is reduced or lost [68, 69]. Approximately 10% of the receivers of CRT experience loss of capture [70], and approximately 6.5% experience anodal capture where LV pacing is causing capture in an electrode placed in RV [71]. To be able to detect loss of capture to rectify the problem, it is necessary to detect loss of capture reliably, which most CRT devices do today using locally evoked response (LER) [36, 72, 73]. The first of the three LER methods is based on measurement of the potential at the pacing electrode after a pace pulse is delivered; the waveform shape and level is then used to determine capture. The second method is similar, but uses bioimpedance measured at the pacing electrode. The third method is using timing information between the A-pace and detection of activated myocardium on the RV electrode to determine if LV capture has occurred. No literature describing this method used to determine RV capture has been found. Another LV-only capture detection algorithm is reported by Ghosh et al. [74]. This method is using potential LER and the RV coil as the reference electrode. In some cases, and most notably where the patient has atrial fibrillation or low pace thresholds, LER methods do not catch all losses of capture [75, 76]. It is to some degree possible to detect loss of capture by using 12-lead ECG, but this requires that the patient is examined by a specialist [77, 78].

It is a goal to keep the pace pulse voltage as low as possible to extend battery life of the CRT device [79, 80, 81], so in order to save power, the pace voltage is set to the threshold plus a small safety margin. Most devices uses some form of capture management today to ensure capture while simultaneously adjusting the pace voltage [82, 83]. Current methods have limitations, and in particular for patients with atrial fibrillation and low pace-thresholds [84, 75, 76], which means that new methods are desired.

Chapter 2

Aim and objectives

The aims of this work was to use electrical bioimpedance to treat and detect cardiac disease.

Covering all aspects of bioimpedance and all heart diseases was unrealistic, so we narrowed the scope down to one particular treatment: Cardiac resynchronisation therapy. This choice then laid constraints on the equipment development.

To reach these goals, these objectives were set down:

- *Evaluate feasibility of getting useful results from measurements in a human heart using pacemaker leads during the acute phase of the implantation by analysing finite element models.* Since we are primarily targeting CRT, we can assume availability of leads in both RV and in LV vein.
- *Design, build, and test a measurement system suitable for use on human hearts.* The necessary equipment is not available off-the-shelf, so measurement equipment must be made. An extra effort must be put into making systems that is safe for use on human hearts.
- *Start building a knowledge base.* Knowledge of possibilities, limitations, and expected results for a number of set-ups is required to utilise the measurement equipment in the best possible way. The initial measurements on human subjects must therefore be exploratory.
- *Demonstrate practical use of electrical bioimpedance in cardiology.* Choose one or more applications where electrical bioimpedance may contribute to improved therapy of heart conditions where pacemakers or CRT devices are implanted.

Chapter 3

Materials, methods, and results

3.1 FEM modelling

3.1.1 Overview

In the initial stages of the work presented here, we described a set of measurement set-ups where we believed bioimpedance measurements could provide information. We decided to explore these set-ups in an *In silico* concept study. The important questions for us to answer were:

- a) Is it feasible to use bioimpedance measurements to extract information on the geometrical changes that are taking place during a heart-beat? And if so:
- b) Which changes are responsible for the impedance change? In other words, what is the contribution to the measured impedance for different parts of the heart.
- c) In which ranges can we expect the measurement results to lie?

As mentioned in chapter 1.3.3, current FEM experiments focus on resulting impedance and sensitivity. As also pointed out, these analyses does not give information on the contribution from different parts. Since the same problem was also met by Humayra Ferdous in her project where bioimpedance was used to diagnose lung disease [85], we worked together to solve the problem. This co-operation resulted in paper I: *Comparison of four different FIM configurations—a simulation study* [50]. This paper deals with two issues: the lack of metrics capable of giving relevant information on the origin of impedance changes, and on a comparison of different electrode systems. It is the first of these issues that is relevant to this thesis. The methodology developed and presented in paper I is relevant for the models used to analyse the results from the FEM experiments. The FEM experiments are only published in this thesis in section 3.1.2.

3.1.2 *In silico* concept study

Materials and methods

The detailed steps involved in making a model is described in paper I: *Comparison of four different FIM configurations—a simulation study* and *From 3D tissue data to impedance using Simpleware ScanFE+ IP and COMSOL Multiphysics—a tutorial* [50, 17]. A very brief summary of the steps is:

- a) Define parameterised geometries.

- b) Add material properties necessary for the simulation.
- c) Define equations for sensitivity and volume impedance density.
- d) Define electrodes.
- e) Define sources.
- f) Set up simulations.
- g) Define graphical representations of simulation results.
- h) Define numerical representations of simulation results.

The model we used was based on very basic geometrical objects such as cylinders and ellipsoids were used to make a human torso with a limited selection of organs as shown in figure 3.1. The included organs are lungs, spine, and heart. All heart geometries are a function of a single parameter which let us emulate a heart beat. Figure 3.2 shows how the heart geometry is during diastole (relaxed heart) and systole (contracted heart). The thickening of heart walls during diastole is also accounted for.

Figure 3.1: *In silico* model of torso. Most geometries are parameterised, and the geometry of the heart can be varied to simulate diastole and systole using a single parameter.

The electrical properties are based on data from *The dielectric properties of biological tissues: II. Measurements in the frequency range 10 Hz to 20 GHz* [14], where lung, heart, blood, and bone are used directly, and the other tissues are based on a mean of several other tissues. The relative permittivities and conductivities are shown in figure 1.10.

For both three and four electrode models, we found changes in transfer impedance from diastole to systole, and the contributions from the two most interesting tissues; the heart and blood. In addition we extracted a number of extra parameters from the diastole analysis. These are Potential on the PU electrodes (U in equation 1.2), negative and positive contributions to total transfer impedance (Z_{NEG} and Z_{POS}), and negative fraction (NF) as defined in paper I [50]. We also calculated the ratio of the negative and positive impedance magnitudes (NF_2) as defined by

Figure 3.2: Parameterised heart geometries. The scale of both images is identical.

$$NF_2 = \frac{|Z_{\text{NEG}}|}{|Z_{\text{POS}}|}. \quad (3.1)$$

V_{PU} is not reported for the three electrode models since this parameter is highly dependent on electrode properties [86], and this model does not model the small electrode very good.

In engineering, the word sensitivity refers to how much the output of a system, typically a transducer, changes per change in input. This definition is only weakly related to the quantity defined in section 1.3.3, which is a problem since the above definition is what we actually need when evaluating a measurement system. To get around this problem, we use a synonym of the word sensitivity, *perceptivity*, to which we attach the engineering definition of sensitivity. In mathematical terms this turns out as

$$\Psi = \frac{\delta Z}{\delta \text{phenomenon}} \quad (3.2)$$

where Ψ is perceptivity¹, δZ is change in measured impedance, and $\delta \text{phenomenon}$ is change in the phenomenon we want to test perceptivity against. Since an impedance change is dependent on both geometry and material (tissue) properties, we may specify this by presenting Ψ_g and Ψ_m , respectively. Note that perceptivity as defined in equation 3.2 is a complex quantity as opposed to the world of engineering, where sensitivity normally is a scalar quantity. From a mathematical point of view, this is no problem, and the perceptivity could even be expanded to be a function of frequency ($\Psi(f)$), but for many cases the simple scalar number is desired. Reduction of a complex, or even frequency dependent, perceptivity to a scalar can be done in many ways, but make sure that the method is specified. Examples are use of real or imaginary values, or magnitude of the Ψ -vector. Unit of perception is not mentioned since the phenomenon of interest may vary.

Since a measured quantity often vary around an offset value, it can be useful to expand the perceptivity concept to what we call *relative perceptivity* defined as

¹May Schrödinger forgive me for recycling the greek letter Ψ .

$$\Psi_r = \frac{\frac{\delta Z}{Z_0}}{\delta \text{phenomenon}} = \frac{\Psi}{Z_0} \quad (3.3)$$

where Ψ_r is relative perceptivity and Z_0 is the starting offset (or bias) an impedance is varying around. In relative perceptivity, the unit of impedance is taken out of the equation, and if the phenomena has no unit, the perceptivity is unit-less.

Of the large number of plots it is possible to generate from the four electrode model, three are extracted and presented in this thesis. For the three electrode models, only VID plots in a plane is shown.

The presented results are for simulations using 50 kHz excitation.

Results

The quantitative results from the four electrode simulations are summarised in tables 3.1 and 3.2, and some of the produced graphical plots are shown in figure 3.3. Table 3.1 illustrates how the impedance is changing from diastole to systole, and how the blood and heart contribute to the transfer impedance. Table 3.2 contain parameters of interest which are not related to the heart cycle. The first parameter is telling the expected potential on the PU electrodes since this may give more insight in signal-to-noise (SNR) issues. The rest of the parameters all deal with how much of the measured transfer impedance is a result of negative contributions.

	Z [Ω]	BC [%]	MC [%]
Diastole	$0.741 - j0.0691$	10.0	33.5
Systole	$0.638 - j0.0590$	8.43	33.1
Relative perceptivity ($ \Psi_{rg} $)	-0.139	-0.157	-0.012

Table 3.1: Simulation results from four electrode simulations. Changes in impedance between diastole and systole together with relative perceptivity. Since the imaginary parts of the impedances were low compared to the imaginary parts, perceptivity was reduced to a scalar by using the magnitude of the complex perceptivity. The model is only geometry-dependent, and we are thus reporting $|\Psi_{rg}|$. "contr." means contribution to total measured transfer impedance. BC and MC are the contributions from blood and myocardium, respectively, to total transfer impedance.

Parameter	Symbol	Value	Unit
Potential on PU when $I_{CC} = 25$ mA	$V_{PU-25mA}$	18.6	mV
Positive contribution to impedance	$ Z_{POS} $	1.47	Ω
Negative contribution to impedance	$ Z_{NEG} $	-0.729	Ω
Negative fraction as defined in Paper I [50]	NF	0.976	-
Magnitude of negative contr. versus positive contr.	NF_2	0.495	-

Table 3.2: Simulation results from four electrode diastole simulation.

Figure 3.3: Graphical results from four electrode measurements.

The three electrode simulation results are shown in tables 3.3 and 3.4. The data are similar to those of the four electrode simulations. For the three electrode simulations, it was important to get an impression of volume impedance density, so a plot for each of the electrode placements are shown in figure 3.4.

The tabular results tell us that we can expect a significant change in impedance between diastole and systole. It also tells us that the blood volume, or rather, the change in blood volume is a major contributor to the change in impedance. The simulation does not tell us anything about the shape of the waveform in the time domain since our model is not good enough to simulate this, and we have simulated only two points (systole and diastole). A qualitative feel of current paths and effects of electrode placements can be obtained by looking at graphical representations of simulation results such as those shown in figure 3.4. The real value is even higher when these figures are manipulated on-screen where it is possible to rotate, zoom, change colours, et cetera.

3.2 Instrument design

Since there is a lack of instruments that are suitable for research on bioimpedance and biopotential measurements in human hearts, we had to design our own system. We considered making the system from scratch, but decided that this would require too much time and resources. Instead, we decided to use existing instruments as a base for bioimpedance and biopotential measurements. This choice means that we have limited possibilities for choosing excitation method. Table 1.5 lists some of the available

	Z [Ω]	BC [%]	MC [%]
<i>Combined CC and PU in RV</i>			
Diastole	$101 - j13.2$	22.9	73.5
Systole	$106 - j13.7$	23.1	72.9
Relative perceptivity ($ \Psi_{rg} $)	-0.050	0.0087	0.0082
<i>Combined CC and PU in LV vein</i>			
Diastole	$110.6 - j15.4$	1.05	79.8
Systole	$110.9 - j15.4$	0.685	79.5
Relative perceptivity ($ \Psi_{rg} $)	0.0027	0.35	-0.0038

Table 3.3: Simulation results from three electrode simulations for combined CC and PU electrode placed in RV and LV vein. Changes in impedance between diastole and systole together with relative perceptivity. Since the imaginary parts of the impedances were low compared to the imaginary parts, perceptivity was reduced to a scalar by using the magnitude of the complex perceptivity. The model is only geometry-dependent, and we are thus reporting $|\Psi_{rg}|$. BC and MC are the contributions from blood and myocardium, respectively, to total transfer impedance.

impedance spectroscopy instruments we considered. Initially, the Sciospec ISX-3v2 and Zürich Instruments MFIA were not available on the market, but the first generation of the Sciospec ISX-3 was made available. The first generation Sciospec ISX-3 is very similar to the ISX-3v2, but differ in one important aspect: It is only capable of doing two electrode measurements. Since we realised that a front-end had to be made in any case, we considered the first generation ISX-3 and the Zürich Instruments HF2IS, but ended up with the ISX-3 for these reasons:

- The first generation ISX-3 was smaller than the HF2IS.
- The first generation ISX-3 was not as expensive as the HF2IS.
- We knew that a the second generation ISX-3 was being developed, and this would fit our requirements.

The front-end would have to perform two tasks: provide safety isolation and convert the two-electrode system into a four electrode system. The principle of converting from a two electrode system to a four electrode system is shown in figure 3.5. This front-end need a way to convert a single-ended potential (U_{CC}) to a differential current source (X_1). There are several ways of implementing such a current source, and most are based on the Howland current source or a derivation of it [87, 88, 89]. But a Howland current source does not include galvanic isolation or any other safety feature which means that other types were evaluated too [90, 91, 92, 93, 94]. During this work, we also designed a new isolated current source, which is presented in Paper II: *Optically isolated current source*. The current source is designed as a H-bridge where the photo-diodes of the linear optocouplers are used instead of the more traditional transistors in a H-bridge. We planned to use a simple circuit based on a commercially available instrumentation amplifier for the conversion of the PU potential to a current (X_2 and R_1 in figure 3.5). Note that it is also possible to replace the ISX-3 in this figure with an AD5933 from *Analog Devices, Inc.*, Norwood, MA, USA [95] with a few more

Parameter	Symbol	Value	Unit
<i>Combined CC and PU in RV</i>			
Positive contribution to impedance	$ Z_{\text{POS}} $	103	Ω
Negative contribution to impedance	$ Z_{\text{NEG}} $	-0.724	Ω
Negative fraction as defined in Paper I [50]	NF	0.007	-
Magnitude of negative contr. versus positive contr.	NF_2	0.007	-
<i>Combined CC and PU in LV vein</i>			
Positive contribution to impedance	$ Z_{\text{POS}} $	112.5	Ω
Negative contribution to impedance	$ Z_{\text{NEG}} $	-0.754	Ω
Negative fraction as defined in Paper I [50]	NF	0.007	-
Magnitude of negative contr. versus positive contr.	NF_2	0.007	-

Table 3.4: Simulation results from three electrode diastole simulation. Combined CC and PU is electrode placed in RV and LV.

Figure 3.4: Volume impedance density plot from three electrode measurement where combined CC and PU electrode is placed in RV or LV vein in the heart.

components.

During the project, we got access to a second generation ISX-3 which is a four electrode instrument with separate CC and PU connections [96]. In addition, the ISX-3v2 came in a very small enclosure with external power supply which we found beneficiary since we wanted a small instrument, and we wanted to use a medical grade power supply that has CF-graded leakage of mains and ground currents. We then discarded the plan of making a front-end as shown in figure 3.5 since a front-end for a four electrode instrument only do not need analogue signal processing using amplifiers. The revised front-end design is shown in figure 3.6.

In addition to the bioimpedance measurement instrument and the front-end, it is necessary to be able to capture several biopotentials such as electrocardiograph (ECG) and electrogram (EGM). ECG is the electrical activity of the heart captured using skin electrodes, and EGM is the local electrical activity of the heart captured using invasive electrodes such as electrophysiology catheters or pacemaker leads. For the biopoten-

Figure 3.5: Front end principle for converting a two-electrode impedance measurement system such as the first generation Sciospec ISX-3 or an Analog Devices AD5933 into a four-electrode system. The instrument will actually measure admittance due to the analog signal processing done in the front-end. X_1 is a voltage-to-differential current converter, X_2 is an instrumentation amplifier, R_1 is a resistor used to convert the PU-voltage to a current, and R_5 is the current sensing resistor in the instrument.

tial measurements, we used the g.USBamp from *g.tec Medical Engineering GmbH*, Austria. This is a medically approved instrument with a CF-rating.

For a complex system, it is important that all possible ways harmful electric energy may be delivered to the heart is accounted for and handled properly. The biopotential instrument is made as a medical instrument, which makes it easy to integrate in the system, while the bioimpedance instrument required significantly more effort to integrate in the system. To make the instrumentation set-up usable in a practical setting, we placed all components on a cart that could be wheeled into the operating room for performing measurements. Figures 3.7 and 3.8 show the set-up.

The electronic design was done using several software packages; LTspice from *Linear Technology*, Milpitas, California, USA, was used for design work and for simulations, while the printed circuit board was made using EAGLE, *CadSoft Computer GmbH*, Pleiskirchen, Germany. Measurements were done using ordinary lab equipment such as multimeters, oscilloscopes, and signal sources.

3.3 Capture detection

An important objective in this work was to demonstrate that bioimpedance measurements could be utilised clinically.

By measuring the impedance in the ventricle using a four electrode configuration with all electrodes on the RV and LV pacemaker leads, we get a waveform that is in some form representative of the LV volume [45]. In addition, our own initial measurements have shown us that the waveform morphology changes as a result of changes in pace modality (RV pacing, LV pacing, or BV pacing). We have also seen that the waveform morphology is very dependent on patient, electrode placement, and pace rate. But since these factors are controllable, we believe that it could be possible to

Figure 3.6: Revised front-end for impedance analyser as presented in Paper III: *Bioimpedance measurements of temporal changes in beating hearts* [60].

detect pace modality by looking at the impedance waveforms.

The eight patients in this study have all been informed about the study, and have signed a consent form. The measurements were done during a normal CRT device implantation or CRT replacement. The study was approved by the regional ethics committee (2014/1223/REK sør-øst A).

In our study, we generated a set of template waveforms for all pace modalities. A second set of waveforms were then compared to the templates in order to classify the pacing modalities for the second set waveforms. The bioimpedance data from several heartbeats were condensed to a single waveform of 401 samples as described in Paper IV: *Use of bioimpedance measurements to verify capture with biventricular pacing*. Pearson's correlation coefficient and a wavelet-based semblance analysis [97] were used to compare the waveforms to the templates.

We have also developed a set of quality measures that may say something about how good the classifications are. But the results gave no conclusive indication of how useful these are.

The study showed that the new method was accurate in 47 of 48 cases for comparisons using both Pearson's correlation coefficient and the wavelet-based semblance analysis. The case with wrong classification were further analysed, and we found that the impedance waveforms for the five heart-beats of raw data were noisy. If we replaced the data with data from the next beats with less noise from the same measurement, we achieved perfect classification of all signals.

Figure 3.7: Measurement set-up overview showing all components and how they are used in the operating room. The parts are: A: Cart, B: Isolation transformer, C: Power supplies, D: Enclosed ISX 3v2 mini and front-end, E: g.USBamp, F: Computer, G: Ethernet optical isolation, H: Bioimpedance cables with pod, and I: ECG and EGM cables. Cable legend: Solid black: Mains power, Dotted black: DC power from power supplies, Solid red: Signal.

3.4 Unpublished work

Some of the work that has been done is not published, however, some of the unpublished work can help the reader to get an impression of the whole picture. Selected parts are presented here.

3.4.1 Pacemaker lead properties

Since pacemaker leads are used to do bioimpedance measurements, knowledge about how these leads may affect measurements is important. Since the leads typically have more than one wire, and the wires are coiled on the inside of the lead, we may expect both parasitic capacitors between the wires in a lead, and series inductors.

We used a Fluke PM6304 RCL meter at 100 kHz with leads hanging in free air to measure capacitance between wires and inductance in wires in a selection of leads.

We found that capacitance varied from 34 pF/m to 230 pF/m, which, for our longest leads means capacitance varied from 30 pF to 200 pF. At our highest measurement frequency, 750 kHz, this means that the parallel impedance ranges from 7.1 k Ω to 1.1 k Ω . The series inductance was from 1.3 μ H/m to 3.8 μ H/m, which, for our longest leads means inductance varied from 1.0 μ H to 3.0 μ H. At our highest measurement frequency, 750 kHz, this means the series reactance ranges from 4.7 Ω to 14 Ω . The natural resonance frequency for the lead is from 6 MHz and up, indicating that we should not expect resonance effects from the leads.

A limitation of the capacitance measurements is that we have not accounted for parasitic coupling to the surroundings which will be present in a clinical setting. A more thorough measurement would try to mimic the real conditions in an animal experiment or using a phantom.

Figure 3.8: Cart with instruments. From the top: Computer running LabVIEW software, g.USBamp, enclosed ISX 3v2 mini and front-end, and power supplies.

The important pieces of information are:

- The actual values of the parasitic components are very dependent on the leads.
- If exact knowledge of lead parasitics is required, a characterisation of the particular lead is necessary.
- Compensation, or calibration, of the measurement system may be required.
- On a general level for the measurements done in this work, inductance can generally be ignored, while capacitance is affecting at least the high frequency measurements.

3.4.2 Pacing, bioimpedance, and EGM

Among the challenges met when using several instruments or devices simultaneously are interference and excessive loading. This is especially true where one or more devices intentionally deliver electric energy to the measurand as is the case where we combine bioimpedance measurements, biopotential measurements, and pacing. In addition to interference, the electrical load a device and its leads present to other devices may be considerable. In a worst-case scenario, the loading may render other measurements useless.

During the first measurements we did on human subjects, we investigated inter-

ference and loading by trying a range of measurement configurations. We also did *in vitro* measurements to see in detail how bioimpedance measurements were affected by pacing. Although not published, this work was presented at the 16th International Conference on Electrical Bio-Impedance, Stockholm, Sweden [98].

The pace signals are voltage pulses that are from around 1 V to 10 V. These voltages are in the order of ten times as high as the biopotential instrument we use to measure ECG and EGM can handle, so it is crucial that we do not measure potential on the same electrodes as we deliver pace pulses. Yet, the pulses will reach the biopotential instrument through the tissue and through capacitive couplings in the leads, and in many cases, the pace pulses shows up as spikes in the ECG or EGMs as shown in figure 3.9. In some cases, the spikes are impossible to see, while in other cases, the spikes are so high with rapid edges that we suspect that we might see effects of saturation of the biopotential instrument's inputs. But the pace pulse is affecting bioimpedance measurements too. The impedance is calculated as the voltage picked up using the PU electrodes divided by the current supplied by the CC electrodes. A pace pulse that reaches any of these electrodes will alter the signals, and thereby alter the measured impedance. If we keep in mind that PU voltages can be in the microvolt range, and that the pace pulses may be up to 10 V, it is obvious that there is a huge risk of interference. The amount of interference is dependent on several factors such as distance from pace electrodes to bioimpedance electrodes, pace voltage, and whether some electrodes are shared between the pacemaker and bioimpedance instruments.

Bioimpedance measurements rely on an excitation signal being injected into the measurand. As with the pace pulse, this signal can be picked up by the biopotential instrument. The signal frequencies we use for bioimpedance measurements (20 kHz and above) should ideally not be picked up by the biopotential instrument which is sampling potentials at 600 Hz. However, since the bioimpedance signal is swept 190 times per second, and since we probably have aliasing in the biopotential instrument, it is to be expected to see some interference in the potential measurements.

Figure 3.9 illustrates how the pace artefacts in the bioimpedance and biopotential measurements may look like. The second plot in the figure illustrate interference from the bioimpedance instrument on a biopotential. We found that sharing biopotential instrument electrodes with bioimpedance CC electrodes is the worst case. The external pacemaker programmer used for pacing has a number of measurement features such as EGM and impedance measurement. We found that this EGM had interference from the bioimpedance measurements. This also meant that capture detection was disturbed.

Although it is not strictly interference of the instruments, it is possible for the instrumentation to interfere with the heart. To be more specific, it is possible for the bioimpedance CC electrodes to deliver electrical energy to the heart, and by that achieve an unintended myocardial capture. There are two methods to avoid this: low voltages and high measurement frequency on the CC electrodes. The risk of afflicting harm caused by unintended myocardial capture is further mitigated by doing measurement in an environment where heart rhythm treatment is done.

We experienced that the biopotential instrument did not load other instruments, but we found that if we connected the pacemaker and bioimpedance instrument PU to the same electrodes, the quality of the measured impedances went down. This was especially clear when we measured small impedances such as with external CC electrodes

and intra-heart PU electrodes.

As a summary, we found that sharing of PU and pace electrodes should be avoided, and intra-heart CC gave EGM interference that needs filtering to be useful.

3.4.3 The first measurements

The first group of measurements on human subjects were done in a laboratory used for implantation of pacemakers, implantable cardioverter/defibrillators (ICD), and CRT devices. This means that the room was equipped as a small surgical room with X-ray equipment, anaesthesia equipment, external defibrillator, and programmers for the aforementioned devices.

All measurements were done on subjects that were hospitalised for normal implantation or replacement of a pacemaker or CRT device. All patients were informed about the study and have signed a consent form. The study was approved by the regional ethics committee (2014/1223/REK sør-øst A). In practice this meant that the surgeon started his normal procedure, and when pacemaker leads were placed in RA, RV, and in LV, we started our bioimpedance measurements. Sterilised cables were used to connect the connector ends of the pacemaker leads to the instruments and to CRT device programmer. This set-up gave us the options to vary electrode configurations and pacing. Different electrode configurations included the configurations shown in figures 1.9b and 1.9c, and we could connect CC+, PU+, PU-, and CC- to any of the available skin electrodes or implanted lead electrodes.

During measurements we could see measured impedance in real-time together with ECG and EGM. The impedance data could be displayed as impedance or admittance, and we could choose rectangular or polar representation. If necessary, the data could be filtered in real-time too. All raw data from the measurements were stored for later post-processing.

Measurements on humans in a clinical setting as compared to measurements in a laboratory presented a series of new challenges that had to be handled. Some of these are presented here:

Physical space in the operating room. An operating room used for patient treatment may have a lot of equipment such as X-ray machine, patient monitor, defibrillator, anaesthesia machine, electrosurgery machine, and so on. This means that it may be challenging to place the measurement equipment close to the patient. The cart we used for the equipment had wheels and the height could be adjusted easily.

Free movement for clinical personnel. It is important that we did not hinder the clinical personnel in their normal work. This proved difficult sometimes, especially since the measurement equipment is placed near the head of the patient, and the nurses need access to the patient.

Keeping track of implantation procedure. The time a normal implantation takes is variable, especially the placement of the LV lead. To ensure that the measurement takes as little time as possible, it is important to be aware of where the surgeon is in the procedure. This is very much a question of experience, and it proved useful to ask experienced personnel available instead of distracting the surgeon.

Focus on sterility. It is crucial to keep the operating zone sterile to avoid infections.

This means focus on sterile measurement cables and clean equipment. Sterilisation of cables is done using a STERRAD system which uses low temperature hydrogen peroxide gas plasma technology [99]. This sterilisation technique allows us to use cables that cannot be sterilised using high temperature.

The patient is awake. Since the patient is awake it is crucial to be calm and make the patient feel safe.

Skin electrodes may be challenging. The skin electrodes we used for bioimpedance CC electrodes were pediatric defibrillation electrodes. These were placed at each side of the patient's thorax, in height with the LV, or as close as possible to this position. This placement could be difficult since one of the larger defibrillation electrode that has to be there was placed very close to it. Another problem with the electrode is that it could sometimes loosen because of high sweat activity, which could result in measurements with poor quality.

Patients are different. The heart of each patient is unique due to different anatomy and due to different morbidity. This means that that we get variable results. Placement of electrodes can sometimes be difficult to see on fluoroscopy, and if an electrode is not placed where we think it is, this may cause changes in signals.

The gained experience with these challenges is enabling efficient measurements and better understanding of measurement result.

3.4.4 Post-processing

The measurement data is presented to the operator in real-time during measurements, and the data is also stored to file. We have stored the data from the bioimpedance measurements and biopotential instruments in separate files during measurements since the data-format and rate differs. In addition, we stored event information about electrode location, pacing, etc. We then converted the data from a LabVIEW-format to a MATLAB format where bioimpedance data, biopotential data, and event information were merged for further processing. The first part of the processing was to resample and align data, then came manual splitting in individual measurements, followed by manual addition of pace data. This part of the post-processing is a candidate for automation since it is time consuming and can to a large extent be done automatically in the measurement software. The next part of the post-processing is filtering, generation of plots such as figure 3.9, and application specific processing. Since many measurements had pace artefacts, we made a filter that removes this automatically. An example of post-processed data is shown in figure 3.10 where the raw data are the same as the ones used in figure 3.9.

Removal of pace artefacts has to be done during post-processing since it is dependent on information on pace timing, and this information is not captured automatically since the pacemaker programmer do not have a synchronisation output.

We used LabVIEW to capture data and first storage in files. There are several software packages available that are useful for storage, post-processing, and display of measurement data. We evaluated several options before we decided that the available software was not well-suited due to lack of support for the complex numbers² the bioimpedance data consists of. Instead, we made an extensive set of functions

²Here, a *complex signal* is a signal where the numbers are expressed as $a + ib$.

in MATLAB that allows us to process and view measurement results. It is possible to export data to a format readable by Acqknowledge, *Biopac Systems Inc.*, Goleta, California, USA, and we did some analysis using Acqknowledge. Storage in a data sharing-friendly format such as HDF5 [100] has been considered, but we decided to let the idea mature before we implemented it.

Figure 3.9: Examples of interference between equipment. The figure is from a three electrode measurement where the top plot shows impedance measured with combined CC+ and PU+ is the LV pace lead electrode in coronar sinus, CC- is skin electrode, and PU- is skin electrode. Impedance is measured at 20 kHz. The next two plots show ECG and EGM in coronar sinus. The bottom plot show pace timing. The event marked A is pacing in atrium, the event marked B is pacing in RV, and the event marked C is the evoked response. The pace artefacts in the impedance measurements are very easy to see, and the artefacts in ECG and EGM are possible to see, even if they are less visible. The noise in the second plot is an artefact from the bioimpedance instrumentation.

Figure 3.10: Post-processed data. The raw data is the same as used in figure 3.9, but the waveforms have been low-pass filtered, and the pace artefacts are removed from the impedance data.

Chapter 4

Discussion

The work presented in this thesis is covering different steps on the way to create useful tools for the use of electrical bioimpedance as a tool in cardiology. Since relatively little work have been done in the field of bioimpedance and cardiology, we had to start at a basic level by evaluate feasibility and by making an instrumentation set-up that was usable on humans before we did our first clinical work.

The first step was to evaluate if it was feasible to do bioimpedance measurements with relevant results on a human during implantation of pacemakers, and in particular CRT devices. We knew the work of Porterfield et al. that it was possible to get bioimpedance waveforms representing LV volume [42]. Due to the limitations of their work, we decided to check feasibility of being able to measure in a similar way, but with CC electrodes placed on the skin by use of FEM analysis of the problem as shown in section 3.1.2. Before this analysis were done, we evaluated methods of extracting relevant information from the models, and found that the classic way of using sensitivity as defined in equation 1.6 did not provide useful information unless the material in the measurand is homogenous as shown in section 1.3.3. Therefore, we looked into more useful metrics to use when evaluating an *in silico* model, which we presented in Paper I: *Comparison of four different FIM configurations—a simulation study*. In this paper, and partially in section 3.1.2, we are defining new metrics that enables us to quantify how a measurement system is responding to a given change. In particular, the parameters perceptivity and relative perceptivity are of importance since they allows us to evaluate the quality or usability of a given measurement set-up objectively. The presented metrics let us know how the changes in the organ or tissue of interest is affecting the actual measured impedance. One limitation of the paper is that the figures shows sensitivity plots instead of volume impedance plots, but as long as the medium is homogenous, the result is only a scaling of the numbers.

The FEM analyses used to check four electrode measurements with CC electrodes on the skin showed that it is possible to get results that reflected heart contractions. The results showed that we could expect very small impedances (less than 1Ω) and 14% change in impedance when going from diastole to systole. The low impedance could be a problem since it means that we are approaching the outside of the impedance range of impedance instruments [61, 96]. The analyses showed that the potential on the PU electrodes are around 19 mV, which probably is large enough to enable measurements with a SNR that is high enough to get useful signals. Table 3.2 illustrates that the

negative fraction (NF) is very high. For cases where NF is very high, it may be easier to get an impression of the qualities of the measurement set-up by using NF_2 as defined in equation 3.1. The region that contributes negatively is where the angle between the current density vectors are more the 90° , and by looking at figures 3.3a and 3.3b, it is possible to get an impression of the origin of the negative contributions to the measured impedance. Figure 3.3c shows the border between the regions of negative and positive contributions. Figures such as these are particularly useful to learn about the model, or the system it models, but even if they are illustrative, the quantitative results are more suited to determine usefulness of a measurement system.

The model of the three electrode systems showed that placement of the combined CC and PU electrode in the RV will give more changes than an LV vein placement. This is because the blood contribution is higher in the RV case. The three electrode models have, as expected [101], very small negative contributions to the transfer impedance. The transfer impedance is varying very little when the combined CC and PU electrode is placed in the LV vein, which can be explained by static properties of the myocardium and surrounding tissue. We do know that myocardial tissue parameters varies through the cardiac cycle [7, 32], and since figure 3.4 show that the region contributing most to the measured impedance is immediately around the electrodes, we believe it is likely that a three electrode measurement will be able to register variations in myocardium through the cardiac cycle.

The models have some obvious limitations; it's simplicity and the material properties. We chose to use a simple geometric model because we believe the model is accurate enough to confirm feasibility of the measurement set-ups we were interested in. The geometry of the heart is the most complex part of the model, and is capturing the thickening of the ventricle walls and reduction in distance between PU electrodes during systole. We believe these are the two most important features that affect the measured impedance, so in that light, we believe that the model is providing useful information. Such a simplification of a modelling problem is not new, and even simpler models of the heart can provide insight in a problem [54]. The tissues parameters are also not perfect. The data from Gabriel et al. [14] have been collected from several animal species and humans which means that parameters may or may not be of representative tissues. The time from the data tissues were living to the measurements varied from zero hours (*in vivo* measurements) to 48 hours, which may cause significant change in parameters as shown by Martinsen et al. [59]. However, one of the most important tissues is blood, which has a significantly higher conductance than the other materials as can be seen in figure 1.10, and will thus increase the probability of getting representative results in the FEM analysis. We do know that the electrical properties of myocardium changes as a result of going through a contraction cycle [102], this is not modelled, and would probably affect the tree electrode measurements. The simplicity of the model and the fact that tissue impedance changes are not reflected will also mean that the model is not telling anything about other phenomena that may contribute to variations in measured impedance such as varying lung geometry and varying lung tissue properties (Gabriel et al. showed that the electrical properties of an inflated and a deflated lung are different [14]). In our model, specificity is high, while in a more complex model, the specificity would probably be decreased.

The encouraging results from the FEM analysis led us into the next part which is

to make equipment suitable for use on human subjects. As mentioned in chapter 1.3.3, there are no instruments that may be used directly, so we had to make our own equipment. In the first path we explored, we intended to design and build a front-end for a suitable high-speed impedance spectrometer instrument or impedance spectrometer integrated circuit with a built-in current source for measurand excitation. The result of this work is presented in paper II: *Optically isolated current source* [103]. This work resulted in a current source that employ a minimum of components while simultaneously provides galvanic isolation which is satisfying requirements for isolation as defined in IEC 60601-1. The experimental bandwidth of this current source is 1.35 MHz, which makes it useful in many bioimpedance measurement ranges. We did show that it may be possible to extend the bandwidth even further by careful design and choice of components. The circuit presented demonstrates that it is possible to exploit that the outputs of the optocouplers are currents instead of converting the currents to voltages which again is converted to currents in an opamp-based circuit. The presented simplification has potential for noise reduction since it has fewer components that contribute with noise than the classical solutions. The presented circuit was intended to be used in a circuit as shown in figure 3.5. This path of work was terminated for two reasons: a) The high resource requirement of developing a front-end with signal processing of both excitation signals and evoked signals and b) developments in commercially available impedance spectroscopy instruments which enabled a simpler front-end.

The decision to change In paper III: *Bioimpedance measurements of temporal changes in beating hearts* [60], we present a measurement system where the front-end were designed for a four electrode system. One of the main purposes of the front-end is to reduce chance of injury to the patient. We chose to use a first order high-pass filter comprised of a capacitor and a series resistor on each of the four signal wires to limit the low-frequency content of the available current. This solution gives a minimum impedance of $50\ \Omega$ in series with the signals, and the impedance is higher for lower frequencies (it is doubled at 6.3 kHz). This solution is making sure that there is little energy available at low frequencies where an AC current may be harmful [67] when considering risk of unintended capture. Another feature of the filter is that it is providing galvanic isolation of the patient from the instrument. The front-end we made is also providing switches that may disconnect the electrodes from the instrument and a flexible choice of connectors. The connector solution allows us to connect the instrument signals via four 2 mm safety connectors of the same type as is used for electrophysiology electrodes in addition to one multi-pin connector that has all signals available. This solution provided good flexibility when doing measurements, and in particular pilot measurements where we explored different configurations.

We chose to use a separate instrument with a CF approved applied part to capture potentials. This instrument together with a computer for controlling the instruments were placed on a cart that was relatively small and mobile together with necessary power supplies. This solution allowed us to move the measurement set-up to a useful position in the operating room.

Post-processing of data required much work to make the tools necessary to process the data. The two main reasons for this are the use of complex measurement variables and multi-domain data: impedance (complex arrays), potential (real arrays), and pace information (boolean arrays). In addition, it is desirable to store information about

the measurand, set-up, and processing that has been done to the data together with the data. We used Matlab, *MathWorks, Inc.*, Natick, Massachusetts, USA, due to its processing power and programmability. There are other choices that would have served the purpose, such as Python, one or more Matlab clones, or LabVIEW. Common for these are that programming would be required. Of the solutions that stand out among post-processing tools intended for medical or biological purposes are Acqknowledge, *Biopac Systems Inc.*, Goleta, California, USA, but since this tool does not have native support for complex values, it was only used to a small degree on data already processed in Matlab. Another issue when working with measurement data is ability to share the data. A common format such as HDF5 would be beneficial due to its openness and ability to handle data from many domains in many formats [100].

The first measurements we did on human subjects were of a very exploratory nature. We explored different settings for the instrumentation, and electrode configurations to gain a picture of what we could achieve. We did find that the measurements were sensitive to changes in cables, cable surroundings, and choice of pace leads. Much of this can be explained by the influence from parasitic devices in the cables and wires. We showed that it is possible to compensate for effects of some of these parasitic devices. It is not possible to compensate for all effects since some of these, such as capacitance from leads lying on the table beside the patient and on the patient, are variable. In addition, there are differences in the pace leads too as shown in section 3.4.1. The sensitivities for effects of parasitic devices described here means that if absolute values are required, great care has to be taken to compensate the measurement results. This is especially important for measurements with high-frequency excitation.

There are two reasons that the reduced accuracy of impedance measurements caused by parasitic devices are not a problem that prohibits us from getting useful measurements. First, all bodies are different, which means that the absolute values are going to be very variable anyway. The variations are caused by varying electrode contact, varying tissue characteristic, varying heart anatomy, and so on. Secondly, we may extract the information we need from the waveform morphologies instead of the absolute values. Use of morphology of waveforms to extract diagnostic information is used extensively in cardiology already when examining ECG waveforms, which shows that the morphology of a signal may have value. In papers III and IV, we have shown that morphology of waveforms change when the activation pattern of the heart changes as a result of changed pacing. We believe the combination of impedance waveforms, EGM waveforms, and pace information can allow us to extract useful information on the contraction quality and timing.

A potential problem is interference between instruments in use and from other sources such as the mains. As presented in section , we did find that the bioimpedance instrumentation could produce rather high noise on the EGM if the CC electrodes were close to or sharing the EGM electrodes. This frequency content of this interference is generally high enough to be filtered away, but some effects from the filtering such as overshoot and ringing could be observed in fast-changing EGM signals. Interference from the mains were not observed, and can be explained by the relatively low impedance of the wires since these are connected to the body. We did see that the pacemaker pulses caused large artefacts if pacing were done on electrodes also used for EGM and impedance measurements. This was expected since the pacemaker is

delivering energy with a wide bandwidth that is within the input bandwidth of the potential measurements and within the frequency range of the impedance measurement. The loading of the pacemaker cables and the pacemaker on the PU leads was affecting the impedance measurement to a large extent, so we had to completely avoid this configuration. In cases where we cannot be absolutely sure what different pieces of equipment have an effect on each other, pilot measurements must be carried out.

Based on the knowledge we gained on the capabilities of the instrumentation, we decided that we could contribute to solving the problem of capture detection for receivers of CRT. A patient receiving CRT requires pacing on both sides of LV to get the intended haemodynamic response from the treatment, and if no capture is achieved on either or both of the pace leads, the treatment is not effective. The methods used to detect capture today are mainly based on local potential response around the electrode, and are not considering the response of the entire LV. In Paper IV: *Use of correlation of bioimpedance measurements to determine capture*, we present a method of detecting pace modality which is using electrical bioimpedance changes originating in the whole LV myocardium and blood volume throughout a heart beat to detect pace modality. Based on the FEM analyses we have done, and the work presented by Porterfield et al. [42] and Zima et al. [37], we believe that the captured impedance waveforms are representative of the evoked haemodynamic response in the LV. By using the morphology of these waveforms to classify pace modality, we are not dependent on very good absolute values on the measurement signals as long as the noise levels are low and interference from other equipment is low. Use of morphology of waveforms to extract clinical relevant information from a patient is not new in cardiology, and is extensively used for analysis of ECG and EGM signals.

The method of capture detection presented in Paper IV is particularly important for patients with atrial fibrillation, low LV pace thresholds, or who experience anodal capture since these patients suffer from poor detection of wrong pace modality. Our method of capture detection can possibly detect capture more reliably than current methods based on locally evoked response.

The method of High voltage on pace pulses are draining CRT device batteries faster than pulses with low voltage. This means that to reduce hospitalisations to replace devices, pacing is done to with a pulse voltage that is equal to the capture threshold plus a small margin. If the method of capture detection is poor, the margin need to be higher which increases battery drainage. We have

The study has a number of limitations, where the most important is that the study is done on patients lying still on an operating table while a real-life system would have to work in a fully implanted system on mobile patients. A fully implanted system will probably be less exposed to interference since the leads are shorter and not as exposed as they are in the set-up we used. On the other hand, it is highly possible that interference from movement artefacts may pose a problem. Since a follow-up study with a fully implanted device is outside the current capacity for us, participation from the pacemaker industry will be required. We did not look specifically at no capture at all or at anodal capture, but we expect that it is relatively easy to detect these since we are able to differentiate between LV and BV pacing which are relatively similar compared to BV pacing versus anodal and no pacing.

This study concludes the work presented in this thesis by demonstrating that elec-

trical bioimpedance can be a useful tool in the field of cardiology, and in particular CRT where we can we can confirm delivery of therapy.

Chapter 5

Conclusion

We have developed equipment suitable for electrical bioimpedance measurement in human hearts, and we have developed a method of detecting capture for CRT devices. We have used bioimpedance to improve treatment of cardiac disease, but not to detect cardiac disease. This means that the aims we set are partially reached. The equipment is in use today in other CRT studies, so we expect to reach the last aim as well.

The objectives are considered individually:

- *Evaluate feasibility of getting useful results from measurements in a human heart using pacemaker leads during the acute phase of the implantation by analysing finite element models.*: The work on finite element models have shown that it is probable to get useful results from four electrode measurements, and to some degree that it is feasible to get results from three electrode measurements. If we connect the work on three electrode models with knowledge of variable tissue properties in myocardium, we can conclude that also three electrode measurement will give useful results. To be able to quantify the feasibility, we developed new measures of quality that are useful for evaluating measurement set-ups in *in silico* experiments. We therefore conclude that the objective is fulfilled.
- *Design, build, and test a measurement system suitable for use on human hearts*: We did build a measurement system that successfully has been used for measurements on human subjects. We have demonstrated that the system is capturing 190 spectrums per second with five frequencies from 20 kHz to 750 kHz. The results are presented in real-time, and are saved to file simultaneously for post-processing. We therefore conclude that the objective is fulfilled.
- *Start building a knowledge base*: We have done a series of measurements with varying set-ups, and we have collected valuable knowledge of possibilities, limitations, and expected results for a number of set-ups. We are still learning and adjusting the information we have, but we have started. We therefore conclude that the objective is fulfilled.
- *Demonstrate practical use of electrical bioimpedance in cardiology*: We developed a novel method to determine loss of capture in pace electrodes used for delivering CRT therapy based on electrical bioimpedance. The method is based

on bioimpedance measurements within the heart, and has been tried in a clinical study. We therefore conclude that the objective is fulfilled.

The work presented here has enabled our group to continue exploiting electrical bioimpedance as a tool in cardiology.

Appendix A

Abbreviations

The list of abbreviations and mathematical functions is grouped in subject groups.

A.1 Impedance

B	Suceptance. Imaginary part of admittance.
CC	Current carrying electrode or terminal.
CC+	Positive current carrying electrode or terminal.
CC-	Negative current carrying electrode or terminal.
CP+	Combined positive CC and PU electrode or terminal.
FIM	Focused impedance measurement.
G	Conductance. Real part of admittance.
NF	Negative fraction of an impedance as defined in Paper I [50].
NF_2	Negative fraction of an impedance, as defined in equation 3.1.
PU	Voltage pick-up electrode or terminal.
PU+	Positive voltage pick-up electrode or terminal.
PU-	Negative voltage pick-up electrode or terminal.
R	Resistance. Real part of impedance.
X	Reactance. Imaginary part of impedance.
Y	Admittance. Inverse of impedance.
Z	Impedance.

A.2 Medical

A	Atrium.
AV	Atrio-Ventricular.
BiV or BV	Biventricular.
CRT	Cardiac resynchronisation therapy.
CRT-D	Implantable CRT device capable of pacing and cardioversion / defibrillation.
CRT-P	Implantable CRT device capable of pacing.
CS	Coronar Sinus.
ECG	Electrocardiogram.

EGM	Electrogram. Electromyogram measured directly on the heart.
ICD	Implantable ca
LER	Locally evoked response.
LBB	Left bundle branch.
LBBB	Left bundle branch block.
LV	Left ventricle.
LVAD	Left ventricular Assist Device. An implanted pump that assists left ventricle.
RA	Right atrium.
RBB	Right bundle branch.
RV	Right ventricle.
SA	Sinoatrial.
V	Ventricle.

A.3 Other abbreviations

$abs(\mathbf{A})$ or $ \mathbf{A} $	Absolute value of variable $\mathbf{A}$, length of vector $\mathbf{A}$, or size of complex number $\mathbf{A}$.
$\angle \mathbf{A}$	Angle of vector $\mathbf{A}$ or angle of complex number $\mathbf{A}$.
$\sphericalangle \mathbf{A}$	Measured angle of vector $\mathbf{A}$ or measured angle of complex number $\mathbf{A}$.
AC	Alternating current. Is used to indicate presence of frequency content on both currents and voltages.
B	Body. A safety classification on medical equipment. The applied part of the equipment is approved for use on the body, but not invasively. Not floating with respect to ground.
BF	Body. A safety classification on medical equipment. The applied part of the equipment is approved for use on the body, but not invasively. Floating with respect to ground.
CF	Cardiac Floating. A safety classification on medical equipment. The applied part of the equipment is approved for direct contact with the heart. Floating with respect to ground.
DC	Direct current. Is used to indicate lack of of frequency content on both currents and voltages.
FEM	Finite element method or finite element model.
FFT	Fast Fourier Transform.
<i>in silico</i>	An experiment or measurement performed on a numerical computer model. The term <i>silico</i> refers to the silicone based microprocessor that does the computations. One of the more common sub-set of model are finite element models.
<i>in vitro</i>	An experiment or measurement performed on material outside a living organism.
<i>in vivo</i>	An experiment or measurement performed on material inside a living organism.
MPH	COMSOL Multiphysics.

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Part II

Papers