

Development of Volumetric Blood Flow Measurement

by

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Abstract

Development of Volumetric Blood Flow Measurement

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This thesis entails the development of a proof-of-concept device which may be used for measuring volumetric blood flow. Blood circulation is primarily determined by measuring blood velocity in arteries. This does not take into account that blood vessel diameter can vary with various medical conditions and result in insufficient oxygenated blood being delivered to organs. Insufficient volume blood flow to the brain and kidney can cause strokes, death of brain tissue, heart attacks and even death.

A device capable of measuring diameter and velocity was developed. Diameter was measured using a bioimpedance catheter while velocity was measured using a self-mixing interferometer. Validation testing as well as in vitro testing was performed on each.

Validation testing and in vitro testing of the bioimpedance catheter was performed in various sized vials filled with horse blood to simulate various sized blood vessels. The voltage over the catheter electrodes was measured and recorded. It could be seen that there is an inverse relation between vial diameter and measured voltage due to the varying impedance in different sized vials.

The self-mixing interferometer was validated by tracking the excitation frequency of a speaker diaphragm. A magnitude peak could be seen on a FFT at various excitation frequencies of the speaker. During in vitro testing it was found that the signal-to-noise ratio was insufficient to reliably measure the Doppler frequency of red blood cells in flow. Various iterations were made to

the device to decrease noise, but ultimately it was determined that the sensitivity of the photodiode used to monitor the self-mixing signal was limiting the device. It was apparent that the signals reflected from the red blood cells were too small to be detected by the specific photodiode used.

It was concluded that it is feasible to measure volume flow by using a combination of bioimpedance and a self-mixing interferometer provided a higher grade laser module with a higher sensitivity photodiode is used. In vivo testing will be necessary to determine the effects of tissue surrounding blood vessels on bioimpedance measurements.

Uittreksel

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Hierdie tesis behels die ontwikkeling van 'n bewys-van-konsep toestel wat gebruik kan word om volumetriese bloedvloeï te meet. Bloedsirkulasie word hoofsaaklik bepaal deur die spoed van bloed in arteries te meet. Hierdie meting is egter nie voldoende nie, aangesien dit nie in ag neem dat die deursnee van arteries kan wissel weens verskeie mediese toestande nie. In so 'n geval kan bloed wat onvoldoende geoksigineërd is aan die organe gelewer word. Onvoldoende bloedvloeï na die brein en niere kan lei tot die dood van breinweefsel, hoë bloeddruk en selfs dood.

As antwoord op hierdie problem is 'n toestel ontwerp wat die deursnee van die arterie en bloedsnelheid afsonderlik kan meet. 'n Bio-impedansie kateter meet die deursnee van die arterie en die bloedsnelheid word met 'n selfmengende interferometer gemeet. Beide metodes het validasie toetse sowel as in vitro toetse ondergaan.

Die toetse op die bio-impedansie kateter is op verskillende grootte skale uitgevoer om verskillende deursnee bloedvate te simileer. Die skale is met perdebloed gevul. Die spanning oor die kateter se elektrodes is gemeet en aangeteken. Daar is opgemerk dat skale met kleiner deursnee groter spannings veroorsaak as gevolg van hoër impedansies.

Gedurende validasie toetse is dit bewys dat die selfmengende interferometer die opwekkingsfrekwensie van 'n luidspreker kan optel. Die sein word met behulp van 'n Fast Fourier Transform (FFT) waargeneem, waar die verskillende

opwekkingsfrekwensies van die luidspreker as amplitude pieke waargeneem kan word. Tydens *in vitro* toetsing is te veel geraas in die sein waargeneem om die Doppler-frekwensie van die rooibloedselle betroubaar te meet. Verandering in die ontwerp van die stroombaan is aangebring om die geraas te verminder, tog het die probleem voortgeduur. Dit is uiteindelik gevind dat die sensitiwiteit van die fotodiode onvoldoende was om die selfmengende sein waar te neem, veral as gevolg van die baie lae amplitudes van die seine van die rooibloedselle.

Na aanduiding van die toetse is dit bevind dat dit moontlik is om volumetriese bloedvloei te meet deur 'n kombinasie van bio-impedansie en 'n selfmengende interferometer te gebruik mits 'n beter lasermodule met 'n meer sensitiewe fotodiode gebruik word. Verdere *in vivo* toetse is nodig om die effek van weefsel rondom die bloedvate op die bio-impedansie te bepaal.

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Nomenclature

Variables

C	Feedback parameter	[–]
D	Diameter	[–]
$F(\phi)$	Interferometric waveform	[–]
f	Frequency	[–]
L	Electrode spacing	[–]
m	Modulation index	[–]
P	Unperturbed laser power	[–]
$P(\phi)$	Perturbed laser power	[–]
Q	Volume flow rate	[–]
u	Flow velocity	[–]
Θ	Incident angle	[–]
λ	Wavelength	[–]
σ	Specific conductivity	[–]

Abbreviations

AC	Alternating Current	[–]
ADC	Analog-to-Digital Converter	[–]
ICA	Internal Carotid Artery	[–]
DC	Direct Current	[–]
ECA	External Carotid Artery	[–]
FFT	Fast Fourier Transform	[–]
GBW	Gain bandwidth	[–]
LCD	Liquid Crystal Display	[–]
LDA	Laser Doppler Velocimeter	[–]
$NIRS$	Near-infrared Spectroscopy	[–]
TIA	Transient Ischemic Attack	[–]
$VSCSEL$	Vertical-Cavity Surface-Emitting Laser	[–]

Chapter 1

Introduction

1.1 Background

Biomedical engineering is a continuously evolving field which combines medical knowledge with innovative engineering to come up with solutions for monitoring, diagnosing and treating medical conditions. Medical staff is often vastly outnumbered at hospitals. Therefore, it may not be possible for them to continuously check up on patients. This necessitates the need for devices capable of monitoring a patients vital signs in real-time with the ability to alert medical staff if required.

Blood circulation is a critical parameter in patients. Insufficient blood circulation, and as a result, oxygenation can lead to severe medical conditions. Currently, blood circulation is most commonly monitored by measuring arterial blood velocity exclusively. Although low arterial blood velocity may be indicative of insufficient circulation it may not be accurate if the patient is suffering from conditions that affect blood vessel diameter. Narrowing of the artery will result in a reduced volume flow provided the velocity remains the same. Variations in blood vessel diameter can be caused by arterial stenosis as well as septic shock.

1.2 Objectives

This thesis proposes the design and implementation of a device capable of measuring changes in volumetric blood flow rate in an artery. The device should serve as a functional proof-of-concept which may be built upon in future research. Specifically, focus will be placed on measuring volume flow in the carotid and renal arteries. These are two primary arteries that provide blood to the cerebral region and kidneys respectively. Insufficient oxygenated blood flow to these organs can be caused by arterial stenosis, septic shock or thrombosis. This may have detrimental effects on health such as strokes, heart

attacks, aneurysms and chronic kidney disease which can lead to death.

The detection of change in flow or low flow can be used as a prognosis to prevent the above mentioned conditions. The relevant therapeutic modalities can be administered to correct the condition before it develops and puts the patient at risk. Various methods of flow measurement are investigated to design and construct the device. The device should be capable of taking continuous measurements to ensure that patients can be monitored in real-time. The device is expected to be of the intrusive type that is directly inserted into the artery by making use of a catheter but alternative methods will also be researched and considered.

1.3 Motivation

Measuring volumetric blood flow as opposed to blood velocity can aid in creating a more objective prognosis since it is a more quantitative method of determining blood circulation to specific organs. As mentioned previously, measuring only velocity can lead to a false positive where flow is deemed acceptable. Narrowing of arteries may however still result in insufficient flow, and as a result, oxygenation of organs using this approach. The primary goals of this device are to detect insufficient blood flow in the carotid and renal arteries to avoid cerebral ischemia and renal hypertension respectively.

Renal hypertension can be caused by increasing age, smoking, diabetes, high cholesterol or heavy alcohol and drug abuse. When renal hypertension occurs the kidneys have a hormonal response that triggers the retention of sodium and water. Due to the low local blood flow, the kidney increases the blood pressure within the entire circulatory system. The patient is then susceptible to the dangers of high blood pressure. This can cause chronic kidney disease, aneurysms, strokes, heart attacks and poor blood supply to the legs.

Similarly to renal hypertension, cerebral ischemia is caused by a lack of adequate blood flow to the brain which leads to a lack of oxygenation in the cerebral region. This results in cerebral hypoxia which can cause death of brain tissue, cerebral infarction or an ischemic stroke. Ischemic hypoxia can also affect other parts of the body indirectly by causing a stroke, cardiovascular arrest or irreversible brain damage.

It is clear that a device capable of measuring the volume blood flow would be useful in diagnosing and treating these conditions pre-emptively.

Chapter 2

Literature Review

The literature review in this section will focus on researching current methods of determining flow as well as medical knowledge required to design a well functioning and feasible device for measuring volumetric blood flow. Primary focus will be placed on methods that can be used to determine velocity and diameter since these two properties will be required to determine volume flow. This research may not necessarily be limited to the medical field since methods currently employed to measure flow in other fields may also be applicable. Additionally, methods of accessing and inserting a probe into arteries will be explored.

2.1 Medical Background

Currently there are various methods of measuring blood velocity, some of which will be discussed in the following sections depending on the relevancy, but few methods exist that are capable of measuring volumetric blood flow in real-time. Such a measurement is advantageous over traditional velocity measurement since it can give a more accurate indication of tissue oxygenation. While monitoring a patient's blood velocity may be acceptable, conditions such as arterial stenosis can result in insufficient volumetric blood throughput. Stenosis in the internal carotid artery for example, can lead to insufficient oxygenation of the brain causing cerebral ischemia. Similarly, stenosis in renal arteries can cause high blood pressure and kidney failure (Blankensteijn *et al.*, 1997).

Accurate measurements require access to the blood arteries that are being monitored, either externally or invasively. Invasive devices are more compact since the probe must be small enough to fit into an artery without restricting the flow excessively. An arterial line, which is a thin catheter, is commonly used to access a patients arteries invasively. The tip of the arterial line can contain sensors used for taking measurements. These catheters are most commonly used for intensive medical care.

An alternative to a catheter is a perivascular probe. Such a probe is not inserted into the artery directly but consists of a cuff which slides over the outside of the artery of interest. Administering such a probe is a very invasive procedure since it has to be placed around the artery. An incision must be made which can be used to slip the cuff over the artery of interest. Such a probe is more commonly used for research and is not a probe type commonly used on patients (Charbel *et al.*, 1998).

2.1.1 Carotid Artery

There are various primary arteries within the body which are responsible for transporting blood from the heart to smaller networks of arteries and capillaries. Two of the primary artery systems consist of the carotid artery and the renal arteries. The left common carotid artery branches off the aortic arch directly while the right common carotid artery branches off the brachiocephalic trunk. Both arteries travel upwards through the neck where they each split into the internal carotid artery (ICA) and external carotid artery (ECA). The internal carotid artery's primary function is to supply the cerebral region with blood while the external carotid artery's function is to supply more superficial features such as the neck and face with blood (Jones.O, 2017 (accessed May 25, 2018)). The components of this arterial system are shown in Figure 2.1.

Measuring the blood flow within these arteries is crucial since carotid artery disease can cause serious permanent damage or even death. The primary cause of this is carotid artery stenosis, which is the narrowing of an artery due to plaque build-up. This reduces the quantity of oxygenated blood being pumped to the cerebral region since it reduces cross sectional area of the artery. Insufficient oxygenation to this region will result in a stroke. If oxygenation is not restored to the cerebral region permanent damage to the brain can occur within minutes. Severe cases may even lead to death (Sobieszczyk and Beckman, 2006).

A velocity reading is not sufficient for determining sufficient blood circulation since stenosis reduces cross sectional area. Although velocity measurements may still be within the acceptable range, they would not be sufficient to determine with certainty whether enough oxygenated blood is being supplied to the cerebral region. A volumetric measurement device is capable of measuring quantity of blood supplied to the region. Additionally, it would be capable of measuring a sudden volumetric change which may indicate the onset of a stroke or a transient ischemic attack (TIA), which is a temporary shortage of blood to the brain. Upon detection the condition may be treated by administration of medication that thins the blood, removal of the plaque causing the

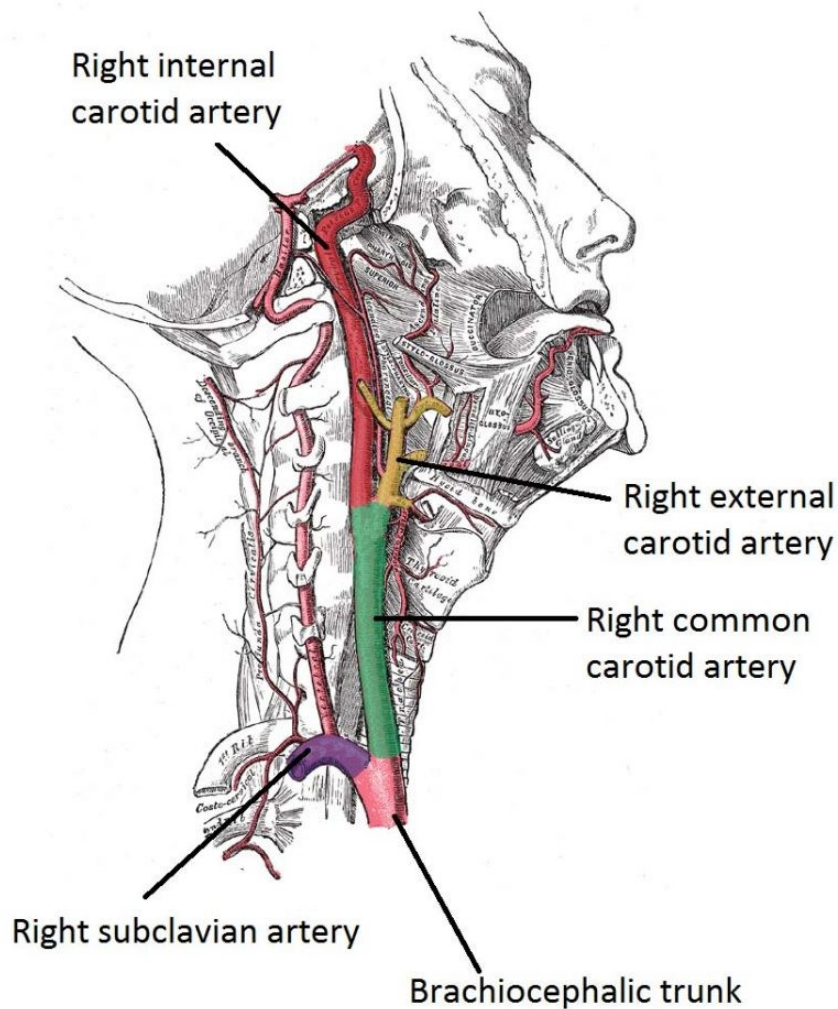


Figure 2.1: Diagram of carotid artery (Jones.O, 2017 (accessed May 25, 2018))

stenosis or by inserting a stent into the artery (Mayfield, 2018 (accessed May 20, 2018)).

2.1.2 Renal Artery

The renal arteries stem off the abdominal artery and supply the kidneys with blood. They are responsible for the majority of blood flow to the kidneys. Since the kidneys are responsible for cleansing of blood it is important that sufficient flow to them is maintained. The kidneys process around a quarter of all cardiac output. The renal arteries contain smooth muscle receptors which cause the arteries to expand or contract according to body blood pressure to ensure consistent flow. Insufficient flow can result in elevated blood pressure which can lead to further medical complications (Leslie and Sharma).

2.2 Blood Flow Measurement Techniques

Various methods of determining volumetric blood flow are investigated in this section. Measuring volumetric blood flow within an artery is not a common procedure and velocity measurements are generally used to give an indication of flow. Research done in this section consists of two components, methods of measuring flow velocity and methods of determining a vessels diameter dynamically. These two parameters may be combined to calculate volume flow using a mathematical relation. Velocity and diameter measurements may be implemented using the same concepts. It was therefore decided to group measurement techniques listed below according to the technology or principle that they implement as opposed to discussing diameter and velocity in separate sections.

2.2.1 Doppler Effect

The Doppler effect is used extensively in various different velocity measurement implementations and can also be used to measure vessel diameter. It is currently one of the most established methods for measuring blood velocity. Various methods that make use of this phenomenon are discussed below.

2.2.1.1 Laser Doppler Velocimeter

Laser Doppler Velocimetry (LDA) is one of the most common methods used for measuring blood velocity. The Doppler effect applies to any wave and can therefore also be applied to light. This method can be used to measure velocity of microscopic particles within a fluid or a solid by utilizing the Doppler effect. In blood specifically, light is reflected by red blood cells. As light is reflected from cells the frequency of the reflected light wave changes in direct proportion to the cells velocity. The frequency change between the incident light and the reflected light is the Doppler shift and can be used to determine the velocity. A photomultiplier tube is used to capture the reflected light. The tube creates a current according to the quantity of light detected.

The frequency change that is measured is very small compared to the base frequency of the laser which can result in inaccuracies since frequencies measured are absolute and not relative. These inaccuracies are minimized by creating a probe volume in which the velocity is measured (Durst, 1981). The probe volume is created by splitting a laser beam into two monochromatic, coherent beams that cross at a specified distance. It is important that the two intersecting beams originate from the same source since this causes interference in the form of light and dark stripes at the intersection point called fringes.

To ensure that the velocity measurement taken is accurate multiple beam pairs can be used. The beams must all pass through the same probe volume and be of different wavelengths so that signals from individual beam pairs can be distinguished by using a filter. As the particles move through the volume they move through the light and dark fringes reflecting light. This alters the amplitude of the reflected light source over time. Superimposing the frequencies of each beam will result in a small frequency variation known as the beat frequency. This beat frequency is analogous to the desired Doppler frequency (Durst, 1981). The Doppler equation for this is given by

$$f = \frac{2V}{\lambda} \sin\left(\frac{\theta}{2}\right) \quad (2.1)$$

where f is the Doppler frequency, θ is the angle between the two laser beams, V is the velocity component perpendicular to the laser beams and λ is the light wavelength.

2.2.1.2 Ultrasound Doppler

Ultrasound Doppler makes use of ultrasound transducers to determine the Doppler shift when a sound wave is reflected from a particle. Commonly Doppler ultrasound is only used to determine velocity. A single transducer with an incident angle of 60° is used for this measurement. An incident angle of 60° ensures the tests can be performed using standardized medical equipment. The Doppler shift from this reading can be used to determine velocity (Nguyen.P, 2015 (accessed August 19, 2018)). Figure 2.2 shows a typical ultrasound setup for measuring flow velocity.

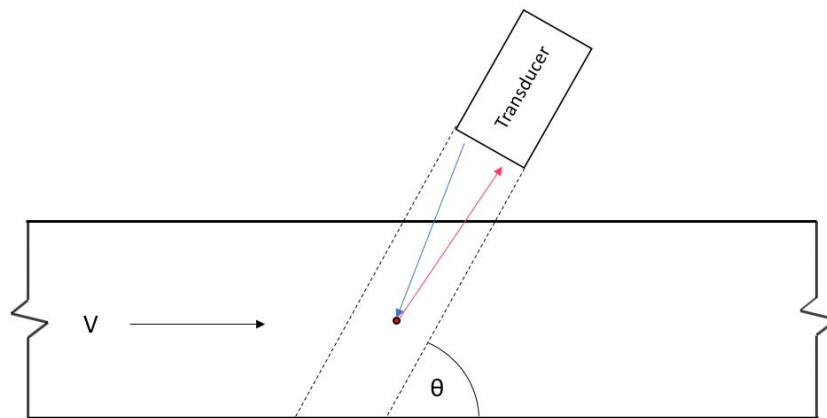


Figure 2.2: Ultrasound Doppler

Ultrasound may also be used to determine diameter although this practise is uncommon in the medical field. Such a measurement is based on the time-of-flight principle which uses the time it takes for the transmitted echo to return to the transducer to determine distance (Marioli *et al.*, 1992). The echo signature will vary depending on the tissue type reflecting the signal. Extracting the time difference between reflections from the near and far blood vessel walls can be analysed to determine diameter. Transducers used need to be perpendicular to the vessel walls to ensure an accurate measurement.

2.2.1.3 Ultrasound Sonography

Ultrasound sonography is a non-invasive method employed for determining the diameter of a blood vessel using a visual method. The most common method is a brightness mode (B-mode) sonograph. The ultrasound waves are produced by an external piezoelectric transducer which transmits the waves into the body. As the waves move through the body they are reflected off the tissue they encounter. The reflected waves are captured by a receiving transducer. The information captured from the reflected waves can be used to create a two dimensional visual representation of the tissue structure below the sampled area.

The blood vessel diameter can be determined either by manually measuring the diameter on the displayed image or by making use of a diameter detection algorithm which can identify the blood vessels. The accuracy of this method is dependent on the image acquisition quality, which can depend on the operator, and diameter detection algorithm used (Stadler *et al.*, 1996).

2.2.1.4 Self-Mixing Interferometry Laser

A self-mixing interferometry laser functions similarly to a LDA by analysing the Doppler shift in reflected light. However, instead of the reflected light being picked up by a photodetector, the light is reflected back into the laser cavity and modulates the optical output intensity. The modulation is caused by the reflected lights interaction with the optical field within the laser cavity. This modulation can be monitored with the photodiode built into the laser. A single laser sensor is required for laser interferometry allowing for a compact and simple to implement solution (Nikoli *et al.*, 2013).

The laser module creates a light beam directed at a moving object. If the object has reflecting properties, as well as a velocity component in the direction of the laser beam then some light is reflected back towards the laser. The frequency of the reflected light is directly proportional to the speed at which the reflection source, in this case the red blood cells, pass through the focal area of the laser. As the light re-enters the laser cavity, constructive and destructive interference

results as the frequency shifted light is amplitude modulated with the outgoing laser beam (Zaron, 2016). The modulation frequency observed in this signal is the Doppler frequency proportional to the flow. The relation between the flow and the Doppler frequency is shown in Equation (2.2).

$$f = \frac{2V \cdot \cos\Theta}{\lambda} \quad (2.2)$$

where λ is the light wavelength of the laser used and $V \cdot \cos\Theta$ is the velocity component of the object in the direction of the laser beam (Pruijmboom *et al.*, 2008). As the modulation occurs in the laser cavity the optical intensity change is detected by the built in photodiode as a power modulation. As mentioned, this frequency can be related to velocity.

Alternatively, the junction voltage of the laser diode may be monitored, which would show a voltage fluctuation as the power intensity within the laser cavity varies. The frequency of this voltage modulation will be equivalent to that seen by the photodiode (Lim *et al.*, 2006). Figure 2.3 shows how the light is reflected off the moving object and directed back into the laser cavity

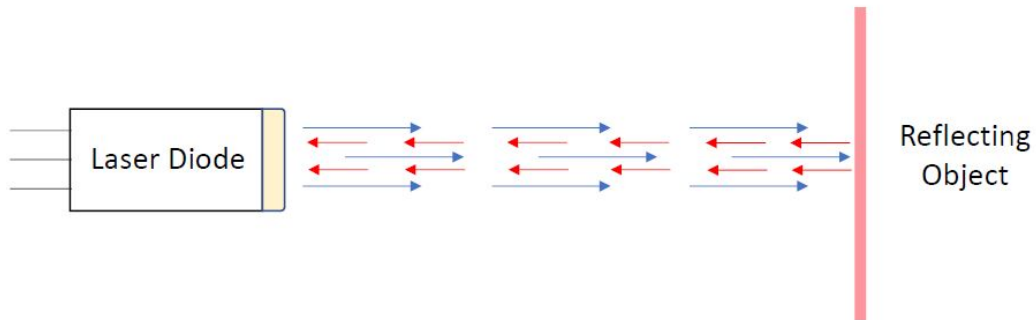


Figure 2.3: Self-mixing laser interferometry

The signal that is obtained depends on the amount of light that is reflected back into the laser cavity which is directly affected by the target reflectivity. The total power output of the laser diode may be described by

$$P(\phi) = P_0[1 + m \cdot F(\phi)] \quad (2.3)$$

where P_0 is power based on zero feedback interference, $F(\phi)$ is the interferometric waveform and m is the modulation index. The latter two parameters are affected by the light feedback parameter defined as C . A weak feedback signal is defined by $C \ll 1$ and will be a sinusoidal wave. A feedback value

around unity ($C \approx 1$) will create a distorted sine wave and $C \gg 1$ will create an asymmetrical sawtooth signal. When the interference signal has a high feedback value the asymmetry of the signal may be used to determine the target's travel direction in addition to velocity (Scalise *et al.*, 2004; Alexandrova *et al.*, 2015).

A single mode vertical-cavity surface-emitting laser (VSCSEL) is ideal for this application due to its narrow spectrum bandwidth. This allows the laser diode to act as an active filter, since it will only detect light waves within its spectrum. This also means that the effects of ambient lighting on such a device will be limited. According to studies performed a self-mixing interferometry laser is capable of modulating the optical intensity even if the reflected light is very weak. Studies exploring the feasibility of self-mixing interferometers determined that accurate readings were possible with a reflection intensity down to 10^{-4} of the laser power output (Prujmboom *et al.*, 2008).

2.2.2 Thermodilution

A common method to determine the cardiac output in a patient is thermodilution. Thermodilution is based on, and improves on Fick's principle which makes use of a marker substance that is injected into the blood stream and the concentration of the marker substance is measured downstream to determine the blood flow.

Instead of injecting a marker substance into the blood stream thermodilution makes use of a cool saline solution. A known volume of the solution, called a bolus, is injected into the blood stream at a known temperature. A thermistor is used to measure the mean blood temperature downstream of the injection. The blood flow rate is inversely proportional to the change in average blood temperature between the injection and measurement point as well as the duration of transit between the two points (Perel and Fick, 2009).

This method is primarily used to determine the blood flow rate through the heart but it should be feasible to adapt this method to determine the flow rate in any artery that is sufficiently large. One of the downsides to this method is that the process is not continuous. This is because a bolus has to be injected, and then the change in temperature needs to be measured downstream. The saline solution cannot be continuously injected. However, if it is sufficient to check on the patient periodically then this method may be viable.

2.2.3 Volumetric Flow by Manipulating Flow Area

Blood flow rate can be measured by monitoring the relation between the blood velocity as well as the cross sectional area through which the blood flows. Blood velocity is inversely proportional to the area through which it must flow. Decreasing the cross sectional area of the artery will increase the velocity if volume flow rate is maintained.

This relation can be taken advantage of by inserting a catheter with an inflatable section into the artery. The velocity of the blood is measured using a standardized method such as laser Doppler. Once the reference velocity reading has been taken, the flexible section within the catheter is pressurized to increase its cross sectional area by a known quantity. The velocity of the blood flow is measured again. The difference in the blood's velocity as well as the known change in cross sectional area can be used to determine the cross sectional area of the blood vessel. Since the velocity is known already the volumetric flow rate can be calculated (Sasaya *et al.*, 1984).

2.2.4 Near-Infrared Spectroscopy

Near-infrared Spectroscopy (NIRS) was devised as a non-invasive alternative to the commonly used Laser Doppler method. Although it can be used non-invasively it is still only capable of taking measurements in arteries that are close to the skin surface. NIRS operates in the wavelength region between 700 nm to 1000 nm (Villringer *et al.*, 1993). It is of particular interest when measuring the volume blood flow within the cerebral region. This technique determines the blood flow through the amount of light absorbed by red blood cells (Elwell *et al.*, 1992).

2.2.5 Magnetic Flow Meter

The conductive properties of blood allow a magnetic flow meter to be used for determining flow. The conductive properties are a result of the iron within red blood cells. This property can be exploited to measure flow by making use of Faraday's law of Electromagnetic Induction. There are various different magnetic flow meter types that will be investigated.

2.2.5.1 Transverse Field Flow Meter

A transverse field magnetic flow meter consists of two electromagnets and two electrodes. The electromagnets are placed on either side of the vessel through which flow is measured. This creates a magnetic field across the flow area. As the conductive fluid flows through the magnetic field the positively and negatively charged particles within it are forced to either side of the vessel wall depending on their charge. The particles move towards the electrodes,

which are commonly made from platinum, that are attached to the sides of the vessel. This creates a positively and a negatively charged electrode between which a potential difference can be measured. The potential difference is directly proportional to the velocity of the conductive fluid. This configuration can be seen in Figure 2.4.

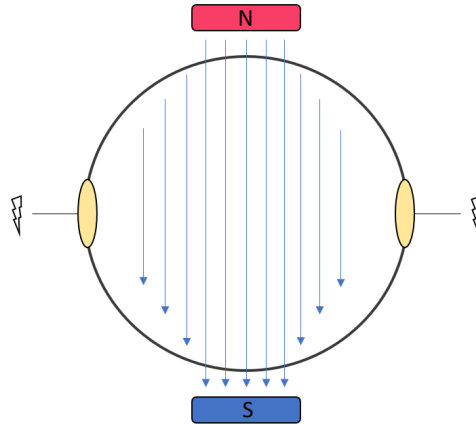


Figure 2.4: Transverse magnetic field flow meter. Flow is perpendicular to diagram

A drawback of this method is that the electrodes also measure interference voltages, which are not desirable since they can be as large as the voltage induced by the magnetic field, resulting in inaccuracies. One of the methods used to filter these interference voltages out is to drive the electromagnets with a pulsed current. This changes the polarity of the magnetic field periodically so the voltage detected by the electrodes changes in polarity accordingly. This can be used to filter out any constant external interference that might be acting on the system such as external magnetic fields. This is called phase-sensitive detection which is particularly important when measuring flow in an artery, since the heterogeneous nature of a blood vessel leads to eddy currents. These eddy currents may result in a large disturbance at zero flow (Kolin *et al.*, 1971).

One of the advantages of a transverse magnetic flow meter is that they do not obstruct the flow of fluids since they are mounted externally. Access to the blood vessel can be gained by making use of a perivascular probe, which is designed so that it can be slipped over the blood vessel (Webster, 2008).

Alternatively, an external magnetic field can be placed across the blood vessel. A probe, consisting of a flexible frame which can be collapsed, is inserted into the artery. Two electrodes are mounted on either end of the flexible wire so that they lie against opposite sides of the blood vessel once the wire is

expanded. This design can be seen in Figure 2.5 (Kolin, 1970). Using this method also requires a shunting effect caused by tissue surrounding the artery to be taken into account, since the tissue can alter the magnetic flux of the external electromagnetic coil (Kolin *et al.*, 1971).



Figure 2.5: Collapsible catheter with electrodes.

The above mentioned magnetic flow meters only determine the velocity of the blood flow. When making use of a collapsible catheter such as depicted in Figure 2.5 it is possible to determine the diameter of the artery by performing a radiograph on the patient. The radiograph is performed so that the expanded catheter displays the maximum projection width. Two indicators on the catheter tube, through which the flexible wire is fed, set at a known distance apart, are used to establish an effective measurement scale. This scale can be used to determine the effective diameter of the artery from the indicated width of the wire loop (Kolin *et al.*, 1971).

2.2.5.2 Eddy Current Flow Meter

An alternative method of measuring the flow using a magnetic field is to use a flow meter that relies on eddy currents induced in the fluid. Eddy currents are generated when a moving conductor encounters a changing magnetic field that is generated by a stationary object. Similarly, eddy currents are also generated when a stationary conductor encounters a varying magnetic field.

The eddy current flow meter works by making use of this principle to introduce distortion in the flow of the conductive fluid by creating a magnetic field through which the fluid flows. The flow meter contains a primary magnetic coil as well as two secondary magnetic coils. These coils are configured as shown in Figure 2.6. An advantage of the eddy current flow meter is that it can be completely encapsulated within a small probe which is inserted into the blood stream by using a catheter. The electronics are therefore not in direct

contact with the blood flow.

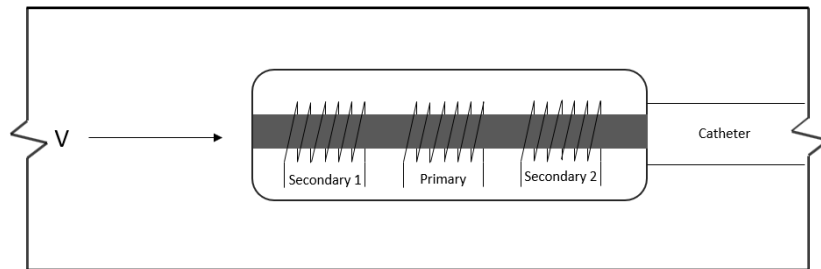


Figure 2.6: Eddy current flow meter indicating primary and secondary coils

Due to the symmetrical staggered design of the secondary coils on either side of the primary coil, as indicated in Figure 2.6, exciting the primary coil will create a voltage of equal magnitude in each secondary coil due to the mutual flux linkage between the coils. This induced voltage is referred to as the transformer voltage. Connecting the two secondary coils with opposed polarities in series results in a net output voltage of zero volts. This effect is only seen if the coils are isolated or if the fluid flow is stationary. If this coil assembly is inserted into a flow of conductive fluid, the fluid generates additional voltage in the secondary coils due to its movement through the induced magnetic field. The voltage due to fluid motion is seen as negative in the upstream coil and positive in the downstream coil. As a result the net voltage that is measured between the secondary coils changes. The net voltage that is measured across the secondary coils is directly proportional to the flow of the fluid (Poornapushpakala *et al.*, 2010).

The transformer voltage is only induced in the secondary coils if there is a change in the magnetic flux. A continuously changing magnetic field is created by exciting the primary coil with an alternating current (Sureshkumar *et al.*, 2013).

The eddy current flow probe concept was initially designed to be used in liquid metal cooled nuclear reactor cores. One of the drawbacks of this method is that it was initially designed to be used in rigid pipes where the diameter is known and constant. It may still be feasible to use this method for volume flow since changing blood vessel diameter will also affect impedance seen by the magnetic coils. This impedance variation will be reflected in measurements taken by the magnetic coils.

2.2.6 Bioimpedance

Bioimpedance takes advantage of tissue conductivity for measurements. This method is commonly used for taking measurements in the cerebral region and in the heart. A diametrical measurement method using this concept can be implemented due to bloods varying impedance with vessel diameter. The variation in impedance is caused by the changing cross sectional area which dictates the volume of blood passing through the artery over a set length, assuming the velocity remains constant. Since blood is conductive, a difference in volume will result in an impedance difference (Aroom *et al.*, 2009).

The impedance attributed to the blood within a vessel can be measured with an impedance catheter tipped with electrodes, either in a bipolar or tetrapolar configuration. A bipolar catheter consists of two electrodes while a tetrapolar catheter consists of four electrodes. In a tetrapolar configuration, the outer two electrodes are excited with a constant current and the voltage over the inner two electrodes is monitored, while in a bipolar configuration the same two electrodes are used for excitation and monitoring.

When the catheter is placed into an artery the blood completes the circuit between the electrodes. As the blood vessel diameter changes the blood impedance seen by the electrodes changes. When injecting a small constant current into the bloodstream via the electrodes, the circuit impedance is proportional to the voltage measured across the sensing electrodes according to Ohm's law. The measured voltage can be related to the diameter of the blood vessel using Equation (2.4) (Kassab *et al.*, 2004; He *et al.*, 1986). This method makes the assumption that a blood vessel can be modelled by a cylindrical vessel.

$$D = \sqrt{\frac{4I \cdot L}{\pi \cdot \sigma \cdot V}} \quad (2.4)$$

In this equation D represents the diameter of the blood vessel, I is the current with which the electrodes are excited, L is the length between the sensing electrodes, σ is the specific conductivity of blood and V is the voltage measured over the sensing electrodes.

When using bioimpedance to take in vivo measurements within arteries, current leakage through the vessel wall must be taken into consideration. Tissue surrounding the vessel will contribute to the total impedance due to the tissues conductance, affecting measurements taken by the electrodes. The blood within the vessel and the surrounding tissue may be treated as a parallel circuit. The parallel impedance can be accounted for by adding an offset error

term which corrects for the current leakage.

A more advanced method to account for this current leakage is to calibrate the catheter by injecting a bolus of saline solution with a different conductivity than blood into the artery in which it is placed. Any transient impedance fluctuation observed due to this injection can be solely attributed to the impedance of the fluid within the blood vessel. By plotting the total impedance against the blood and fluid conductivity during this injection, and extrapolating the impedance to zero, the parallel impedance of surrounding tissue can be determined.

It should also be noted that individual blood cells follow the Frick-Morse electrical equivalent model which is shown in Figure 2.7. The model states that, at low frequencies the current only flows around cells which accounts for the resistance R_e , while at high frequencies current will pass through the cell membrane (which accounts for the capacitance C_m) and the intracellular medium (indicated by R_i) (Giannoukos, 2014).

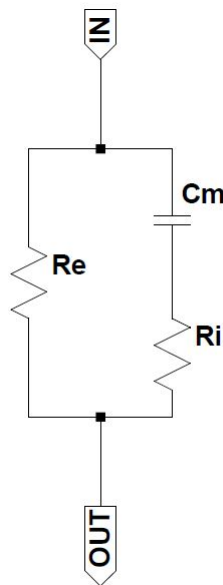


Figure 2.7: Frick-Morse model

The frequency range in which this model is valid is known as β dispersion and is applicable between 10kHz and 10MHz (Ali, 2002). Below this frequency range is what is referred to as the α dispersion range. In this range R_e dominates the model and the effects of intracellular capacitance and resistance may be neglected. Tissue conductivity is increased as the applied frequency is increased. This creates a trade-off between increased sensitivity and having

additional factors that affect measurements such as the cellular impedance. The desired frequency range should be chosen by considering the required sensitivity (Giannoukos, 2014).

Chapter 3

Concept Design

In Chapter 2 different methods of determining flow and velocity were researched. This chapter focuses on determining each methods advantages and disadvantages to find those that are most feasible. The cost and feasibility of implementation is taken into consideration, since some methods may require complex or difficult to obtain equipment. By taking all these factors into consideration a process of elimination can be conducted which leads to the most suitable solution.

3.1 Engineering Requirements

Designing a well functioning device requires a clear requirements list. These requirements include operating parameters of the device, what conditions it will be used in and the accuracy of the device. Having a thorough understanding of these parameters during the design phase is vital to ensure the designed device will function as expected. The following requirements were determined by analyzing the scope initially set forth for this project.

1. Device must be capable of measuring the diameter of a vessel.
2. Device must be capable of measuring the velocity of blood in vessel.
3. The primary focus of the device is to detect changes in volume flow while measuring absolute flow is a secondary focus. Measuring change in volume flow is more important since a sudden drop in volume flow is indicative of various medical conditions.
4. Measurements should be capable of being taken in real-time to ensure that patients can be monitored continuously.
5. The device should preferably be in the form of a catheter that can be inserted into the patient's arteries.

6. The device may not obstruct the flow of blood within the artery excessively.

3.2 Review of Researched Methods

While conducting the literature review in Chapter 2 it became apparent that measuring real-time diameter is not a common procedure. Most volume flow methods, not necessarily limited to the biomedical field, do not measure the diameter in real-time, but rather the diameter of the vessel is approximated by a mean value and is assumed to remain constant. This is not feasible, because with this assumption the velocity is always a direct indication of the total volume flow which is not necessarily true. The patient may be suffering from arterial stenosis which can drastically reduce the volume flow and give an invalid reading if a mean diameter value is used.

It was also found that there is no single method that is capable of measuring volumetric flow. Blood velocity and vessel diameter need to be measured independently and combined using the general mathematical relation for volume flow rate as shown in Equation (3.1) (Cengel and Cimbala, 2013). In this equation, Q represents volume flow rate, D is the vessel diameter and u is the flow velocity.

$$Q = \frac{\pi \cdot D^2 \cdot u}{4} \quad (3.1)$$

The most common methods for measuring velocity and diameter were researched. Some of these methods were found to have more relevance or to be more suited than others. After a preliminary analysis various methods were discarded since it was apparent that they would not be suitable. Parameters that were analysed to determine the feasibility of a method include size of the device, complexity of the device, whether it requires training to operate and cost. The viable methods that remained are summarised in Table 3.1. Also indicated is whether the particular methods are suitable for measuring velocity, diameter or both.

Table 3.1: Summary of viable options

Velocity Measurement	Diameter Measurement
Laser Doppler Velocimetry	-
Self Mixing Interferometry Laser	-
Eddy Current Flow meter	
Manipulation of flow area	-
-	Bio-Impedance
-	Ultrasound sonography
Ultrasound Doppler	Ultrasound Doppler

Each of the remaining flow methods was analyzed to determine the advantages and disadvantages of each and whether they are capable of meeting the requirements set forth previously. This will aid in reaching a conclusive decision about which method or combination of methods is most suited to measuring volume flow.

3.2.1 Laser Doppler Velocimetry

Advantages

- Established method of measuring fluid velocity.
- Makes use of a light beam which does not cause interference or is affected by components which may be used for diameter measurements.
- Can be used non-invasively if the artery of interest is close to the skin surface.
- Fiber optics can be used to redirect laser beams.

Disadvantages

- Only capable of measuring velocity.
- Requires splitting of laser beam which adds complexity.

3.2.2 Self-Mixing Interferometry Laser

Advantages

- Uses a single laser module for emitting and receiving signal.
- Narrow bandwidth of laser diode results in it acting as a filter for received signal.
- Capable of picking up very small reflected light feedback.

- Makes use of a light beam which does not cause nor is affected by electrical components which may be used for diameter measurements. This is especially beneficial in the small confines of the catheter tip.
- The laser module can be external with an optical fiber redirecting the light beam into the artery.

Disadvantages

- Only capable of measuring velocity.

3.2.3 Ultrasound Doppler

Advantages

- Uses the same principle for measuring velocity and diameter. This simplifies implementation since it won't be necessary to design circuitry for two fundamentally different concepts.

Disadvantages

- Alignment of probe may pose a problem since velocity sensor must be parallel to flow and diametrical probe must be perpendicular to vessel wall. Incorrect alignment may overestimate readings.
- Resolution is limited since measurement is reliant on speed of sound within the tissue which is slow compared to other methods which use Doppler shift of a light wave.

3.2.4 Volumetric Flow by Manipulating Flow Area

Advantages

- Single catheter capable of taking all necessary measurements.

Disadvantages

- Dilation of inserted catheter may be dangerous if it obstructs blood flow too much.
- Not capable of taking a continuous reading .
- Inflatable section in catheter adds complexity. Accurate pumping system will be necessary.
- Still requires additional hardware to determine velocity .

3.2.5 Ultrasound Sonograph

Advantages

- Established method of measuring velocity.
- Easily accessible machine in hospitals.
- Procedure is non-invasive.

Disadvantages

- Large machine compared to intravenous solution.
- Trained medical staff has to actively operate machine. Not feasible for continuous measurements.
- Visual processing necessary unless diameter is manually determined by operator from image which can introduce human error.

3.2.6 Eddy Current Flow Meter

Advantages

- Completely enclosed probe. No contact necessary between electronics and blood since measurements are taken by monitoring magnetic field.
- It may be possible to determine volume flow from a single probe since both diameter and velocity should affect voltage in the secondary coils. This will be tested experimentally.

Disadvantages

- Readings may be affected by tissue surrounding the blood vessel, which also interacts with the generated magnetic field.
- It may not be feasible to create a strong enough magnetic field with a probe small enough to be inserted into a blood vessel.

3.2.7 Bioimpedance

Advantages

- Simple hardware implementation. Catheter only requires electrodes in contact with the blood.
- One of few methods found that are capable of measuring diameter in real-time.

Disadvantages

- Measurements may be affected by impedance caused by tissue surrounding the blood vessel.

3.3 Design Selection

Section 3.2 considered the most feasible diameter and velocity measurement techniques and determined advantages as well as disadvantages of each. Initially experimentation was done on the feasibility of measuring velocity using an eddy current probe. The appeal of this method was due to the probe being fully enclosed and that it could potentially measure volume flow since it was reasoned that readings are affected by quantity of red blood cells flowing over the secondary coils, which is affected by the diameter of the vessel, as well as their speed. After testing various coil configurations within a simulated flow system using a peristaltic pump it was concluded that it is not feasible to create a strong enough magnetic field while simultaneously keeping the probe small enough to be inserted into the blood stream. Additionally, generating a magnetic field caused the coils used to heat up noticeably, which would also be undesirable within the blood stream. Additional information on testing done can be reviewed in Appendix A.

After it was determined that it would not be feasible to use an eddy current flow meter, self-mixing interferometry was chosen as the velocity measurement of choice. This method was appealing since the sensing region can be redirected into the blood stream via a single optical fiber, which is used to emit and receive a signal. In conjunction with the self-mixing interferometer, bioimpedance was chosen as the method of choice for measuring diameter. This is an ideal combination for creating a compact and functional catheter.

The two solutions mentioned above were chosen due to their simple but effective functionality, their ability to take continuous measurements and because they make use of fundamentally different concepts. Self-mixing interferometry makes use of a laser beam which measures reflected light while bioimpedance measures impedance dependent voltage by injecting a small current. Since one method is based on light and the other is based on an injected electric current the interference between the two measurements will be minimized.

3.4 Validation Criteria

The requirements that the device needs to meet once it is completed were listed in Section 3.1. The devices effectiveness is gauged by determining whether these requirements have been met and to what degree they were met. The most crucial requirements are its ability to measure diameter and velocity accurately

and consistently. This is determined by comparing measurements obtained during testing to measurements obtained from known reliable methods. Since diameter and velocity measurements are simple to determine accurately for validation testing these methods may include solutions such as pumping fluid through various known diameter vessels with a pump where flow rate can be set.

Chapter 4

Device Design

This chapter covers the detailed design of the solutions that are implemented. This includes the physical design of the catheter and the electronic circuitry responsible for driving the electrodes, laser and taking measurements. The flow chart shown in Figure 4.1 gives an overview of the electrical circuitry layout that is implemented for the impedance catheter and the self-mixing interferometer. As is apparent from the flow chart, the circuitry for the two will be independent components of the final design. This simplifies circuitry layout as well as troubleshooting should any problems occur during testing.

4.1 Impedance Catheter

It was determined in Section 2.2.6 that the cross sectional area of an artery is directly related to the amount of blood that flows through it. The impedance of the blood is inversely proportional to this cross sectional area and thus the diameter. This means the blood in a larger vessel is expected to have a smaller impedance than in a small vessel when assuming the vessel is a cylindrical model with a set length. The impedance of blood can be measured using an electrode tipped catheter within the artery that is in direct contact with the blood stream. This measurement can be related to diameter.

4.1.1 Electrical Design

The electrical design details all the electrical components that are related to the impedance catheter. This includes the excitation circuitry of the electrodes as well as the amplification and filtering necessary to monitor the signal across the sensing electrodes. The basis on which the impedance catheter functions was discussed in Section 2.2.6.

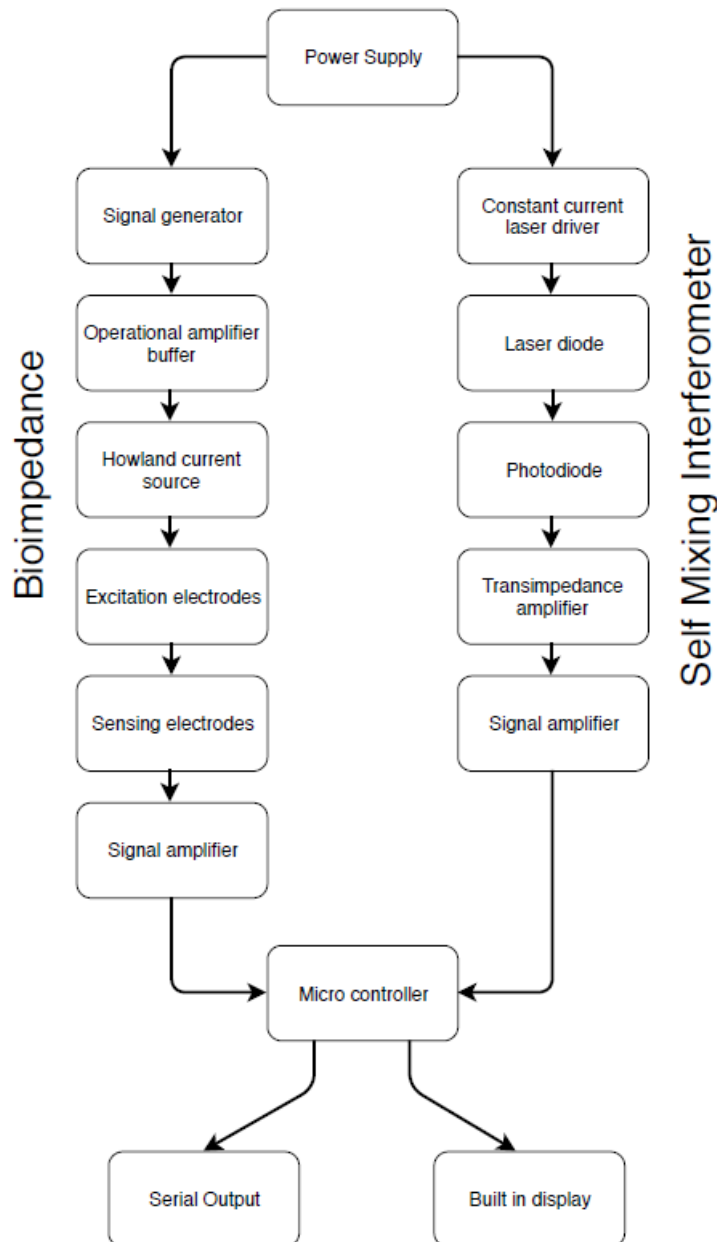


Figure 4.1: Overview of device electronics

The impedance catheter is powered by a constant alternating current. The current must remain constant, independent of the load impedance of the fluid that completes the circuit between the excitation electrodes. This ensures that the only variables in the taken measurements are voltage and impedance. This is achieved by powering a constant current source with a constant sinusoidal wave. The IC8038 waveform generator was chosen to create a sinusoidal signal. The waveform generator is simple to implement since the duty cycle and

frequency can all be set by two timing resistors and a capacitor. Two identical values are used for the timing resistors (R_a and R_b) which creates a uniform wave by setting a 50% duty cycle. The frequency of the generated signal is determined by these timing resistors in conjunction with an external capacitor (C), using the following relation

$$f = \frac{0.33}{R_a \cdot R_b \cdot C} \quad (4.1)$$

An excitation frequency of 5 kHz was chosen to ensure the device operates in the α dispersion range of blood. As discussed in Section 2.2.6, capacitance and intracellular resistance within this frequency range are negligible. This minimizes the number of factors which may affect measurements taken, which is desirable. The amplitude of the generated sinusoidal wave can be controlled using a potentiometer which is placed on the output. This output feeds into an operational amplifier (op-amp). This acts as a buffer with unity gain to ensure a low output impedance for the current source it feeds into. Figure 4.2 shows the configuration of the IC8038 signal generator with biasing resistors R_a , R_b and the external capacitor C as suggested in the manufacturer datasheet (Renesas, 2001). The configuration also shows the buffer op-amp with amplitude modulation potentiometer in the waveform output.

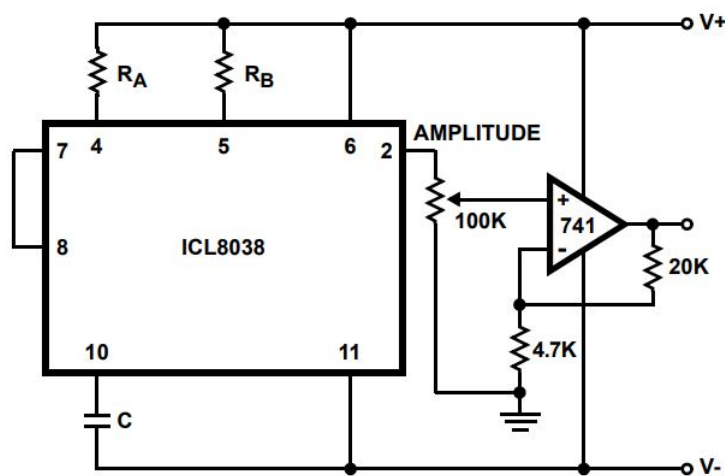


Figure 4.2: Waveform generator (Renesas, 2001)

The sinusoidal signal drives a constant current source, in this case a Howland current source. A Howland current source provides a constant current irrespective of the load impedance. This is important since varying blood vessel diameters will result in varying impedance between the catheter electrodes. Powering the electrodes with a constant current means that the only

other varying parameter according to Ohm's law is voltage. Therefore, the impedance in a vessel can be determined implicitly by monitoring the voltage over the sensing electrodes. This voltage can then be related to diameter. The current source consists of an operational amplifier (UA741) with biasing resistors at the inputs which are used in conjunction with the input voltage amplitude to set the operating current. Additionally, matched resistors connect the output back to the inputs. The output current can be determined by Equation 4.2.

$$I_L = \frac{V_{in}}{R_1} \quad (4.2)$$

As seen in the equation, the output current is only affected by the input voltage. The load impedance does not feature in this relation and as a result, change in load impedance will not have an effect on the load current. The current can be set exclusively with the potentiometer in the output of the signal generator. The current drives the excitation electrodes of the impedance catheter which are shown with the schematic for the current source in Figure 4.3.

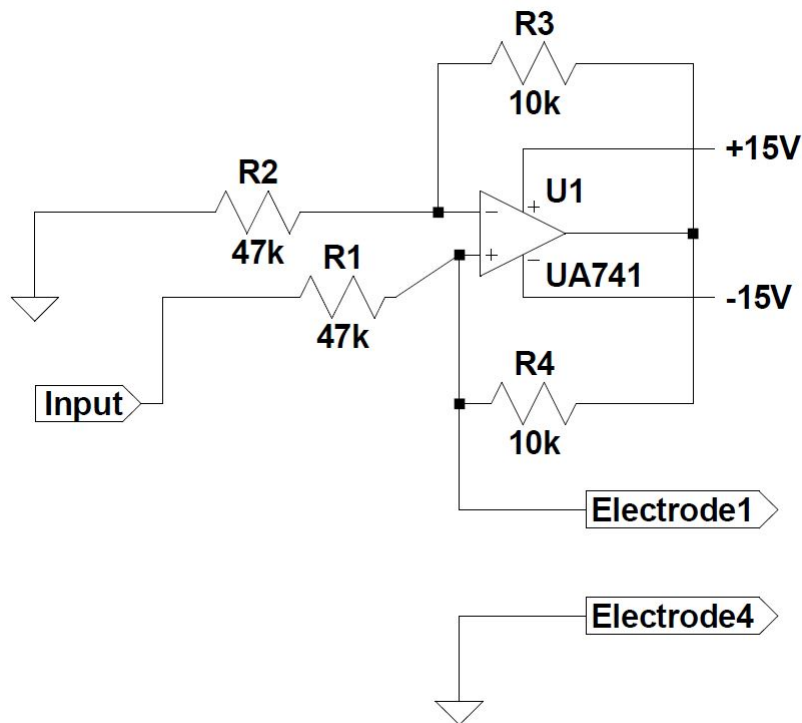


Figure 4.3: Howland current source

As the conductive blood completes the circuit between the electrodes, current flows through it. Due to the sinusoidal excitation, the current flowing between the outer electrodes fluctuates between the positive and negative maximum set current. This creates an electric field between the outer electrodes. Since the inner sensing electrodes are inside this electric field a sinusoidal voltage will be induced in them. The voltage measured over these electrodes directly relates to the impedance seen by the electrodes. A higher voltage reading is a result of a high impedance while a smaller voltage is due to a lower impedance. Different diameters will thus result in different voltages due to the volume of blood between the electrodes.

The voltage measured across these electrodes is in the millivolt range and needs to be amplified. The signal is relayed to an AD620 instrumentation amplifier which amplifies it. This will give a greater voltage resolution and as a result make it simpler to determine the diameter reliably. To remove any DC offset which may be induced in the sensing electrodes by external factors they are AC coupled to the amplifier. An instrumentation amplifier was chosen since it has input buffers ensuring high input impedance which will not affect readings taken.

The gain on the AD620 is set by a single external resistor. A potentiometer was used so that the gain could be adjusted as necessary. This was done since validation testing and in vitro testing may use fluids with slightly different conductivities. The signal may then be scaled as necessary for each test. Additionally, a zener diode was attached between the power supply and the offset pin of the AD620. This creates a DC offset around which the sinusoidal signal swings. This allows the output signal to be fed into a microcontroller's Analog-to-Digital Converter (ADC) which does not allow for negative voltages to be read. Figure 4.4 shows the circuit schematic used for the electrode amplifier.

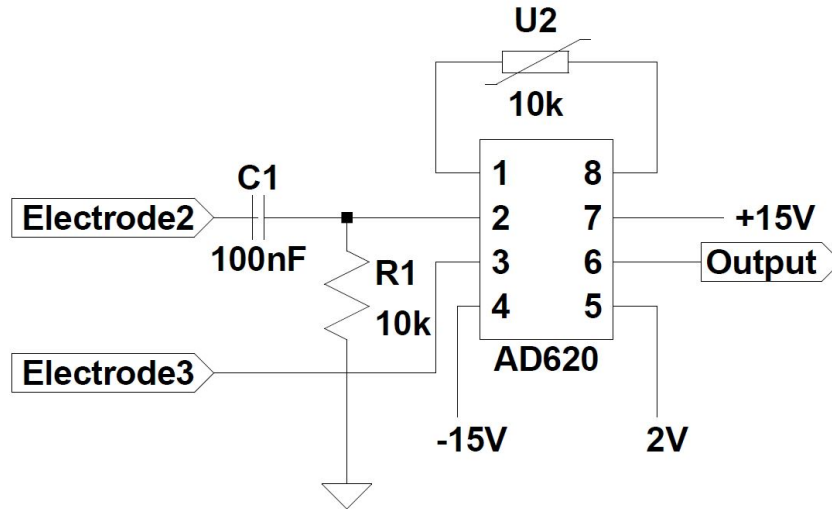


Figure 4.4: Sensing electrode amplifier

4.1.2 Probe Design

The physical design focuses on the components that constitute the tip of the impedance catheter that is inserted into the artery. The most important aspects of this are the electrode configuration as well as their physical dimensions. A tetrapolar electrode configuration was chosen for the impedance catheter, since it was found from literature in Section 2.2.6 that such a design is more robust than a bipolar one, especially at frequencies below 100 kHz, since the electrode impedance does not affect readings. When designing an impedance catheter the most crucial design parameters that must be taken into consideration are (Kassab *et al.*, 2004):

- Distance between excitation and sensing electrodes should be similar to the anticipated mean vessel diameter.
- Equidistant spacing between the excitation and sensing electrodes.

These two parameters affect the homogeneity of the created electric field which affects readings. Homogeneity refers to the strength and directionality of the field. The mathematical relation used to determine the diameter from the impedance, as stated in Equation 2.4, makes the assumption that the blood vessel is a cylindrical model and that the created electric field is indeed homogeneous. If the field is non-homogeneous theoretical values will vary from experimental measurements. A correction term can be added to account for

this deviance. A study conducted by (Kassab *et al.*, 2004) modeled the optimal catheter diameter in relation to the vessel diameter as shown in Figure 4.5. This figure indicates that it is beneficial to design the impedance catheter for a optimal operating range. The catheter will have maximum sensitivity within this range.

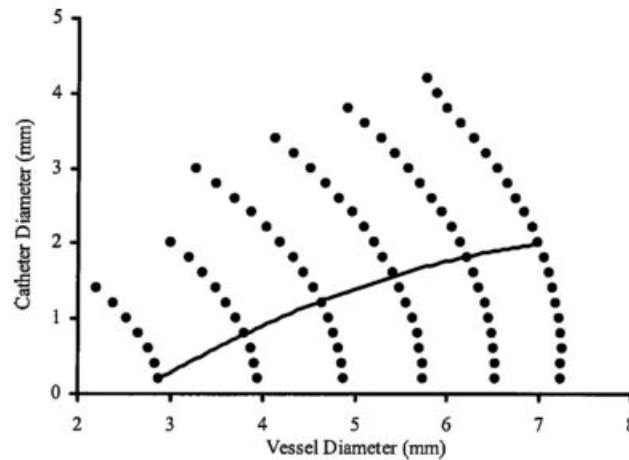


Figure 4.5: Impedance catheter optimal diameter according to (Kassab *et al.*, 2004)

The catheter is primarily intended for within the carotid artery to determine the onset of cerebral ischemia, as well as the renal artery to determine renal hypertension. According to a study performed by (Krejza *et al.*, 2006) the mean diameter of the internal carotid artery was found to be 6.10 mm for females and 6.52 mm for males. Assuming an average of these two values, Figure 4.5 indicates that for a mean vessel diameter of 6.31 mm the optimal catheter diameter is 1.8 mm. Additionally, due to the design criteria mentioned above, the distance between the excitation and sensing electrodes was chosen to be 6.5 mm to ensure the catheter dimensions adhere to the considerations previously mentioned. Spacing between the sensing electrodes was chosen to be 1 mm.

The configuration of the catheter is shown in Figure 4.6. The excitation electrodes are indicated in blue being driven by the constant current source while the sensing electrodes, indicated in red, are attached to an instrumentation amplifier to measure the voltage across them.

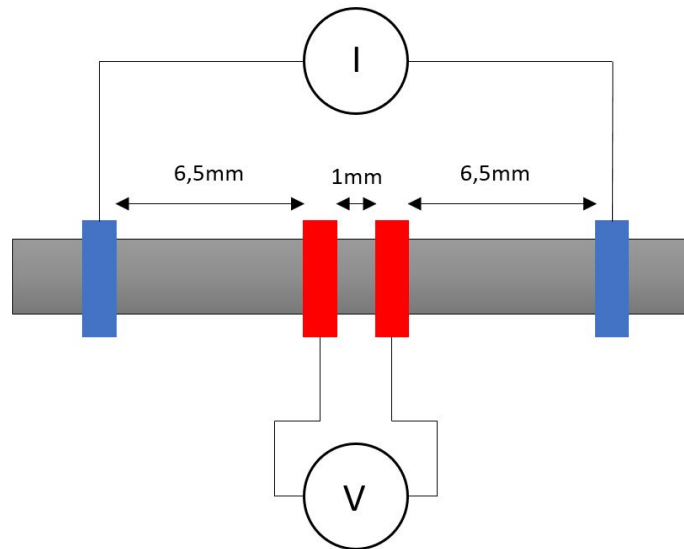


Figure 4.6: Impedance catheter dimensions

4.1.3 Software

Data reading as well as interpretation is performed on a Teensy 3.2. This microcontroller was chosen for its high resolution ADC, as well as its high sampling rate. A regular Arduino would have been barely sufficient for this task since it has a maximum sampling rate of 10 kHz. Although this would still be acceptable according to Nyquist's criterion, where the sampling frequency should be at least two times the measured frequency, it is preferable to have a sampling rate that exceeds this Nyquist criterion.

The output of the amplifier signal is sent to an ADC on the Teensy microcontroller. The sampling rate is set as 20 kHz by using an interrupt timer. Each time an interrupt is triggered the ADC reads a value into a buffer. The buffer is large enough to store 128 values. Once it is full a Fast Fourier Transform (FFT) is performed. A peak is detected in the 5 kHz frequency bin since this is the primary frequency component used to excite the electrodes. This magnitude is inversely proportional to the vessel diameter. After the magnitude has been determined the buffer is cleared. The FFT is calculated periodically once the buffer is full again.

4.1.4 Iteration

The impedance catheter was found to function satisfactorily during testing so no major iteration was necessary. As mentioned previously, the gain of the electrode amplifier had to be manipulated using the potentiometer when changing from tests performed with a saline solution to tests performed with horse blood to ensure the output of the amplifier did not saturate.

4.2 Self-Mixing Interferometry laser

The previous section outlined the design detail of the impedance component of the catheter used to measure the diameter of a blood vessel. This section focuses on the design detail of the velocity component. Self-mixing interferometry was chosen as the most optimal solution for this. It requires little additional hardware and since it makes use of light there should be no interference between the electrodes used to measure diameter and the velocity acquisition within the bloodstream.

4.2.1 Electrical Design

Self-mixing laser interferometry uses the light reflected from particles within the sensing region to determine velocity. The reflected light interferes with the outgoing signal in the laser cavity. This creates an amplitude modulation which can be detected by a built-in photodiode. The photodiode generates a current based on the light intensity detected. The amplitude modulation will create an alternating current corresponding to the Doppler frequency of the moving particles. Since the laser will be too large to fit into the tip of the catheter it will be necessary to redirect the laser beam into the tip of the catheter via an optical fiber.

An Optek OPV314AT vertical-cavity surface-emitting laser (VCSEL) laser diode was chosen since it includes a monitoring photodiode and comes mounted in a ST style fiber optic coupling. This negates the necessity of manually coupling the laser beam into a fiber optic cable using external components, ensures a good connection and allows the use of a normal fiber optic pigtail cable. This laser operates in the near infra-red region with a wavelength of 850 nm. Near infra-red was chosen since this wavelength band is commonly used in the medical sector due to its deeper penetration depth when compared to visible light or infra-red light. The deeper penetration is due to it not being absorbed by water or haemoglobin as readily (Sakudo, 2016).

The laser diode is powered by a constant current to ensure a consistent light intensity output and to limit maximum power. The chosen laser's specifications allow for a maximum direct current of 12 mA. Any prolonged current spike greater than 12 mA can destroy the laser diode. A constant current circuit was built using a LM317 voltage regulator as the basis. The circuit is shown in Figure 4.7. A feedback resistor which regulates the current is placed between the output and adjust pin. The resistor is chosen by calculating the required resistance with Ohm's law using the LM317 reference voltage of 1.25 V and the desired laser current of 7 mA. This biasing current was chosen since it exceeds the laser's threshold current of 3 mA, below which no laser light is gener-

ated, and is below the maximum safe current. From the laser diode datasheet it is indicated that powering the laser with this current will provide an output of 1 mW. Additionally, smoothing capacitors are placed at the input and across the laser diode to prevent excessive output fluctuations. Finally, a regular diode is placed across the laser diode to protect it if the polarity is switched.

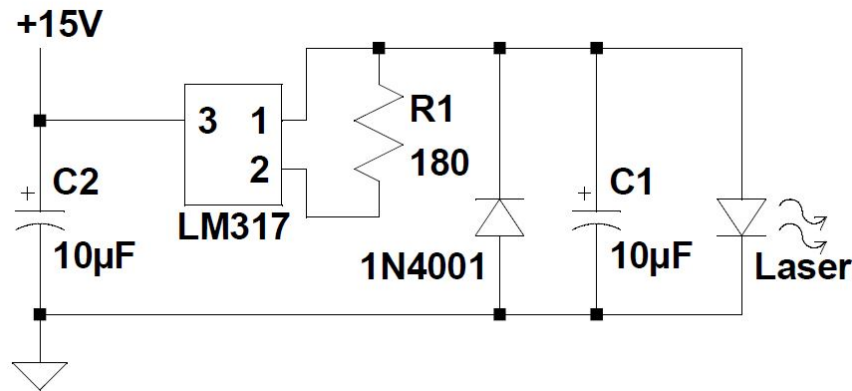


Figure 4.7: LM317 based laser driver

As mentioned previously the returning laser light causes a power modulation in the laser cavity. This signal can be monitored with the built-in photodiode. The signal consists of a constant offset current due to the laser's on-state as well as a much smaller alternating current superimposed onto this constant offset. The small alternating current is caused by the backscatter from moving particles and is the signal component of interest. The laser module datasheet states that the photodiode produces a constant monitor current of 30 μA at 7 mA laser driving current. Since this voltage is caused primarily by the DC offset the expected superimposed AC component will be much smaller. The desired signal component is expected to be in the nanoampere range and therefore large amplification is required.

The necessary amplification is obtained by passing the signal into a transimpedance amplifier. This converts a current signal into a voltage and amplifies it. The benefit of a transimpedance amplifier compared to a regular op-amp is that it is specifically designed for photodiode monitoring and therefore generally has a higher bandwidth than a regular op-amp. The Texas Instruments OPA380 amplifier was chosen for this application due its 90 MHz bandwidth (at unity gain) and very low bias current of 50 pA. When amplifying currents as small as those anticipated from the photodiode, particularly the AC component, it is important to choose an amplifier with a low bias current since this acts as an additional parallel current source which will be amplified and create a voltage offset in the output. This may limit the amount of amplification

that can be applied to the photodiode signal. The configuration used for this amplifier is shown in Figure 4.8.

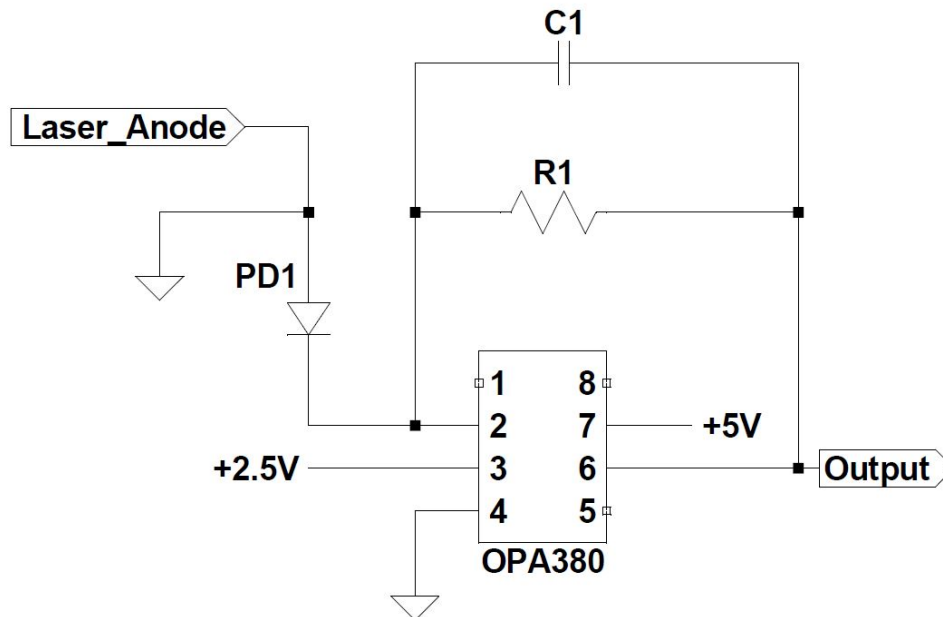


Figure 4.8: Transimpedance amplifier

When choosing an IC amplifier, it is crucial to ensure it is capable of the desired gain at the desired frequency since an amplifier's bandwidth range decreases as the gain is increased. It must therefore be ensured the chosen amplifier is still within its operational range when dealing with high bandwidth signals. The necessary amplifier bandwidth was determined from the theoretical maximum flow achieved in the testing setup which was related to a maximum frequency of 210 kHz using Equation 2.2. This calculation will be explained in more detail in Chapter 6. The OPA380 amplifier datasheet indicates that it functions satisfactorily in this bandwidth region up to a gain of 100k which is sufficient for this application.

The OPV314AT laser module has three connection pins which are for the laser diode anode, photodiode cathode and combined laser cathode/photodiode anode legs respectively. The configuration is shown in Figure 4.9. This configuration allows the photodiode to be operated at no bias or in reverse bias. For this application reverse bias was chosen. This causes the photodiode to operate in the photoconductive mode as opposed to photovoltaic mode. Operating in photoconductive mode increases the depletion layer width, which results in a decreased junction capacitance. The decrease in capacitance allows for a faster response time and also higher bandwidth. Additionally, the diode response is

linear in the photoconductive mode. A drawback of using the photodiode in the photoconductive mode is that it is more suited to high frequency and may result in more noise at lower frequencies. It also results in an increase of dark current, which is the current flowing through the diode in the absence of light. This current creates a DC offset and must be taken into consideration when calculating the gain used for the amplifier.

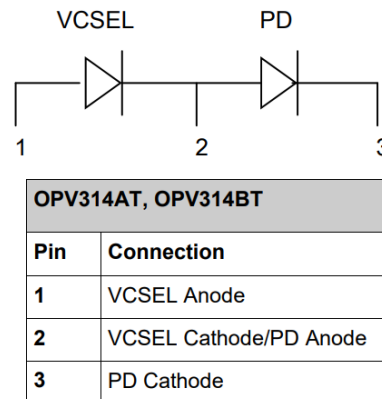


Figure 4.9: Laser pin configuration as obtained from datasheet

Transimpedance amplifiers are susceptible to parasitic noise due to the small magnitude of signals that need to be amplified. Even small noise signals that may be caused due to surrounding electro-magnetic interference will be amplified and make it difficult to distinctly identify the photodiode signal from the noise background. The noise can be limited by inserting a feedback capacitor in parallel with the gain resistor to limit the amplifier bandwidth. Stable amplifier operation requires correct selection of the gain resistor, feedback capacitor and gain bandwidth (GBW). Values for these components may be obtained from three design steps as shown below. These calculations were obtained from the transimpedance amplifier's manufacturer website (Texas Instruments, 2018).

1. The gain resistor is chosen using the following equation

$$R_1 = \frac{V_{oMax} - V_{oMin}}{I_{min}}$$

where V_{oMax} is the maximum output voltage of the amplifier and V_{oMin} is the minimum voltage. The maximum voltage is determined by how close the amplifier can swing to the supply voltage and the minimum voltage is determined by the applied photodiode biasing voltage at the non-inverting terminal. For the desired application the operating range is between the biasing voltage of 2.5 V and the maximum output voltage of the amplifier, which is 4.5 V. It was determined from the laser datasheet

that the mean current generated by the photodiode at 1 mW is 30 μA . This results in a maximum allowable gain resistor value of 66 $\text{k}\Omega$. Initially a 56 $\text{k}\Omega$ resistor was chosen as the gain resistor. This had to be decreased to 22 $\text{k}\Omega$ to avoid saturation of the op-amp when the lasing power was increased to 12 mA during in vitro testing.

2. The feedback capacitor value can be determined using the equation

$$C_1 \leq \frac{1}{2 \cdot \pi \cdot R_1 \cdot f_b}$$

where R_1 is the gain resistor value and f_b is the desired frequency bandwidth. For the iterated design with the 22 $\text{k}\Omega$ resistor a 15 pF capacitor was chosen as the feedback capacitor. This allowed for the desired bandwidth while attenuating high frequency noise.

3. Finally the minimum gain bandwidth of the transimpedance amplifier is chosen to ensure it is capable of measuring frequencies in the desired range. This can be calculated using the following equation

$$\text{Gainbandwith} > \frac{C_1 + C_s + C_d + C_{cm}}{2 \cdot \pi \cdot R_1 \cdot C_1^2}$$

where C_s is the photodiode capacitance, C_d is the differential input capacitance of the amplifier and C_{cm} is the common mode capacitance at the inverting terminal. It was determined from this equation that the gain bandwidth requirements for this application are met and exceeded by the OPA380 transimpedance amplifier.

Ideally all amplification should be performed by the transimpedance amplifier. Unfortunately, the primary component of the photodiode signal is a DC offset. The amplification factor is therefore restricted by this DC component since a large gain may cause saturation of the amplifier output. A two stage amplification was therefore implemented. The amplified signal from the transimpedance amplifier was passed through a bandpass filter to remove the DC component and attenuate high frequency noise. This isolates the desired AC component of the signal which is then again amplified using an AD620 instrumentation amplifier. The circuitry for this second stage amplifier is shown in Figure 4.10. The output of this amplifier is also fed through a bandpass filter. Cut-off ranges for these filters are discussed in the following iteration section.

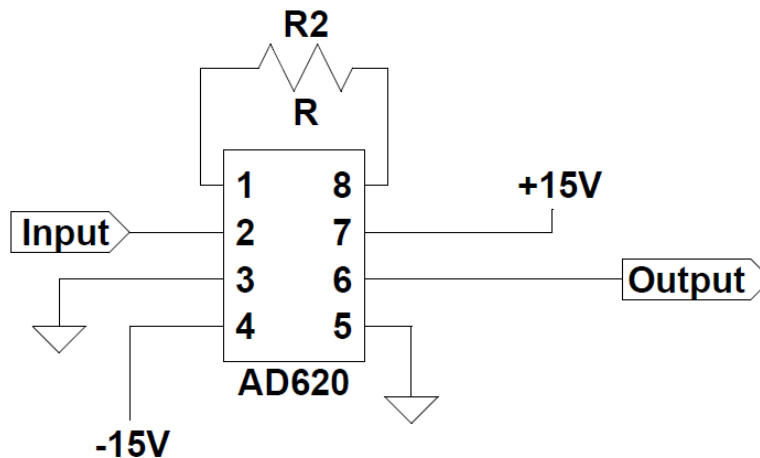


Figure 4.10: Stage 2 amplifier

4.2.2 Probe Design

This section discusses the hardware component of the self-mixing interferometer that is inserted into the blood stream. The primary components consist of the laser module, fiber optic cable, the laser driver and a transimpedance amplifier as described above. This circuitry powers and measures the power modulations of the laser via the photodiode. Since the photodiode is built into the laser package the system is self aligned and does not require calibration. This means the returning laser beam will be focused on the photodiode sensing area perfectly. Additionally, the laser is inside a fiber optic coupler so no additional hardware is necessary to couple the laser beam into the fiber optic cable. It is sufficient to plug a suitable fiber optic cable into the connector. A 50/125 μm multimode ST pigtail fiber was chosen to reroute the laser beam into the blood stream. This size was listed as optimal for the chosen laser in its datasheet. The ST connector of the fiber is inserted into the coupler and the sensor end is cut using a fiber cutter to ensure a perpendicular termination. The fiber end is inserted through the impedance electrodes and epoxied in place. This constitutes the sensor end which is inserted into the bloodstream.

4.2.3 Software

Similarly to the determination of the diameter, the signal coming from the second stage amplifier is sent to the second ADC on the Teensy. The Teensy has two independent ADC's which can be used simultaneously. An additional interrupt timer is used to set the sampling rate and read values into a buffer. Once the buffer is full an FFT is performed. The FFT generated from the photodiode signal shows a primary frequency component that corresponds to

the detected Doppler frequency. The buffer clears and fills again periodically to recalculate the FFT.

4.2.4 Iteration

This section covers iterations that were performed on the self-mixing interferometer as a result of observations that were made during validation and in vitro testing. This includes specific values for filters based on the frequency spectrum obtained during pump calibration. It was determined that the anticipated frequency range in which the self-mixing signal would be found during flow tests was between approximately 24 kHz and 210 kHz.

The function of implemented filters was primarily to filter out any low frequency noise caused by AC mains and lights as well as high frequency noise. Bandpass filters were therefore implemented to have a lower cut-off frequency of 1 kHz and a upper cut-off frequency of 250 kHz. The upper cut-off frequency was chosen, since 105 kHz would be the frequency corresponding to the average velocity. Since it was determined in Section 6.2 that the flow profile is parabolic, the velocity in the centre of the tube would theoretically reach up to twice the average velocity and hence the corresponding detected frequency would be 210 kHz.

During in vitro testing it was found that the background noise was very dominant in the photodiode signal. In an attempt to minimize this noise the photodiodes operation mode was changed from photoconductive to photovoltaic mode, since this mode is less susceptible to high frequency noise. This was done by removing the bias voltage on the non-inverting terminal of the transimpedance amplifier and connecting it to ground. This alteration unfortunately did not cause any noticeable improvement in the signal-to-noise ratio.

As an additional attempt to decrease signal noise a MAX3766 laser driver was implemented on a custom designed printed circuit board (PCB) in conjunction with an OPA380 transimpedance amplifier. This was done to mitigate any noise that may have been caused by the LM317 voltage regulator across the laser diode. The designed PCB had a double sided ground plane to minimize the risk of additional noise being caused by ground loops. Neither of these measures made any appreciable difference to the noise in the signal. Figure 4.11 shows the designed PCB.

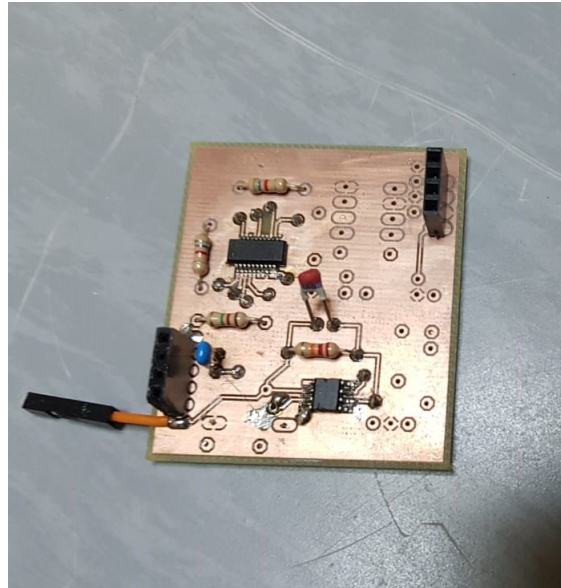
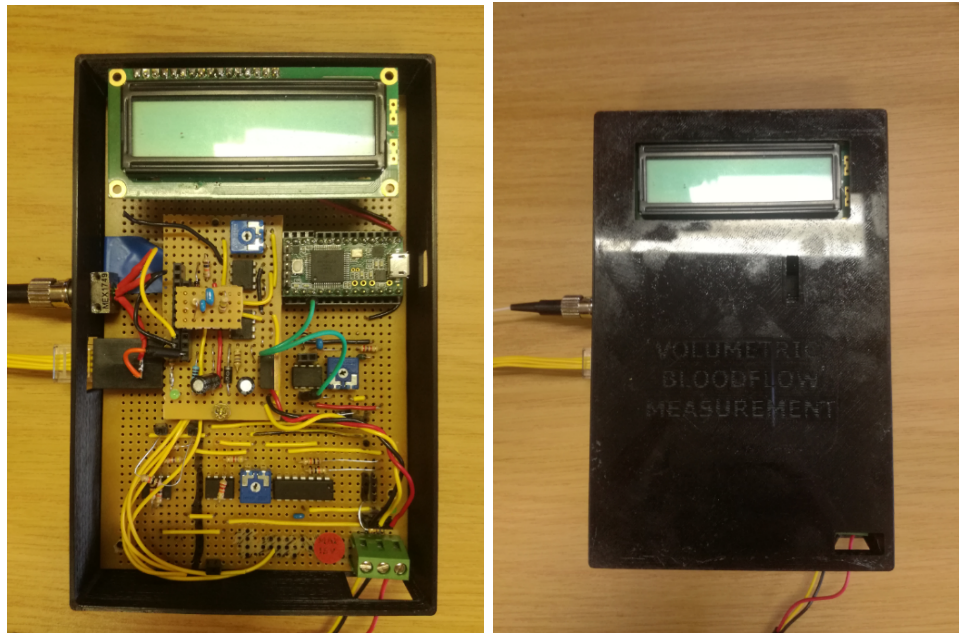


Figure 4.11: Laser driver PCB with transimpedance amplifier

4.3 Electronics Overview

The electronics for the velocity measurement as well as the diameter measurements were placed on separate PCB's to minimize the interference between them. An enclosure for all the required circuitry and components was designed using CAD software and 3D-printed. Housing all components within a compact portable enclosure allows the device to be easily moved around while minimizing risk of damaging the electronics.

A liquid crystal display (LCD) was added to the enclosure which could be used for monitoring the FFT magnitudes and debugging. The USB port of the microcontroller was left accessible for interfacing with a computer since viewing the FFT on a computer allows more accurate analysis and recording. Figure 4.12 shows the designed enclosure with populated electronics. Catheter connections for the fiber optic and the electrode connection can be seen on the left of the enclosure. The catheter was designed to be removable for simplicity and to test different configurations if necessary. The power terminal which distributes power to the two separate PCB's can be seen at the bottom of the enclosure.



(a) Open enclosure

(b) Closed enclosure

Figure 4.12: Blood flow meter enclosure

4.4 Catheter Assembly

The previous sections in this chapter discussed the electronics required to take measurements with the impedance catheter. Correct assembly of the catheter is vital for optimal operation. The impedance component of the catheter consisted of 2 mm diameter copper bands. Initially it was determined in Section 4.1.2 that the ideal diameter electrode is 1.8 mm but 2 mm had to be chosen due to restrictions in availability. The copper electrodes were electroplated using gold to ensure they are inert. This is crucial to ensure that they do not oxidise when a current is passed through them while they are submerged. Each electrode was connected to the excitation and sensing circuitry using a 0.1 mm enameled copper wire soldered to the inside of the electrode.

The inner diameter of the electrodes was bored out, prior to electroplating, to 1.5 mm. This allowed the multimode fiber optic used for the interferometer as well as all the electrode wires to pass through them. The electrodes were fixed to the fiber optic using epoxy glue using the spacing dimensions given in Section 4.1.2. The final assembled catheter is shown in Figure 4.13.



Figure 4.13: Assembled impedance catheter

Chapter 5

Validation

The previous chapter discussed the design implementation of the impedance catheter and the self-mixing interferometer. This chapter documents the functionality of the device as determined by doing validation testing. Knowing how well the device functions is important for in vitro and in vivo testing since this reduces the number of unknown components. If it is known that the device functions as intended it is easier to analyze abnormalities in measurements since they are most likely caused by the testing setup and not the device.

The diameter and velocity measurement capabilities of the catheter were tested and validated individually to ensure one measurement does not affect the other and vice versa.

5.1 Diameter Measurement

The validation for the impedance component of the catheter consisted of testing its ability to differentiate between different diameters via measured voltage, as well as the repeatability of these measurements. As a precursor to performing these measurements, it was necessary to determine whether the driving circuitry was functioning correctly, since the catheter design relies on a constant current to determine the impedance change. Having an output current which varies with load impedance would add an unknown variable. This would affect accuracy and repeatability in a negative way since measured voltage would not be solely related to impedance any more.

This functionality was determined by modelling the driving circuitry of the electrodes, which consisted of the Howland current source being driven by a sinusoidal signal, in LT Spice. A transient analysis was conducted with varying output impedances to simulate different loads. The theoretical currents obtained from the analysis were recorded and are shown in Figure 5.1.

Theoretical behavior of the current source was compared to actual behavior by performing various tests on the designed circuitry with output impedances matching those used in the simulation. The currents measured during these tests are also shown in Figure 5.1. As can be seen in the graph the simulated and measured values are similar except at very low and very high impedance loads. This may be attributed to LT Spice using an ideal op-amp model for simulations which will deviate slightly from real-world op-amps. From this test it was concluded that if a 10 k Ω resistor is added in series to the load, the current source will always operate in the impedance range where the current remains constant. From the comparison between the simulated and measured current it was determined that the current source was working satisfactorily.

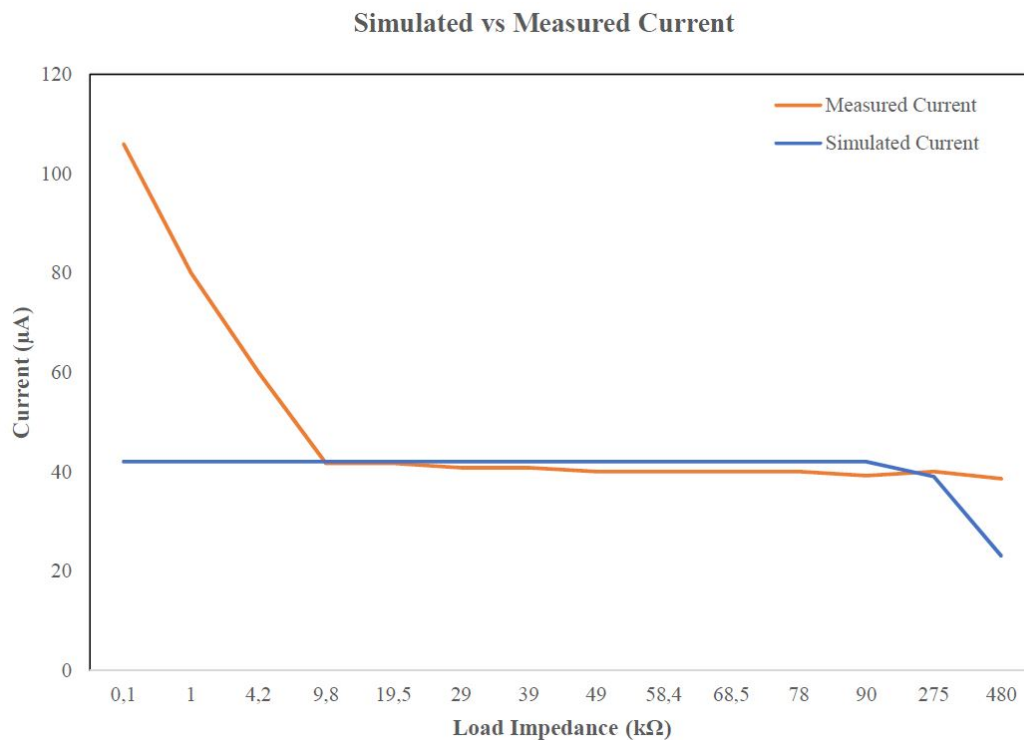


Figure 5.1: Graph showing the ideal operating range of the Howland current source

5.1.1 Methodology

Diameter measurement validation was conducted to determine functionality of the device before conducting in vitro testing. Various cylindrical vials that ranged from the lower extremity of the catheters designed working range to the upper extremity were prepared. Specifically, vials ranging from 4 mm to 9 mm were prepared in 1 mm increments. All vials had the same height and

were filled to the same level to ensure there is no additional impedance change which could be caused due to volume increase in the axial direction. The vials were filled with saline solution. The saline solution is conductive and allows current to flow between the outer electrodes creating the electric field necessary to take measurements over the inner electrodes. The saline solution used had a concentration of 0.9% NaCl to simulate the salinity of blood. The catheter was placed in each vial and the measured peak voltage was recorded using a Tektronix TDS 2014C oscilloscope. The tests were conducted five times to ensure results were repeatable.

5.1.2 Results

Results obtained from the tests described above are shown as mean values in Figure 5.2 with the standard deviation for each diameter. Individual measurements taken for each test can be found in Appendix B. From the figure it is apparent that the different impedance values due to fluid volume in each vial results in different voltage readings. The measurements are also in-line with expected measurements where a larger impedance is present in smaller vials resulting in a larger voltage.

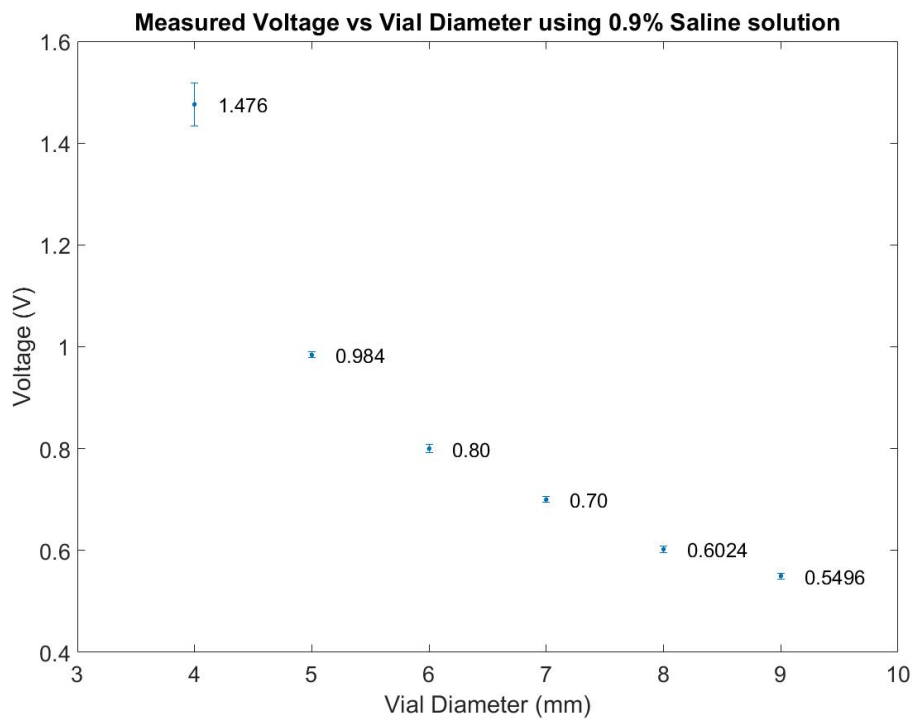


Figure 5.2: Graph showing voltage measured in different diameter vessels with 0.9% saline solution

Table 5.1 shows the mean voltage values and the standard deviation obtained for each diameter. The standard deviation is also shown on Figure 5.2 by error bars.

Table 5.1: Mean and Standard deviation of diameter testing using saline solution

Diameter	Mean	Standard Deviation
9 mm	0.550 V	0.0061 V
8 mm	0.600 V	0.0067 V
7 mm	0.700 V	0.0057 V
6 mm	0.800 V	0.0080 V
5 mm	0.985 V	0.0057 V
4 mm	1.476 V	0.0428 V

The validation testing done indicated that the impedance measurement component of the catheter was working as desired and that it was ready for being used for in vitro testing.

5.2 Velocity Measurement

The functionality of the self-mixing interferometer was tested using a validation method before performing in vitro tests, since it was uncertain how prevalent the Doppler frequency scattered from the red blood cells would be. It was therefore crucial to ensure that the device was functioning correctly and that it was capable of detecting the amplitude modulation signal that occurred in the laser cavity. It was also necessary to determine in what frequency range the device works acceptably.

5.2.1 Methodology

The device's ability to detect a particular frequency was tested by measuring the vibrating frequency of a speaker. The diaphragm of the speaker vibrates at the excitation frequency which is applied and controlled with a signal generator. The laser beam is reflected from the moving object and back through the fiber into the laser cavity. The diaphragm's driving frequency is detected by positioning the end of the fiber over the diaphragm. Since the intended use of the interferometer is to measure flow in the direction of the laser beam the fiber needs to be positioned perpendicularly. As the diaphragm is excited by a particular frequency, it will create a vibration. The change in displacement

should be identifiable as a modulation frequency when monitoring the photodiode.

The output signal of the photodiode is amplified as explained in Section 4.2.1 and monitored via a Tektronix TDS 2014C oscilloscope. The oscilloscope allows the signal to be viewed as a waveform as well as a Fast Fourier Transform. It is difficult to extract a single frequency from observing a waveform if it is layered with noise. The Fast Fourier Transform was therefore used to identify the driving frequency for this test since it displays independent frequency bins. It should be noted that the horizontal axis had a scale of 2.5 kHz/division for all tests except at 1kHz where 500 Hz/division was used. This was chosen to accommodate the entire operating range of the speaker within a single window of the oscilloscope (0 Hz-25 kHz). At 2.5 kHz/division scale the resolution of each frequency bin was 100 Hz meaning that measured frequencies are rounded to the nearest 100 Hz.

The test was conducted at various frequencies within the speaker's operating range to determine how capable the interferometer is at measuring various frequencies. The amplitude of the signal driving the speaker was 10 V. A limitation in this test is the operational range of the speaker since it is a standard tweeter and has an upper limit of 20 kHz.

5.2.2 Results

The testing procedure detailed above was performed at various frequencies within the speaker's operational range. Table 5.2 summarises the frequencies the speaker was excited at using the signal generator and the corresponding frequency that the interferometer detected. As previously noted the FFT bin resolution was 100 Hz.

Table 5.2: Interferometer frequency response

Excitation Frequency	Measured Frequency
1009 Hz	1100 Hz
4960 Hz	5000 Hz
10 060 Hz	10 100 Hz
19 930 Hz	20 000 Hz

Figure 5.3 shows the FFT analysis of each test. The primary frequency seen across the photodiode at each excitation frequency is shown in the top right of each sub-figure. For all tests the signal is clearly visible as a peak. It is however

also noted that there is a large amount of background noise within the signal. This noise could not be filtered out since it is within the frequency range in which the signal is expected to be. Filtering in this spectrum would attenuate noise but also result in the desired signal component being attenuated.

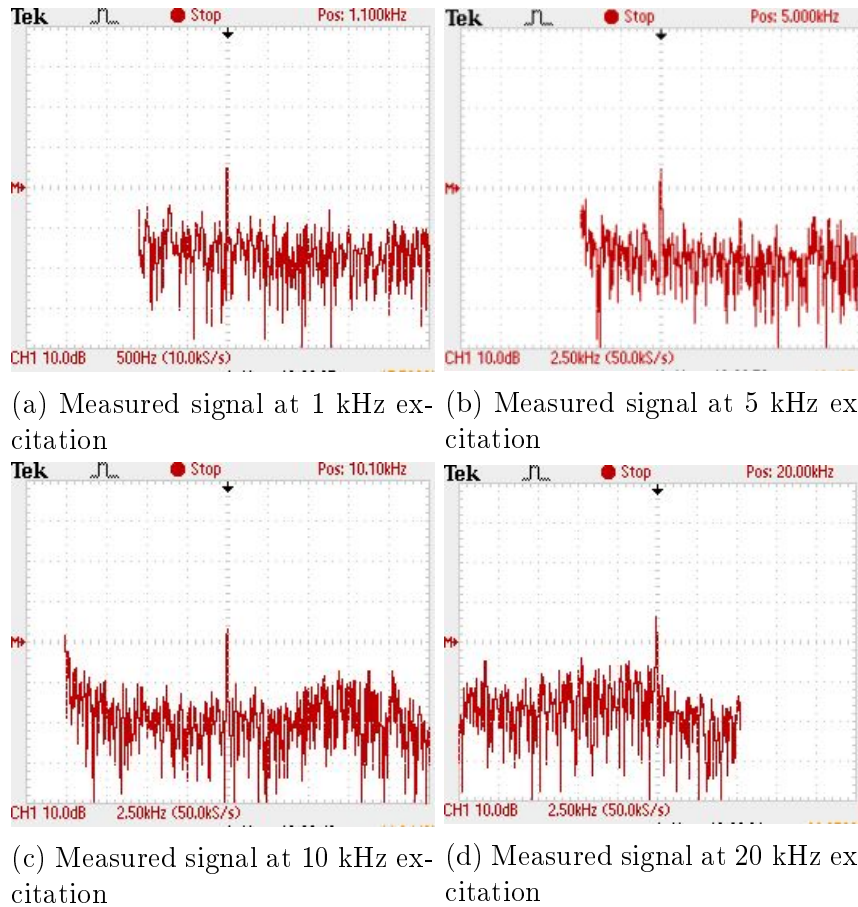


Figure 5.3: Frequency excitation using speaker

Analysing the frequencies detected by the photodiode in the time domain showed that the waveform was sinusoidal. This indicated that the self-mixing interferometer operated in the low feedback regime. This waveform can be seen in Figure 5.4 at 10 kHz. All other tested frequencies showed the same waveform shape. In the figure, the high frequency noise can be seen superimposed on top of the input signal.



Figure 5.4: Waveform of signal obtained in the time domain at 10 kHz

From these results it is apparent that the interferometer is capable of measuring the frequency at which the speaker is excited with good accuracy. The testing also indicated that the interferometer is susceptible to noise since the modulation signal is small and requires large amplification. This results in small noise signals also being amplified. In comparison to the red blood cells that will flow through the sensing region, the diaphragm displacement is large. The returned signal has a large amplitude due to this large displacement. This results in a signal-to-noise ratio large enough to distinctly see the excitation frequency. When reviewing the FFT's it can be seen that the speaker excitation frequency has a gain of roughly 10 dB in all cases. An additional test was performed where the amplitude of the signal driving the speaker was halved to see how this affected the signal-to-noise ratio. It was found this reduced the gain by 5 dB which is a significant decrease.

Although the interferometer functionality was validated, difficulties may be encountered during in vitro testing since the signals obtained from flow are expected to be smaller than those obtained from the speaker diaphragm which already showed small signal-to-noise ratios.

Chapter 6

In Vitro Measurements

This section of the report includes in vitro testing procedures that were conducted with the designed device. In vitro testing is necessary to determine the functionality of each component of the system before it can be tested in vivo. Independent testing is done on the velocity and diameter components of the catheter. This is done to ensure the testing setup of one will not affect the other and vice versa.

The impedance component of the catheter is tested on its ability to accurately determine the diameter of various size vessels in a controlled environment while the interferometer is tested on its ability to measure velocity. The biggest differentiation between validation and in vitro measurements is that in vitro measurement is conducted with animal blood, while validation used alternative fluids and methods. Specifically, horse blood is used for testing. The blood was obtained from the Medical Research Council (MRC) and is used with ethical approval.

6.1 Diameter Measurement

The following subsections outline the methodology that was used to take measurements, results of these measurements and a discussion in which the results are interpreted.

6.1.1 Methodology

Diametrical measurements were performed similarly to the validation testing in Section 5.1 by taking measurements in various size vials. The specific conductivity of the sample blood had to be determined since this variable is necessary to determine theoretical values using Equation (2.4), which are used for comparison. The specific conductivity can vary depending on the red blood cell count, temperature and health of the blood. Since these factors were not

known for the sample blood the specific conductivity had to be determined experimentally.

A small 10x10 mm jig consisting of a rectangular vessel was built. The jig was filled with one cubic centimetre of blood. Electrodes at either end injected a current using the same Howland current source built for the impedance catheter. Measured voltage across the electrodes can be used to determine the specific conductivity using a permutation of Equation (2.4) modified for use with a rectangular vessel instead of a cylindrical vessel. The specific conductivity obtained using this method may not be exact since the electric field in the jig may not be completely homogeneous, but it gives an approximation which can be used consistently throughout calculations. For the blood sample used, the specific conductivity was determined to be approximately 0.7 Siemens per meter (S/m). It should also be noted that since the specific conductivity of blood can vary depending on various factors, results obtained during testing are specific to the horse blood used. If the same tests were to be conducted with different blood samples, different voltage measurements would be obtained and calculated theoretical values would also vary.

Vials with diameters ranging from 4 mm to 9 mm with 1 mm increments were used to represent different diameter blood vessels. The vials were all filled to the same level. Filling the vials to the same height ensures that the only variable is the diameter of the vials. It was initially noted that blood sedimentation occurs rapidly when it is placed into the testing vials which caused a constant decrease of voltage in consecutive measurements. This is likely attributed to a change in conductivity as sedimentation occurs. This problem was overcome by continuously agitating the bottle from which blood was drawn. This ensured that the blood remained homogeneous. Vials were filled one at a time with the homogeneous blood and the measurement was taken. Measurements were recorded with a Tektronix TDS 2014C oscilloscope. This procedure was repeated five times at each diameter.

6.1.2 Results

Measurements taken during these tests are shown in Figure 6.1. The figure also shows theoretical values that were obtained using Equation (2.4) and plotted for comparison. A table showing individual measurements obtained is shown in Appendix B.

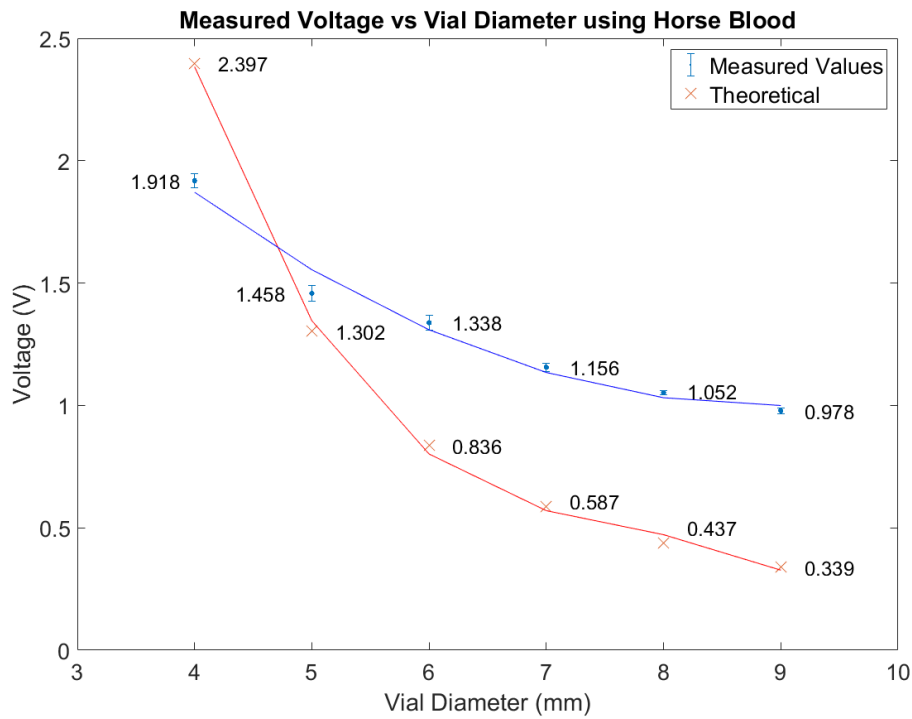


Figure 6.1: Measured voltage at specific diameter

Reviewing Figure 6.1 it can be seen that there is a clear correlation between diameter of the testing vial and the voltage measured. The results will be analysed more in-depth in the following discussion section. Table 6.1 shows the mean and standard deviation values obtained for measurements at each diameter. The standard deviations are also indicated on Figure 6.1 by error bars. Additionally, performing a regression analysis on the measured values revealed that they followed a trend which could be expressed by Equation (6.1) where V represents the voltage and d is the vessel diameter.

$$V = 0.0356d^2 - 0.6372d + 3.8501 \quad (6.1)$$

Table 6.1: Mean and Standard deviation of diameter testing

Diameter	Mean	Standard Deviation
9 mm	0.978 V	0.011 V
8 mm	1.052 V	0.008 V
7 mm	1.156 V	0.017 V
6 mm	1.338 V	0.032 V
5 mm	1.458 V	0.032 V
4 mm	1.918 V	0.029 V

Table 6.2 shows the statistical significance between theoretical and measured values. These P-Values were obtained using a single sample T-test.

Table 6.2: Significance test

Diameter	p Value
9 mm	$p < 0.00001$
8 mm	$p < 0.00001$
7 mm	$p < 0.00001$
6 mm	$p < 0.00001$
5 mm	$p = 0.000406$
4 mm	$p < 0.00001$

Figure 6.2 plots the actual measured diameter values versus the theoretical calculated values. It can be seen that there is an evident correlation between the two value sets. The spread between the minimum and maximum values obtained from measurements is however smaller than the spread between the minimum and maximum values obtained through theoretical calculations.

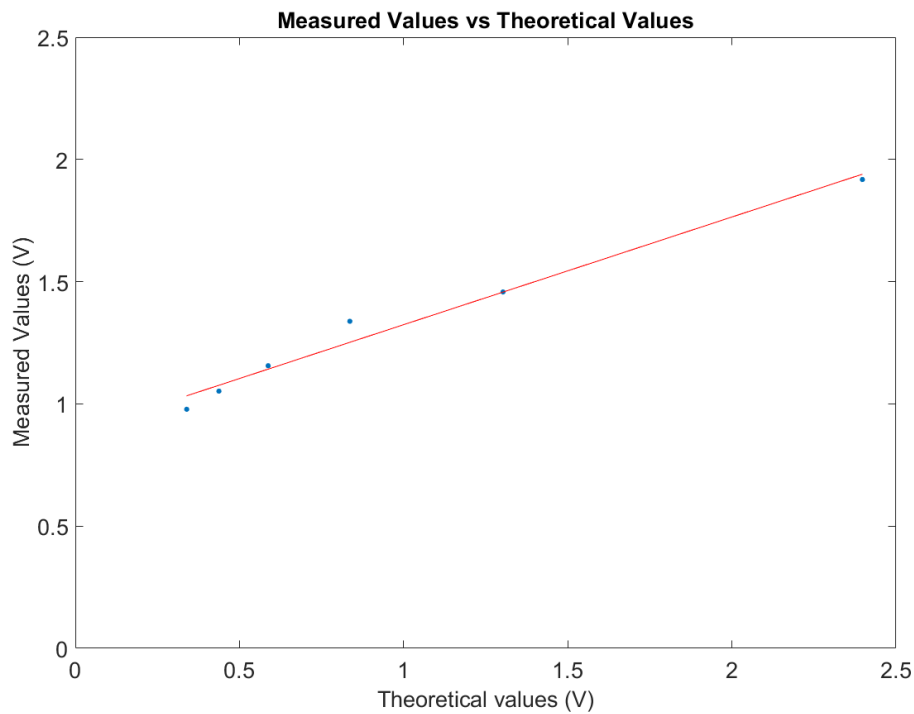


Figure 6.2: Measured values vs theoretical values

6.1.3 Discussion

It is evident when reviewing Figure 6.1 that there is a definite inverse relation between the vessel diameter and voltage measurement. This is in-line with expectations since a smaller vessel has a larger impedance due to containing less blood volume. This results in a larger voltage at a constant current according to Ohm's law. The relation between the voltage and the diameter can be seen to be hyperbolic which was also expected since the voltage is inversely proportional to the square of the diameter according to Equation (2.4). At smaller diameter ranges voltage changes are more drastic due to this square value.

The statistical relevance of the results was analyzed and the calculated mean and standard deviation are shown in Table 6.1 while the statistical relevance between measured and theoretical values is shown in Table 6.2. From these values the preliminary assumption can be made that obtained results have good repeatability although they do not align with calculated values.

Theoretical voltages were calculated for each diameter using Equation (2.4). Figure 6.1 shows these theoretical voltages for each diameter so that they can be directly compared to measured values. It was observed that experimental results differ from theoretical values, although they show the same trend. The voltage change is less prevalent in the measured values when comparing them to calculated values. Figure 6.2 still shows that there is a clear linear correlation between measured and theoretical values. Determining a Pearson Correlation Coefficient between the two data sets gave a value of 0.98. A value above 0.7 is commonly accepted to display a strong linear correlation. Since the calculated P-values are less than 0.05 it is apparent that there is a significant difference between calculated and measured values indicating Equation (2.4) may require a correction factor as mentioned in Section 2.2.6.

It can also be seen that measured values have a larger discrepancy at the extremities of the operating range when compared to theoretical values. In Section 4.1.2 it was stated that the catheter is designed for a mean diameter of 6.31 mm. Readings taken in vials with diameters of 5 mm and 6 mm seem to have the closest relation to their calculated theoretical values.

Since it was found that measured values do not correspond completely to theoretical values obtained with Equation (2.4), a regression analysis was performed with the measured values. Equation (6.1) is a second order equation that corresponds to the trend of the measured values. Such an equation may be used for interpolation of voltages that relates to any diameter within the operating range.

The following explanations are the anticipated causes which may have resulted in a variation between theoretical and measured values.

- The theoretical values are calculated from a formula which assumes that the electric field that develops in the vessel is perfectly homogeneous. The homogeneity of the field is affected by the spacing between the sensing and excitation electrodes. This spacing should be slightly larger than the vessel diameter. Since the catheter was designed for a diameter of 6.3 mm the spacing was optimized for this range. Using the catheter in other size vessels will result in suboptimal electrode spacing in relation to the diameter. This may result in a non-homogeneous electric field which will affect measurements or result in reduced sensitivity resulting in less pronounced voltage changes.
- Imperfections in the manufacturing of the catheter. The catheter used was a prototype designed for validating the feasibility of the chosen concepts. As a result, non-uniform spacing of electrodes caused due to assembly may have had an effect on measurements and accuracy. Additionally, it was determined that the optimal electrode diameter is 1.8 mm but due to availability the chosen electrodes were 2 mm diameter.
- The specific conductivity of the blood used was determined experimentally. Hence, the value used was an approximation and there may be a slight discrepancy with the actual specific conductivity. This will affect any theoretical values that are calculated based on this value.

Although it was found that the theoretical values do not correlate directly to measured values in terms of magnitude, they still displayed the same trend and the linear correlation between them was strong. The measurements taken prove that it is certainly feasible to determine diameter by using an impedance catheter. However, since theoretical values did not correspond perfectly to measured values it is suggested that diameter should not be calculated from the measured voltage using Equation (2.4). Rather, it is suggested to calibrate the catheter in vessels with known diameters using a specific blood sample and performing a regression analysis which gives an equation relating diameter to voltage. This was done and Equation (6.1) was obtained. This relation is specific to the used blood sample. Different blood samples may have a different specific conductivity which will result in a different regression formula.

6.2 Velocity Measurement

The following subsections outline the experimental setup that was used to determine velocity measurements, the results of these measurements and a discussion in which the results are interpreted.

6.2.1 Methodology

Experimental measurements were conducted to determine the interferometers capability of determining velocity by detecting the Doppler frequency of red blood cells in the sensing region. This was performed by using a setup that simulated a basic blood circulatory system. Horse blood was circulated through a silicone medical grade hose by means of a peristaltic pump. A small incision was made in the side of the tubing to allow the fiber optic to be passed through. The fiber optic's orientation was such that it was facing the oncoming bloodstream. Once the fiber optic was inserted, the incision was covered with epoxy to ensure no blood would leak through it.

The pump's rotation speed could be set manually thereby altering the flow rate. Calibration testing of this pump was performed at various RPM settings to determine the flow velocities the pump could achieve. The results that relate the RPM to flow are shown in Appendix C. As was expected, the fluid flow varied linearly with RPM. This can be seen by the inserted trend line.

The calibration testing performed for the pump indicated the flow range spectrum that could be used for taking measurements. This spectrum ranged from 0 ml/s to 26 ml/s. The theoretical Doppler frequency that corresponded to various flow rates was calculated so that experimental measurements could be compared against them once they were taken. This calculation also gave an expected range in which frequency measurements would be found. This allowed frequency cut-off points to be determined for the bandpass filters used in the amplifiers. The implementation of these filters was discussed in Section 4.2.4. The Doppler frequencies were obtained by determining the velocity at each flow rate using Equation (3.1) and using this value in Equation (2.2). The theoretical frequencies corresponding to various flow rates are shown in Table 6.3.

Table 6.3: Theoretical Doppler frequencies corresponding to flow

Flow (ml/s)	Theoretical Doppler Frequency
6 ml/s	24 kHz
11 ml/s	44 kHz
16 ml/s	64 kHz
21 ml/s	85 kHz
26 ml/s	105 kHz

The velocity profile that develops in the tubing is important for determining velocities from measured frequency values. The velocity profile is determined by whether the flow is turbulent or laminar. This parameter may be determined using the Reynold's number given in Equation 6.2 (Cengel and Cimbala, 2013).

$$Re = \frac{u \cdot L_c}{\nu} \quad (6.2)$$

where ν is the kinematic viscosity, u is the velocity and L_c is the characteristic length which is taken as the diameter of the tube. An approximate kinematic viscosity of $2.7 \text{ mm}^2/\text{S}$ with a characteristic length of 3.5 mm , which corresponds to the inner diameter of the tube, was used. Using 0.045 m/s , the maximum velocity the pump can achieve as obtained from calibration, gives a Reynolds number of 58.3 . Flow is laminar if the Reynolds number is below 2100 , which indicates all flow will be in the laminar region.

From this calculation it can be concluded that the velocity profile in the tubing will be parabolic. As a result, measured velocity in the center of the tube will be double the average velocity. Since Equation (2.2) gives the average velocity, the frequency ranges shown in Table 6.3 should be doubled to obtain the frequency range in which the signal is expected to be present at each flow rate.

The experimental procedure for measuring velocity consisted of setting the pump to five different flow rates and taking measurements using a FFT on a Tektronix TDS 2014C oscilloscope during each test. The goal was to determine whether a frequency spike could be detected in the frequency region that matched the flow speed according to Table 6.3 in each test.

6.2.2 Results

During testing it was found that the interferometer exhibited a large amount of noise which proved to be problematic in extracting the frequency corresponding to a particular flow speed. Figure 6.3 shows a FFT of the noise spectrum when the device was off as a reference versus when the device was operational with the fiber placed in the blood flow. This FFT was taken when the pump was off and no flow was present in the circulation system. As can be seen, the noise component is significant.

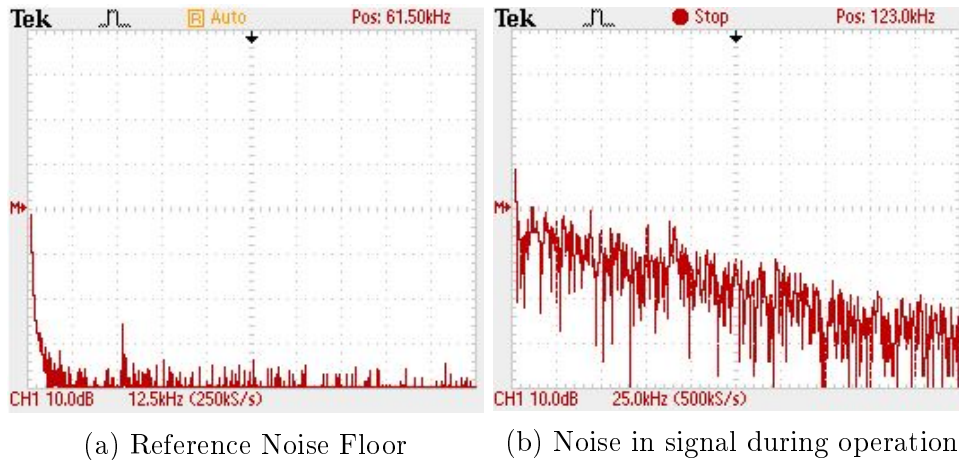


Figure 6.3: Noise FFT

No noticeable frequency spike could be measured on the FFT as the flow rate of the pump was varied.

6.2.3 Discussion

The FFT spectrum in the results section above shows a large amount of noise in the signal when the device is powered on. This noise combined with the low power feedback from the red blood cells meant that the signal-to-noise ratio was small. As a result of this, no noticeable frequency change could be observed in the FFT spectrum as the fluid velocity was changed since the signal was either too small or lost within the noise.

Various modifications were made to the circuitry in an attempt to decrease the noise and improve the signal-to-noise ratio. Implemented methods included

- Making adjustments to filter values and bandwidth limiting capacitors. This pertains specifically to the feedback capacitor used in the transimpedance amplifier. A larger sized capacitor (30 pF) was tested to limit bandwidth but this did not produce a noticeable change since most of the noise was found in the lower frequencies. As a result, limiting the bandwidth had little effect.
- Implementing a different laser configuration that operates in photovoltaic mode instead of photoconductive mode since this mode creates less noise at low frequencies.
- Implement a different laser driver intended for fiber optic communication. This was done to minimize noise in the power being supplied to the laser diode. The output was monitored on both laser drivers and it was found

that there was no noticeable noise difference in power being supplied to the diode.

- Design a PCB with a ground plane to avoid ground loops which may add additional noise. This also allowed circuit trace lengths to be kept as short as possible.
- Shielding electronics from electromagnetic interference by enclosing them in a metallic enclosure which acts as a Faraday cage.
- Increasing the lasing power by increasing the laser diode bias current to the maximum limit of 12 mA as specified in the datasheet.
- Adding 100 μm diameter plastic granules to the fluid which are larger than red blood cells in an attempt to increase the amount of light reflected and increase the signal amplitude.

Implementation of these methods decreased the noise in the output signal but not sufficiently to have an acceptable signal-to-noise ratio. It was concluded that since the interferometer worked in the validation testing phase as was shown in Section 5.2 using large displacements, the primary limitation of detecting a signal was the sensitivity of the photodiode. The sensitivity was deemed insufficient to detect the small amount of light that is reflected from the red blood cells among the ambient noise. This may be attributed to the suboptimal laser module that was used. It is intended for fiber optic communication and as a result the photodiode is primarily intended for detecting binary signals. Due to this, sensitivity of the photodiode itself may be insufficient to determine a power modulation as small as that caused by the light reflected from red blood cells. The laser datasheet did not give any specifications for the photodiode and therefore its exact sensitivity was unknown.

This statement is also supported by the waveform shape of the signal found during validation testing. It was found that the signal was sinusoidal. This indicates that the interferometer was operating in the low feedback regime, even with the large inputs received from the speaker diaphragm. This indicates that the returned signal was weak and therefore a good sensitivity would be required to detect it, especially in the case of the even weaker signal being returned by the red blood cells.

Although the in vitro testing for measuring blood velocity was unsuccessful in this study, this concept has been validated by other studies before. A study performed by Nikoli *et al.* (2013) performed a similar experiment where a self-mixing interferometer was used to measure the velocity of milk in tubing by inserting a needle containing a fiber optic into the fluid flow. They found that the Doppler frequency obtained from monitoring the photodiode could indeed

be approximated by Equation (2.2) and that it is feasible to use self-mixing interferometry to measure fluid flow.

Chapter 7

Conclusion

The following chapter gives a summary of implemented solutions, discusses the findings made during testing and whether the initial objectives were met. Suggestions on future work that could be done to improve and expand the functionality of the device and a conclusion about the study are also given.

7.1 Summary

The aim of this thesis was to develop and test a proof-of-concept device that is capable of measuring volumetric blood flow. Most current methods used for measuring blood circulation are only capable of measuring blood velocity, which may not be representative of total volume blood flow. Various medical conditions can result in acceptable velocity readings while volume blood flow may be insufficient due to reduced vessel diameter. Insufficient volume flow to the cerebral region and kidneys can cause strokes, brain damage, chronic kidney disease and death due to insufficient oxygenated blood being circulated.

7.1.1 Velocity Measurement

It was determined that the most feasible method for measuring velocity within an artery was to implement a self-mixing laser interferometer. A single fiber optic used to redirect a laser beam into the artery made this method attractive considering size was a major factor due to the probes intravenous nature.

The device consisted of a laser module with a built-in photodiode. The photodiode monitored the power modulation that occurred due to the interference between the outgoing signal and the signal component that is reflected off a moving object and back into the laser cavity. The frequency of this modulation is proportional to the velocity of the moving object.

Validation testing showed promising results with the interferometer being able to detect the excitation frequency of a speaker by monitoring the diaphragm's displacement. Following the validation, *in vitro* tests were conducted to determine the accuracy and repeatability of the interferometry laser by measuring velocity within a simulated circulation system. Silicone tubing with a diameter similar to the desired blood vessel's diameter was used to circulate animal blood. The fluid velocity was controlled by a peristaltic pump.

Unfortunately, there was a large amount of noise in the photodiode signal that could not be filtered out. The signal-to-noise ratio was insufficient to detect the Doppler frequency of red blood cells flowing through the sensing region in front of the fiber. Various iterations were made to the design in an attempt to decrease the noise and improve the signal-to-noise ratio. None of the implemented iterations made an appreciable difference to obtained measurements. It was concluded that the sensitivity of the photodiode was insufficient to measure the very small signal generated by the red blood cells.

Although the self-mixing interferometer could not measure flow velocity due to limitations in the hardware sensitivity, the concept was proven to work in validation testing using large inputs. The objective initially set forth to implement a method that could be used to measure blood velocity was therefore considered partially met.

7.1.2 Diameter Measurement

Research done indicated that methods used to measure diameter in real-time were less common compared to velocity measurements. It was decided that bioimpedance would be the most feasible solution to measure diameter. This method uses an impedance catheter to obtain a voltage reading which can be related to diameter. A tetrapolar catheter was constructed with circuitry to excite the electrodes as well as measure the voltage across them.

The effectiveness of the impedance catheter was determined by performing validation and *in vitro* testing. This consisted of inserting the catheter into various vials with different diameters. The vials were filled with saline solution for validation and animal blood for *in vitro* testing. Voltage measurements which can be related to diameter were taken in each vial. It was found that the impedance catheter was capable of distinguishing between different diameters as a result of the impedance within different sized vials. It was however found that voltage differences between different sized vials were less pronounced than theoretical values suggested. This was attributed to the electrode size being designed for an optimal working range with decreased sensitivity towards diametrical extremities. A linear regression was performed on measured values to obtain a calibration equation that could be used to interpolate diameter from

the voltage measured in a vessel with unknown diameter. Both validation and *in vitro* testing showed good repeatability.

The concept of measuring diameter in a vessel by using bioimpedance was proven to work. The objective initially set forth to implement a method capable of measuring blood vessel diameter was therefore considered to be met.

7.2 Future Work

The designed device was intended as a proof-of-concept. Naturally, building as well as testing the device revealed various aspects that may be built upon or improved in future work.

It was found that the velocity measuring interferometer was limited by noise and low sensitivity. Proposed future work includes improving the interferometer's capability to measure velocity in blood flow. The concept was still validated as working with large inputs, and has been used by other studies for the measurement of velocity in flow. It is therefore still a feasible method for measuring volume blood flow. Its functionality may be improved by rebuilding the interferometer with higher grade components, suited more specifically for use as a self-mixing interferometer. This pertains especially to the laser module, which was mainly intended for general fiber optic communication and therefore contained a photodiode with limited sensitivity. Additionally, measurement equipment more suited for measuring very small signals may be beneficial.

A major future step that will be necessary for the continued development of this device is to perform *in vivo* testing once the velocity measurement has been rectified to work in flow. This will determine how the device functions when surrounded by tissue. This is especially important for the bioimpedance measurement. Tissue surrounding the artery during *in vivo* testing will affect impedance measurements taken by the electrodes since the tissue impedance will contribute to the measurement. It will be necessary to calibrate the catheter upon insertion to negate this. This can be done by injecting a small amount of saline solution. This will momentarily change the impedance seen by the electrodes since the conductivity in the blood vessel changes. Since the measured change in voltage is exclusively due to impedance change in the vessel, this measurement can be used to determine what part of the impedance is caused by surrounding tissue. This portion of the signal may then be discarded.

An additional future use proposed by the supervisor was that this device's implementation would be beneficial in the neonatal sector, where it could be

inserted into an umbilical catheter, to monitor blood flow of infants.

7.3 Conclusion

The aim of this study was to address the limitations currently experienced in blood circulation measurement, since this is almost exclusively done by monitoring blood velocity. These limitations were addressed by developing a proof-of-concept device for measuring volume blood flow. It was identified early during researching various options that the velocity and diameter measurements would have to be done independently.

Initially, an eddy current flow meter was implemented. Preliminary tests were done to test the feasibility of this method. It was determined that due to the size constraints within the artery it was not feasible to create a magnetic field sufficient for this application without generating excessive heat and an alternative approach had to be taken.

Bioimpedance was chosen for measuring diameter while self-mixing interferometry was chosen for measuring velocity. These methods were chosen above others since both are capable of taking continuous measurements. This is a valuable feature should further development be conducted on the device, because it will allow for continuous monitoring. Additionally, both methods allow absolute measurements to be taken. Bioimpedance was proven to work successfully during validation and in vitro testing. It could be proven that the voltage measured with an impedance catheter can be related to vessel diameter. Self-mixing interferometry was proven to work during validation but was limited by a poor signal-to-noise ratio during in vitro testing. The small power signal modulation caused by light reflected from red blood cells could not be detected. This was attributed to the limited sensitivity of the photodiode built into the laser module.

The methods implemented were proven conceptually to work. Although the flow velocity could not be detected in this case, it is still anticipated that this combination of bioimpedance and a self-mixing interferometer are feasible for developing a device capable of measuring volume blood flow, provided measures are implemented to improve the signal-to-noise ratio of the interferometer.

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Appendices

Appendix A

Eddy Current Experimental Testing

Various coil designs were tested in an experimental setup that simulated a circulatory system. The magnetic coils were placed into a clear PETG pipe which was connected to the circulation system via a 8 mm silicone tube. A 12 V pump was used to circulate saline solution. For testing purposes the entire system was scaled up when compared to a blood vessel to simplify assembly of the magnetic coils. One of the coil configurations used is shown in Figure A.1.



Figure A.1: Wound coils shown in circulation system

The primary magnetic coil was excited by an amplified 5 kHz sinusoidal signal. A sinusoidal wave causes continuous change in magnetic field which is necessary to taking measurements. Amplification was provided by a LM1875

power amplifier operating between -10 V and +10 V.

Various coil winding configurations were tested. A plastic core was used for all coil windings since a core with a high magnetic permeability such as iron will result in most of the magnetic flux being conducted through the core and not the surrounding fluid. This makes it difficult to detect any change in flux since the permeability change in the fluid will be small compared to the permeability of the core. Three coil configurations that were tested include:

- 200 turn excitation coil, 20 mm long with 200 turn 20 mm secondaries on either side. Secondaries were wired in series to take a differential voltage reading. 0.1 mm enamel copper wire was used for all coils.
- 200 turn excitation coil, 20 mm long. Since 200 turn secondary was placed downstream of the excitation coil. 0.1 mm enamel copper wire was used. Since the differential coil setup did not give any conclusive results this setup was used to measure absolute as opposed to differential change.
- 200 turn excitation coil, 20 mm long. A 200 turn secondary coil was placed on top of the excitation coil to minimize any losses due to the distance between the primary and the secondary. This signal was too noisy to be able to take any reliable readings.

Measurements were taken using an oscilloscope. The oscilloscope probes were attached to amplifiers connected across the primary as well as the secondary coils to check for changes in either the voltage or the phase as the flow of saline solution was changed. After testing multiple iterations and combinations of coils, amplifiers and fluid conductivities it was concluded that the method would not be suitable to measure volume flow of blood within an artery and alternative methods would have to be explored.

Appendix B

Measurement Results

Table B.1: Diameter measurements using 0.9% Saline Solution

Diameter	Test 1	Test 2	Test 3	Test 4	Test 5
9 mm	0,552 V	0,54 V	0,548 V	0,552 V	0,556 V
8 mm	0,608 V	0,604 V	0,6 V	0,592 V	0,608 V
7 mm	0,696 V	0,704 V	0,692 V	0,704 V	0,704 V
6 mm	0,792 V	0,792 V	0,8 V	0,808 V	0,808 V
5 mm	0,984 V	0,984 V	0,992 V	0,984 V	0,976 V
4 mm	1,51 V	1,5 V	1,51 V	1,42 V	1,44 V

Table B.2: Diameter measurements using Horse Blood

Diameter	Test 1	Test 2	Test 3	Test 4	Test 5
9 mm	0.96 V	0.98 V	0.98 V	0.99 V	0.98 V
8 mm	1.05 V	1.05 V	1.06 V	1.04 V	1.06 V
7 mm	1.81 V	1.16 V	1.16 V	1.14 V	1.14 V
6 mm	1.3 V	1.32 V	1.33 V	1.38 V	1.36 V
5 mm	1.45 V	1.44 V	1.48 V	1.42 V	1.5 V
4 Smm	1.94 V	1.95 V	1.9 V	1.92 V	1.88 V

Appendix C

Pump Calibration

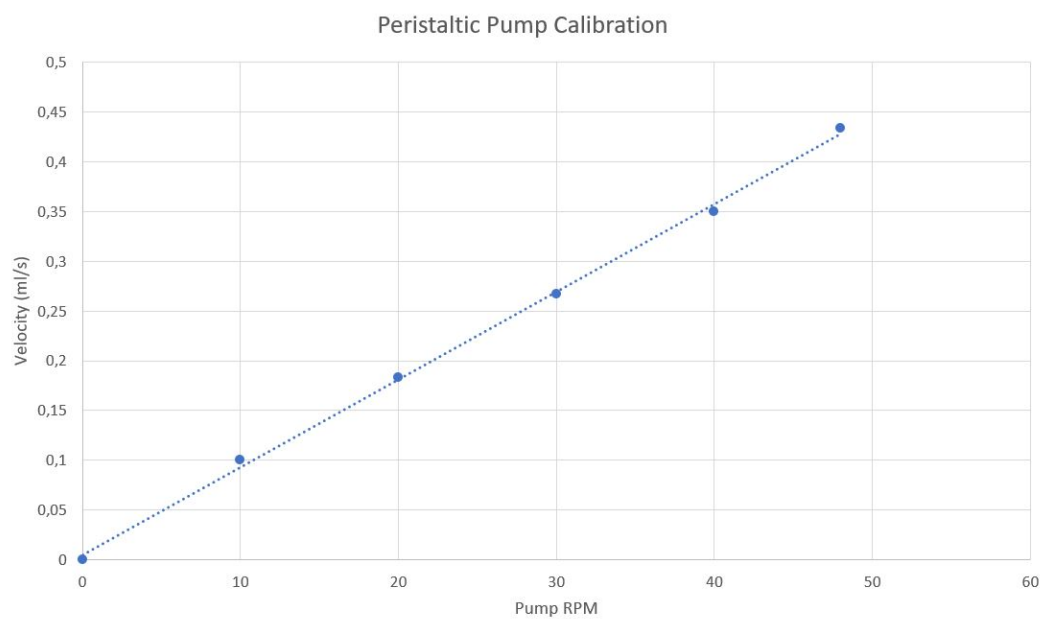


Figure C.1: Graph showing the measured flow rates of peristaltic pump at specific RPM