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Clinical Compatibility of an Implantable Pressure Sensing Device

With Consideration of the Intracranial Pressure Application

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Supervised by: Associate Professor David Budgett and Dr. Daniel McCormick

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Bioengineering
The University of Auckland, New Zealand
February 2015
Abstract

Implantable pressure sensing devices have the potential to improve patient management and treatment outcomes in a wide variety of conditions, including monitoring intracranial pressure (ICP) in hydrocephalus patients. The intracranial pressure application requires a long-term implantable device with high accuracy, resolute stability, a rechargeable power supply and must not exclude hydrocephalus patients from existing diagnostic medical procedures – namely medical imaging.

ICP is the gold-standard indicator for patient health in the hydrocephalus condition, where the accumulation of cerebrospinal fluid in the ventricles of the brain leads to an increase of ICP. Current treatment involves implanting a shunt to redirect the excess fluid, however shunt failure rates are high (up to 40% in the first year of implantation) and difficult to diagnose. Standard diagnostic procedures require costly medical imaging of ventricle size followed by burr-hole surgery to insert an acute transcutaneous lead ICP sensor into the brain parenchyma. In this thesis the feasibility of a lifetime fully implantable ICP measuring device is investigated. Such a device will comprise of a pressure sensing catheter (where the sensor is implanted in the parenchyma), connected to an electrical unit outside the skull, under the skin. The unit contains signal conditioning circuitry, wireless communication antenna, and an inductive power pickup coil allowing the implant to sit dormant until interrogated by an external reader wand.

This thesis reports on the clinical compatibility of a pressure monitoring system. Pressure measurement stability over time has been a major cause of failure for previous attempts at a long term ICP device, and this research has shown some (but not all) pressure sensors do have adequate stability over one year of operation within a model of the challenging environment of full implantation. An implantable device was tested in animal in-vivo experimentation including using the high fidelity sensor to make accurate recordings of rat LVP, and validating the device’s ability to measure ICP in acute large animal experiments. MRI compatibility was investigated for the device, including the development and validation of numerical models for RF heating analysis to guide prototype design. It is concluded that the implantable pressure sensing device has the potential to perform in the clinical environment, by screening for pressure sensor performance and avoiding critical lengths of the sensor catheter to limit patient risk in the MRI.
Acknowledgements

Firstly, I would like to express my absolute gratitude to my supervisors Associate Professor David Budgett and Dr Daniel McCormick for their sustained support and guidance throughout this project.

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I am extremely grateful for the financial assistance from Tech NZ and Millar Limited, without which this research would not have been possible.

Thank you to my fellow students, research, technical and administrative staff at the Auckland Bioengineering Institute for creating such an outstanding environment for research. Peter Blythe and Steve Olding, thank you for help and patience in design and construction of experimental set ups.

Finally, a massive thank you to Matt, for your unwavering support since day one of university – I promise to at least attempt to return the favour in the upcoming final months of your PhD. Mum, Dad, Reuben, Rose, and Hannah; thank you each for your individual and unique ways of providing support and encouragement.
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## Nomenclature

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<th>Description</th>
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<tbody>
<tr>
<td>ASTM</td>
<td>American Society for Testing and Materials</td>
</tr>
<tr>
<td>AIMD</td>
<td>Active Implantable Medical Device</td>
</tr>
<tr>
<td>AWG</td>
<td>American Wire Gauge</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>bpm</td>
<td>Beats Per Minute</td>
</tr>
<tr>
<td>CE</td>
<td>Conformité Européene (European Conformity)</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebral Spinal Fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
</tr>
<tr>
<td>DBS</td>
<td>Deep Brain Stimulator</td>
</tr>
<tr>
<td>DC</td>
<td>Direct Current</td>
</tr>
<tr>
<td>DIVA</td>
<td>Discrete Vasculaculture</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDP</td>
<td>End Diastolic Pressure</td>
</tr>
<tr>
<td>EM</td>
<td>Electromagnetic</td>
</tr>
<tr>
<td>ESR</td>
<td>Equivalent Series Resistance</td>
</tr>
<tr>
<td>ETV</td>
<td>Endoscopic Third Ventriculostomy</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDTD</td>
<td>Finite Difference Time Domain</td>
</tr>
<tr>
<td>FEM</td>
<td>Finite Element Method</td>
</tr>
<tr>
<td>FO</td>
<td>Fibre Optic</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable Cardiac Defibrillator</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial Pressure</td>
</tr>
<tr>
<td>ICP_A</td>
<td>Intracranial Pressure measured via an Acute sensor</td>
</tr>
<tr>
<td>ICP_T</td>
<td>Intracranial Pressure measured via implanted Telemetry</td>
</tr>
<tr>
<td>i.p.</td>
<td>Intraperitoneal</td>
</tr>
<tr>
<td>IPT</td>
<td>Inductive Power Transfer</td>
</tr>
<tr>
<td>ISM</td>
<td>Industrial, Scientific and Medical</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organisation for Standardisation</td>
</tr>
<tr>
<td>LC</td>
<td>Long Catheter implantable pressure sensing device</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>LVP</td>
<td>Left Ventricular Pressure</td>
</tr>
<tr>
<td>MICS</td>
<td>Medical Implant Communication Service</td>
</tr>
<tr>
<td>MoM</td>
<td>Method of Moments</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>OD</td>
<td>Outer Diameter</td>
</tr>
<tr>
<td>PCB</td>
<td>Printed Circuit Board</td>
</tr>
<tr>
<td>PEC</td>
<td>Perfect Electric Conductor</td>
</tr>
<tr>
<td>PM</td>
<td>Pace Maker</td>
</tr>
<tr>
<td>RF</td>
<td>Radio Frequency</td>
</tr>
<tr>
<td>RMS</td>
<td>Root Mean Square</td>
</tr>
<tr>
<td>S-AIMD</td>
<td>Standard Active Implantable Medical Device</td>
</tr>
<tr>
<td>SAR</td>
<td>Specific Absorption Rate</td>
</tr>
<tr>
<td>s.c.</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SC</td>
<td>Short Catheter implantable pressure sensing device</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
</tr>
<tr>
<td>TS</td>
<td>Technical Specification</td>
</tr>
<tr>
<td>WB-SAR</td>
<td>Whole Body Specific Absorption Rate</td>
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**Symbols**

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<th>Symbol</th>
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<td>$A_c$</td>
<td>Coil area ($m^2$)</td>
</tr>
<tr>
<td>$B_0$</td>
<td>Static magnetic field strength (Tesla)</td>
</tr>
<tr>
<td>$B_1$</td>
<td>Radio frequency field strength (Tesla)</td>
</tr>
<tr>
<td>$C_1$</td>
<td>Primary tuning capacitance (Farads)</td>
</tr>
<tr>
<td>$C_2$</td>
<td>Secondary tuning capacitance (Farads)</td>
</tr>
<tr>
<td>$d_{1in}$</td>
<td>Inner diameter of primary coil (m)</td>
</tr>
<tr>
<td>$d_{1out}$</td>
<td>Outer diameter of primary coil (m)</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------------</td>
</tr>
<tr>
<td>$d_{2in}$</td>
<td>Inner diameter of secondary coil (m)</td>
</tr>
<tr>
<td>$d_{2out}$</td>
<td>Outer diameter of secondary coil (m)</td>
</tr>
<tr>
<td>$dP/dt$</td>
<td>Pressure signal rate of change (mmHg/s)</td>
</tr>
<tr>
<td>$\varepsilon_r$</td>
<td>Relative permittivity</td>
</tr>
<tr>
<td>$f$</td>
<td>Frequency (Hz)</td>
</tr>
<tr>
<td>$f_0$</td>
<td>Resonant frequency (Hz)</td>
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<tr>
<td>$F_g$</td>
<td>Gravitational force (Newton)</td>
</tr>
<tr>
<td>$F_m$</td>
<td>Magnetic field induced force (Newton)</td>
</tr>
<tr>
<td>$k$</td>
<td>Magnetic coupling coefficient</td>
</tr>
<tr>
<td>$L_1$</td>
<td>Primary self-inductance (Henrys)</td>
</tr>
<tr>
<td>$L_2$</td>
<td>Secondary self-inductance (Henrys)</td>
</tr>
<tr>
<td>$M$</td>
<td>Mutual inductance (Henrys)</td>
</tr>
<tr>
<td>$\mu_r$</td>
<td>Relative permeability</td>
</tr>
<tr>
<td>$N$</td>
<td>Number of turns in coil</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Angular frequency (Radians/s)</td>
</tr>
<tr>
<td>$P_{ICP}$</td>
<td>Pressure sensors proposed for use in ICP application</td>
</tr>
<tr>
<td>$Q$</td>
<td>Quality factor</td>
</tr>
<tr>
<td>$R_1$</td>
<td>Primary windings resistance (Ω)</td>
</tr>
<tr>
<td>$R_{10}$</td>
<td>Single turn equivalent primary windings resistance (Ω)</td>
</tr>
<tr>
<td>$R_2$</td>
<td>Secondary windings resistance (Ω)</td>
</tr>
<tr>
<td>$R_{20}$</td>
<td>Single turn equivalent secondary windings resistance (Ω)</td>
</tr>
<tr>
<td>$R_L$</td>
<td>Load resistance (Ω)</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Electrical conductivity</td>
</tr>
<tr>
<td>$X$</td>
<td>Link potential</td>
</tr>
<tr>
<td>$z$</td>
<td>Coil-to-coil spacing distance (m)</td>
</tr>
</tbody>
</table>
1. Introduction

An implantable pressure sensing device has the potential to benefit a variety of patients through the monitoring of intracranial pressure (ICP) of hydrocephalus patients, intraocular pressure of glaucoma patients, bladder pressure of neurogenic bladder dysfunction patients, intra-arterial pressure of hypertension patients and ventricular or aorta pressure of heart failure patients. The measurement of ICP is considered throughout this thesis due to the chronic nature of the Hydrocephalus disorder requiring long term monitoring and the complications associated with current standard treatment methods. Hydrocephalus is a common paediatric neurological disorder where a disruption in the absorption or production of cerebral spinal fluid (CSF) leads to the accumulation of fluid in the brain, increasing ICP and can be fatal if left untreated. This chapter introduces the condition, treatment, complications and the importance of ICP in patient management. In this thesis, an implantable pressure sensing device is presented, developed and tested towards the long term medical device application, including MRI compatibility.

1.1. Implantable Pressure Sensor Application

The implantable pressure sensor device will be developed with consideration towards the ICP application, the details of which will be outlined in this section.

1.1.1 Hydrocephalus

Hydrocephalus, commonly known as “water on the brain” is one of the most common paediatric neurological disorders, with the congenital condition occurring in approximately 3 of 1000 live births [1], [2]. The landmark feature of hydrocephalus is the accumulation of cerebral spinal fluid (CSF) in the ventricles of the brain causing their expansion [1], [3]. Determining the rate of incidence of the disease is difficult; hydrocephalus can present itself as an isolated entity or in association with other neurological disorders such as cerebral palsy, intracranial haemorrhage, central nervous system infection or complications of prematurity and trauma [1], [3].

Traditional CSF flow theory describes intracranial CSF circulation as a pressure differential driven bulk flow. Starting with CSF production at the choroid plexus, fluid flows through the
ventricular system to be absorbed at the arachnoid granulations. According to this theory, hydrocephalus is an imbalance between CSF formation and absorption [2], [4]. Non-communicating (obstructive) hydrocephalus occurs when there is an obvious obstruction disturbing normal CSF flow in the ventricular system. Communicating hydrocephalus describes the condition when there is no obvious obstruction and it is assumed an obstruction to flow outside the ventricular system in the subarachnoid space is the cause behind malabsorption of CSF [5]. Although bulk flow theory provides a simple explanation for the occurrence of hydrocephalus, it has recently been replaced with a more complex model of CSF flow. Absorption has been discovered to occur more widely across the CSF circulation system and be highly dependent on arterial flow and pulsations, while production is not limited solely to the choroid plexus. The true nature of CSF flow, particularly with hydrocephalus, remains poorly understood; the lack of quantitative understanding of intracranial dynamics is often held responsible for the shortfalls of hydrocephalus treatment [4], [6], [7].

1.1.2 Treatment

Since its development in the 1950’s ventricular shunt insertion for excess CSF drainage continues to be the principal means for treating hydrocephalus, shown in Figure 1-1. Most commonly, CSF is shunted to the peritoneal cavity and flow is controlled with a differential pressure valve that opens in response to ICP [8]–[10].

![Figure 1-1: A hydrocephalus shunt](image)

Endoscopic third ventriculostomy (ETV) is the main alternative treatment to shunt insertion. ETV has only recently grown in popularity as advances in surgical techniques have significantly improved the safety of this once risky procedure. Surgery involves drilling a hole
in the floor of the third ventricle to provide a pathway for CSF flow from the ventricular system to the basal subarachnoid space. The procedure is typically regarded as suitable for patients suffering non-communicating hydrocephalus, however patient selection remains a challenge. ETV is estimated to be suitable for approximately 25% of hydrocephalus patients with the remainder requiring treatment by shunt insertion [10]. ETV is attractive as it overcomes shunt dependency with varied success rates that are considered within the range of 65-75% [11]–[13]. When ETV fails, patients generally display an increasing ICP with enlargement of the ventricles and shunt insertion is often required [14].

1.1.3 Complications

The development of the hydrocephalic shunt in the 1950’s greatly improved the prognosis for patients suffering hydrocephalus; however, the complications associated with these shunts are considerable [8], [15]–[18]. The cost of treating hydrocephalus in the US alone is estimated as $1 billion and approximately half that cost is due to shunt revisions [17]. Numerous new developments in hydrocephalus shunt technology have occurred in the past 60 years; however it is now known that these have not significantly improved failure rates. Overall, 40% of shunts fail in the first year following implantation, 50% have failed after two years, and for the years following the total failure rate increases by approximately 5% [8], [13], [15]. Failures are typically due to blockage, infection or mechanical malfunction and require invasive shunt revision to overcome. In addition to shunt failure, hydrocephalus patients commonly experience severe headaches and nausea. More severe symptoms brought on by incompetent or failing shunts include gait and vision interference, seizure and subdural hematomas [11], [16], [19]. The majority of complications and symptoms are closely associated with incorrect CSF flow management, chiefly over drainage [16], [20].

Shunt obstruction is the cause of over 70% of shunt revisions with ventricular catheter occlusion the most common form of blockage [8], [15]–[17], [21]. The material causing the occlusion is predominantly choroid plexus and glial tissue [16], [22]. In addition to being the most common source of shunt malfunction, ventricular catheter occlusions are difficult to diagnose and generally demand invasive surgery to fix [16]. The cause of these occlusions has traditionally been attributed to a combination of the placement of the catheter in the ventricle, the flow pattern of CSF, and over drainage of CSF causing the ventricular walls to periodically collapse against the catheter [3], [22]–[24]. Emerging evidence suggests that the influence of
catheter placement is only important in extreme situations and it is largely the nature of CSF flow that leads to ventricular catheter occlusions [24].

1.1.4 Intracranial pressure

Intracranial pressure (ICP) is a measure of the relationship between brain tissue, CSF, and blood. A healthy individual’s ICP is typically between 5-13mmHg with some cyclical variations due to arterial pressure and respiration, and additional changes due to coughing, posture and straining [4], [25], [26]. A sustained ICP above 15 mmHg defines intracranial hypertension and is associated with acute hydrocephalus, intracranial haemorrhage and presence of an intracranial mass lesion. If left undetected, intracranial hypertension can cause severe damage to blood vessels through expansion of the ventricles and displacement of brain tissue [4], [27].

In hydrocephalus patients, correct management of ICP is vital for prevention of prolonged periods of over drainage or under drainage leading to ventricle collapse or continued ventricle expansion respectively. With hydrocephalus, ICP pulsations due to arterial pressure are seen as large as $2.7 \times$ normal CSF flow pulsations [7], [28]. These measurements, along with prolonged raised ICP in hydrocephalic patients, support the notion of a less compliant hydrocephalus brain. Decreased compliance indicates hydrocephalus inhibits the brain’s ability to tolerate changes in ICP and is linked to slit ventricle syndrome where ventricular size becomes independent of ICP [29]–[31]. Alongside imaging techniques, ICP monitoring for a direct measurement of shunt function has become an extremely valuable tool in the diagnosis of shunt and patient condition [5], [11], [27], [32], [33].

1.1.5 Acute ICP monitoring

ICP monitoring is commonly used in an acute setting whenever brain swelling is a concern. Commonly, the technique is used to monitor patients after neurosurgery to remove a tumour or repair a blood vessel and most often for those suffering head trauma or hydrocephalus patients experiencing complications [26], [27], [34]. Raised ICP is the most common cause of death in patients with head injury, indicating the value of monitoring ICP [26], [35], [36].

The most frequently used acute ICP monitoring methods include a solid-state pressure sensor catheter inserted into the brain parenchyma and a lead running external to the body transmitting the pressure measurement and powering the sensor, or a fluid filled catheter running from the
ventricle to an external pressure transducer [26], [37]. Alternative methods include placing a pressure sensor, fluid-filled catheter, pressure screw or bolt in the subdural, epidural or subarachnoid spaces, however these locations provide a less accurate measure of ICP [38], [39]. The four main methods of obtaining a measure of ICP are illustrated in Figure 1-2.

![Diagram of ICP monitoring sites](image)

**Figure 1-2: Illustration of the four commonly used sites for insertion of ICP monitoring catheters.**

Catheter tip transducers inserted into the parenchyma are the favoured method for obtaining continuous ICP data as they are not dependent on patient position; however the transducers are associated with significant zero-drift (see Table 1-1). With re-calibration in-situ not possible, these transducers typically require replacement after 5 days due to the increasing drift error. Fluid-filled catheters are dependent on patient position and are also associated with severe drift, however in-situ recalibration is possible as the transducer is external. Intra-ventricular catheters have the advantage of also allowing for the drainage of CSF should the pressure become too high [34], [40]. Regardless of configuration, all current systems require a percutaneous lead, and therefore introduce a severe infection risk. Infection rates increase exponentially with time, and along with the influence of sensor zero drift, ICP monitoring in the acute setting for longer than 5 days per sensor is considered dangerous and invalid [34], [37], [41], [42].

In shunted hydrocephalus patients, shunt reservoirs can be also used to allow for minimally invasive ICP measurements. These reservoirs are only useful for determining the effectiveness of a working shunt at managing ICP and once the ventricle is occluded will give false ICP readings. Alternatively, measuring the pressure in the reservoir of a patient with suspected shunt failure can be useful in confirming failure [42], [43]. However, repeated piercing of these reservoirs exposes the risk of introducing infection directly into the shunt and ventricles [3].
For more comprehensive monitoring or to analyse ICP waveforms, percutaneous techniques similar to trauma patients are used to monitor hydrocephalus [34].

1.1.6 Chronic ICP monitoring

Conditions requiring continual ICP measurements include hydrocephalus treated by ventricular shunts or endoscopic third ventriculostomy and idiopathic intracranial hypertension [44]. Existing methods for obtaining reliable ICP data depend on invasive procedures such as lumbar puncture or implantation of an ICP monitor with an external connection. Repeated use of percutaneous ICP monitors and their associated infection risks and limits on measurement duration support the need for a reliable fully implantable ICP sensor system [44]–[46].

The concept and value of applying telemetry to develop a fully implantable chronic ICP monitor was expressed as early as 1965, particularly for application in hydrocephalus patients [47]. In 1967, Atkinson, Shurtleff and Foltz developed and implanted an absolute ICP sensor which communicated with radio telemetry. Their sensor was vulnerable to multiple sources of error, including being highly sensitive to changes in barometric pressure and altitude, however it did reflect the importance ICP has in the progression of hydrocephalus and lead to further developments towards a long-term implantable ICP monitor [47].

In the 1970s, differential pressure sensors were developed to overcome barometric pressure dependency and designs focussed on shunt failure detection emerged [48], [49]. Cosman et al developed a differential pressure sensor with in-situ calibration capabilities and reported on successful implantation in 16 patients for up to 14 months. This device became commercially available despite its 24% failure rate within one week of implantation [49]. A 12.7mm burr hole was required and the monitor provided intermittent subdural ICP measurements via passive telemetry [48]. Although this device was designed to allow for calibration after implantation, the calibration process was highly complicated and required hospital admission. Data acquisition and sensor calibration involved a pressure balance method analogous to the blood pressure sphygmomanometer. The device measured ICP from the subdural space which provides a less accurate measure than the parenchyma or ventricles and the design often lead to complications where readings could not be made due to swelling and incorrect implant size [49].

In 1980, Nulsen et al reported on clinical experience of an ICP sensor implanted in three patients [50]. The device transmitted data by telemetry and was used for a maximum of 37
days. ICP waveforms were not visible in the data; however it was found to be “technically effective and therapeutically useful” [50]. Electronic and encapsulation failure were key complications and limited the longevity of the device.

In contrast, Gucer et al reported on the excellent longevity of another chronic ICP monitor in 1988 after a 10 year follow-up [51]. The epidural sensor device was successfully implanted in 127 patients without complication; however the sensor remained in only 13 subjects long enough for long-term data analysis. The capacitor-based ICP sensor contained a flexible diaphragm as one side of the capacitor, such that a measure of pressure could be obtained from a change in capacitance. The sensor was accurate enough to pick up ICP waveforms, however suffered severe drift of approximately 0.5 mmHg per week [51]. Drift was the main fall back of this ICP sensor along with mechanical failure of the sensor including leakages in the packaging and cracking of the diaphragm. The drift resulted in patients displaying ICP’s up to 220 mmHg when they actually had an ICP in the normal range, revealing the monitor’s dependence on invasive and not entirely accurate lumbar puncture readings to compensate for drift [51].

The Rotterdam Teletransducer was initially developed in the mid 1970’s and successful implantation in patients was reported in 1982 [52]–[54]. A key focus throughout the development of this device was to address the sensor zero-drift problem common to ICP transducers. Bench top tests showed good performance for up to 2 months with stability of ±2 mmHg, but past 2 months drift increased and became unpredictable [54]. Despite this, the monitor was implanted in a total of 22 patients, 11 for only 1 week. Hydrocephalus patients used the device to provide intermittent ICP readings while trauma patients were monitored continuously. Successful and accurate readings were obtained in all implanted patients, although drift was a major problem and limited the efficacy of the device [54]. The main cause of the drift was put down to moisture leakage at the epoxy-resin connections, causing errors of up to 30 mmHg in some cases [52].

In 1997, the outcome of implanting the OSAKA telesensor in 94 hydrocephalic patients for monitoring ICP was reported [55]. The study showed the sensor caused no adverse effects, however once again zero drift was a major complication. The OSAKA sensor is designed to be used in line with a shunt; therefore it provides a measure of the pressure in the shunt line. This sensor also contained a passive resonant circuit, whose resonant frequency was altered by the effect of pressure acting on the bellows to move the ferrite core. In order to minimise the
devices protrusion from the skull, a 15mm burr hole is required. The drift characteristics were inconsistent across the group, typically between ±5 to ±25 mmHg per year [56]. Such drift can be compensated for by comparing the ICP value to that obtained by puncturing the on off valve, however this process complicates the motivating factor for using telemetry to allow ICP measurements to be made with ease and without the need for invasive action. The sensor also only measures pressure through the shunt line, not a direct measure of ventricular pressure, which would lead to incorrect, misleading ICP values when the shunt becomes obstructed or malfunctions [56].

Medtronic’s Chronicle device, an implantable hemodynamic monitor for measuring right ventricular pressure in the heart, has previously been adapted for the application of ICP [46]. The result of this adaptation was tested in four dogs, showing promising results with minimum drift over a maximum of three months, staying within ±3 mmHg [46]. The implanted unit is shown below where a solid state pressure catheter sits inside the brain ventricle and the telemetry and sensor electronics are contained in a pacemaker-type can that is implanted under the skin. Although this device has minimum drift, it’s size means a redesign would be required for the specific application of ICP monitoring rather than right ventricular heart monitoring. The pressure sensor catheter has a diameter of 2.9mm, larger than most ICP probes, and was seen to cause some trauma in the dog brain. The bulky encased electronics is also unnecessary and unsuitable for the application of ICP, however its low drift makes it a promising device for chronic ICP monitoring in hydrocephalus and trauma patients [46]. Medtronic’s device has also recently been used as a tool for researching the pathophysiology of hydrocephalus using animal models [57].

The most recent advancement towards a chronic ICP device is the successful CE approved Raumedic Neurovent-P-tel implantable ICP device, shown in Figure 1-3 [58], [59].

Figure 1-3: Raumedic Neurovent-P-tel fully implantable ICP device with CE approval for 3 months of use.

The device has approval for three months of use, and supporting publications which demonstrate positive results with a reduction in imaging dependency for patient monitoring and complementary use with adjustable pressure setting hydrocephalus shunts [58], [60]–[63]. The device uses a 5 Fr capacitive based pressure sensing catheter which is implanted in the brain parenchyma attached to a 30mm diameter telemetry unit implanted outside the skull, under the patient’s skin. An external unit provides wireless power to the device which can
return an ICP signal at a sampling rate of 1 or 5 Hz [63]. The Raumedic Neurovent-P-tel ICP device has been an important development towards establishing a widely available ICP implant for lifetime monitoring, however there are potentially significant limitations associated with the device, including its relatively low sampling rate, large size and significant expense.

1.2. Critical device requirements

The accuracy, longevity, safety and efficacy of implanted medical devices must be firmly established to justify therapeutic use or substantiate monitoring requirements. Proven device biocompatibility is required to meet approval standards for implantation in the human body and use in hospitals throughout the USA (governed FDA approval) and Europe (governed by CE approval). In general, it is desirable for implanted active medical devices to be of a small size – for the ICP application, a comparison can be made against hydrocephalus shunt valves, for example the Medtronic CSF-Flow Control Valve dimensions are: $18 \times 32 \times 7.5$ mm (height $\times$ width $\times$ depth) [64]. Longevity of operation is a key consideration for the ICP device which is designed to reduce the rate of invasive surgery and patient exposure risk with current acute monitoring techniques. The sensor stability, power source and encapsulation means will define the durability of the device. Encapsulation techniques are widely established in existing active implantable medical devices such as pacemakers (PM), deep brain stimulators (DBS) and implantable cardio defibrillators (ICD) utilising a combination of commercially available biocompatible materials and hermetic sealing methods. It is anticipated that such techniques can be applied to the ICP device in later development and will not be considered in this research. The pressure sensor stability, responsible for the failure of multiple previous attempts at an ICP device (see Section 1.1.6), will be introduced and further investigated in Chapter 2. As a power source, inductive power transfer (IPT) will allow the fully implantable device to operate on demand, providing theoretically indefinite power, when the external primary coil is in range. IPT can also work in conjunction with a finite power source, such as an on-board rechargeable battery or super capacitor. The ability to continue use of medical imaging techniques to monitor hydrocephalus patients, particularly MRI, is vital for the potential clinical uptake of the ICP implant and therefore MRI compatibility is a significant consideration in the development of this device.
1.2.1 Bio compatibility

Biocompatibility of a medical device is a prerequisite to clinical success. Biocompatibility is a broad term which has proven difficult to define, for individual materials a widely used concise definition is:

"Refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy" [65], [66]

However, medical devices are (generally) made up of multiple materials and while the individual materials can be proven biocompatible alone, the overall geometry, surface, and operation of the complete device will ultimately determine the biocompatibility. There has been a recognised need to shift in defining biocompatibility relative to specific materials, to instead be applications based [65]. There are several sub-definitions of what makes a device compatible with the human body, and relevant to the ICP application is the specific biocompatibility of long-term implanted devices:

“The biocompatibility of a long-term implantable medical device refers to the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting any undesirable local or systemic effects in that host” [65]

Before clinical studies on new medical devices can be FDA approved, their biocompatibility must be determined following ISO 10993: Biological Evaluation of Medical Devices [67]. The ICP device development will utilise widely established biocompatible materials for components such as the outer casing, catheter, and potential implantable battery. A wide variety of active implantable medical devices (AIMD’s) provide evidence towards the established means of achieving biocompatible electronic circuits. With the ICP application, the pressure sensing catheter operates from a mechanical interface between the ICP and the pressure sensing element which is a feature of concern for biocompatibility. In similar applications, Raumedic’s implantable ICP monitor utilises a similar piezoresistive pressure sensor with a polymer coating between the brain CSF and sensing element [62] and in CardioMEMs heart failure monitor a glass diaphragm acts as the boundary to the pulmonary aortic blood pressure and the sensing device [68]. Evidence of existing biocompatible encapsulation and AIMD’s provide
confidence in the potential to utilise existing methods and materials in the final clinical device. Biocompatibility is assessed on the device as a whole, which will ultimately be required in later stages of device development for clinical use. Though meeting biocompatibility standards for the final complete device is outside the scope of this research, a general understanding of biocompatibility is important to avoid future complications.

1.2.2 Sensor stability

Specific to the ICP application, the pressure sensor itself must be highly stable and specifically suffer little zero drift. The low magnitude of the ICP signal (in the order of 10 mmHg) makes the sensor stability a key requirement. The currently CE approved Raumedic implant for long term ICP monitoring has been demonstrated to drift less than 2 mmHg/year in a study in mini-pigs [58]. In all prior attempts to develop a long term ICP implant, drift has been a key barrier to the success of the device. Due to the difficulty to carry out sensor recalibration once it is implanted, a highly stable sensor with low drift is the key determinant of a successful long term implantable ICP device.

There is potential to carry out recalibration of sensor characteristics in specific scenarios. Sensor scale factor or sensitivity can be assessed through patient exposure to a controlled change in atmospheric pressure. Sensor zero-drift is a larger concern due to reliance on invasive means such as a reference acute sensor implantation or shunt tapping (provided the shunt is not occluded) which expose the patient to significant risk or rely on assumptions and would not be suitable procedures to carry out regularly.

Current transcutaneous acute ICP sensors are associated with significant drift which, along with infection use, limit their longevity to approximately 5 days of use. A summary of existing acute ICP systems and their associated drift is described in table Table 1-1.
Chapter 1. Introduction

Table 1-1: Available ICP monitors and their associated drift, modified from [41].

<table>
<thead>
<tr>
<th>ICP monitor</th>
<th>Zero Drift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camino (Integra LifeSciences)</td>
<td>First 24 hours: ±2 mmHg, next 4 days: &lt;1 mmHg/day</td>
</tr>
<tr>
<td>Codman (Johnson &amp; Johnson)</td>
<td>3 mmHg/day</td>
</tr>
<tr>
<td>Neurovent (Raumedic Systems)</td>
<td>1-2 mmHg over 5 days</td>
</tr>
<tr>
<td>Ventrix (Integra LifeSciences)</td>
<td>First 24 hours: ±2 mmHg, next 48 hours: &lt;1 mmHg/day</td>
</tr>
<tr>
<td>Fluid-filled transducers</td>
<td>±2 mmHg/8hours</td>
</tr>
</tbody>
</table>

Even with devices which meet the required less than 2 mmHg/year drift, for a lifetime device this will cause significant error in the static ICP value within a few years. However, there is substantial information for clinicians to be found in the dynamic, ICP waveform measurement. Therefore, as well as stable zero drift, a long term implantable pressure sensor must also demonstrate highly stable bias and scale factor after calibration.

1.2.3 MRI compatibility

Magnetic resonance (MR) imaging (MRI) is a medical imaging technique widely used for diagnosis and disease tracking due to its ability to obtain 3D high resolution images of soft tissues without requiring contrast media or exposing patients to ionizing radiation. Hydrocephalus patients represent a population exposed to frequent medical imaging in order to monitor the progress of the disorder or the efficacy of treatment. Patients can either undergo high radiation dose computerised tomography (CT) imaging or, if available, MRI. Due to advancements in imaging techniques, MRI has recently become the method of choice for imaging the brain, spine, musculoskeletal system, head, neck, and heart [69]. There is estimated to be over 25,000 scanners in use worldwide and the number of MR scans performed has seen a dramatic increase [69]. While the use of MRI techniques has increased, so too has the rate of active implantable systems such as pacemakers, implantable cardioverter/defibrillators, and cochlear implants. Previously, the presence of such electronically active implantable medical devices (AIMD) would have been an immediate contraindication to utilising MR imaging techniques. However, recent developments in the classification of MRI compatible devices has seen a shift where AIMD’s, after sufficient testing, can be approved as MR conditional if specific conditions are met [70]–[75]. The conditions include specific patient or device conditions of use and a specified MR environment defined by magnet strength and scan specific absorption rate (SAR) limits [70], [76]. In 2010, a new ISO technical specification for defining
the conditional safety of AIMD’s was developed to expand on the existing five ASTM standards, which were developed for passive implants [70], [72], [76], [77]. This recognized both the need and potential for safe use of AIMD’s in the MR environment, and developed a demand for AIMD design to consider the device’s conditional safety in the MRI.

MR images are obtained through exploiting the nuclear magnetic resonance (NMR) phenomenon where electromagnetic radiation is absorbed and emitted by nuclei immersed in a static magnetic field. During imaging, hydrogen ions within the body (present in any tissue containing water molecules) are aligned under the static magnetic field \(B_0\), excited by the pulsed RF field \(B_1\), and the resulting NMR emission measured. This emission signals are manipulated by applying gradients which vary over space to determine slices to be imaged in either the x, y or z direction. The standard coordinate orientation is demonstrated relative to patient and scanner in Figure 1-4, and used throughout this thesis.

![Figure 1-4: MRI co-ordinate system orientation](image)

An image is ultimately produced by performing a 2-D Fourier transform of the spatial frequencies in the emitted signal. Four key systems form the basis of MR imaging and have the potential to cause safety concerns with a patient containing an implant: the static magnetic field, static magnetic spatial gradient field, gradient magnetic field and radio frequency field. These four systems interact in the active scanner, which makes device-patient-MRI interactions difficult to predict. The systems are generated and controlled by the MRI’s static magnet, RF transmit/receive coils, gradient coils, and the computer (located in a separate room outside the MR shield).

The static magnetic field is generated by a large superconducting electromagnet immersed in helium which forms the bore of the MR machine around which the remaining scanner systems are built. The magnet generates the static magnetic field \(B_0\), whose strength (measured in
Tesla (T)), and uniformity determine the fundamental image quality. In a typical cylindrical bore scanner, the $B_0$ field is directed along the length of the patient, assigned as the $z$-direction. Standard clinical strengths include 1.5 to 3T, with 7T machines beginning to emerge from research to clinical use. The magnetic field is manipulated with ferromagnetic blocks and shim coils in order to generate a uniform homogeneous field across the bore in the region to be imaged.

Gradient coils further manipulate the $B_0$ field by producing spatial gradients in the $z$-direction which localise image slices causing resonance in the protons for slice selection. The gradient coils are also used to phase- and frequency-encode the protons to be measured. Gradient fields are in the order of 100mT/m, and power limited to avoid the stimulation of peripheral nerves. The MRI contains three sets of gradient coils for each main axis of direction resulting in $\frac{\partial B_z}{\partial x}$, $\frac{\partial B_z}{\partial y}$, $\frac{\partial B_z}{\partial z}$ field gradients.

The RF coil generates the $B_1$ field during a pulse sequence through emitting RF energy. RF coils may only transmit, or both transmit and receive signals, or only receive. The $B_1$ field is applied perpendicular to $B_0$, inducing a change in orientation of the polarised hydrogen ions. The pulse sequence resembles a sinc function in the order of kW, which can be manipulated for a wide variety of scan sequences designed to focus on specific tissues or structures in the body. Safety requirements on the level of RF energy emitted/absorbed by the patient are defined through SAR limits depending on the body region being scanned and the operation mode of the MR machine and are summarised in Table 1-2 [72], [78].

<table>
<thead>
<tr>
<th>Operational Mode</th>
<th>Whole Body Averaged (W/kg)</th>
<th>Partial Body Exposed Part (W/kg)</th>
<th>Head SAR (W/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2</td>
<td>2-10$^1$</td>
<td>3.2</td>
</tr>
<tr>
<td>First level controlled</td>
<td>4</td>
<td>4-10$^1$</td>
<td>3.2</td>
</tr>
<tr>
<td>Second level controlled</td>
<td>&gt;4</td>
<td>&gt; (4-10)$^1$</td>
<td>&gt;3.2</td>
</tr>
<tr>
<td>Short SAR</td>
<td>SAR limit over any 10 s period must not exceed 2x stated values</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$Partial body limits scale dynamically according to the ratio “exposed patient mass/patient mass”

Table 1-2: IEC 60601-2-33 Medical electrical equipment SAR limits for MRI.
The bird cage volume body coil is typically built into the scanner bore and is the most commonly used for imaging the head and torso, often operating in transmit/receive mode. Smaller surface RF receive coils can be used to improve signal quality by focusing on a smaller area. The RF body coil has the potential to emit the maximal RF energy into the patient and is therefore a key consideration in MRI safety and patient risk.

### 1.3. Patient-device-MRI interactions

Given the reliance of hydrocephalus treatment on medical imaging, and the rise in MRI use for general medical diagnosis, it is necessary to understand the effect of the MRI environment on the pressure sensing device proposed for clinical applications. This section describes the patient, device, and MRI interactions, their cause and the standards in place to evaluate MRI safety of AIMD’s.

A patient containing any implant in the MR environment is exposed to the risk of MR induced force, torque and heating of the implant which have the potential to result in patient injury. The implant also may cause image artefact, reducing the diagnostic quality of the procedure. With AIMD’s, there is the additional complication of the MR interfering with the electronics operations, inducing currents and damaging or altering device function. These five main interactions are covered by standard testing methods; ASTM standards F2502, F2213, F2182, F2119 [79]–[82] from the American Society for Testing and Materials, the new active implant technical specification from the International Organisation for Standardisation ISO/TS 1052 [72], and widely utilised and published methods from Frank Shellock, author of the annual Reference Manual for Magnetic Resonance Safety, Implants and Devices [83], [84]. These methods can be used to demonstrate and determine conditions for safe operation of the MRI machine with patients containing implants, such as refined SAR limits, specific RF coil use, patient positioning and landmark positioning.

Medical implants and devices are classified as MR Safe, MR Conditional, or MR Unsafe, subsequent to testing their interactions with the patient and the MR environment [75]. MR Safe classified implants pose no risk to the patient entering the MR environment due to the implant/device being completely non–magnetic, -electrically conductive and -RF reactive. MR Conditional implants require specific defined patient, device, or MR environmental conditions to be adhered to in order to remove the risk of harmful interactions. These implants do contain magnetic, electrically conductive, or RF reactive components but have been sufficiently tested...
to define the magnitude of risk and determine the limitations on how the device and patient can safely use the MR machine. If the device contains significant ferromagnetic components resulting in obvious risk to the patient it is classified as MR Unsafe and patient’s containing such devices are immediately contraindicated for MRI. AIMD’s have the potential to achieve MR Conditional approval for use in the MRI.

Magnetic field interactions are unique to particular scanner designs in MRI strengths and can vary widely and in an unintuitive manner between different scanners. In particular, should a device be found to have safe heating in a 3T/128 MHz scanner, it cannot be assumed to be safe in a lower strength, e.g. 1.5T/64 MHz MRI. There have been multiple cases of higher heating occurring in lower strength scanners for a lower given SAR. Similarly, long or short bore static magnets will have different field concentrations inducing different static field effects for the same magnet strengths. Different manufacturers may also have different field characteristics for both the static and RF fields. It is therefore necessary to carefully define the MRI environment for which the implant has been investigated for potential interactions, independent of the machine’s make or model (i.e., in terms of field strength or SAR).

1.3.1 Static field

The MR’s uniform static magnetic field ($B_0$) can induce forces and torques on implants in the MR environment. $B_0$ interactions have the potential to cause severe injury to the patient if large enough to cause movement or dislodgement of the implant. These interactions are continuously present in the MRI room due to the presence of the static magnet and do not depend on the active scanning operation of the MR machine.

The magnitude of induced force is dependent on the magnetic susceptibility or volume and shape of ferromagnetic material in the implant, the implant’s overall shape and mass, and the strength and spatial gradients of the static field. The induced force causes a translational attraction towards the magnet and is maximal at the point of maximum spatial gradient in the $B_0$ field, typically in an off-axis position. ASTM F2052: Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment outlines testing methods to quantify the induced force and classify the safety of an implant. The test is based on the deflection angle test developed by New et al [85], and illustrated in Figure 1-5, where the device to be tested is suspended by string weighing less than 1% of device weight and its deflection angle measured at the worst case, static magnet gradient maximum position. If the device is deflected by less than 45°, it is
deemed safe as the magnet induced deflection force ($F_m$) is less than that acting on the device due to gravity ($F_g$) and therefore any risk associated with static force in the MRI is no greater than normal activity under the earth’s gravitational field [79], [85].

![Diagram illustrating the deflection angle test for measuring induced force by the MRI on an implant.](image)

Magnetic induced torque causes a rotation of the implant to align the long axis of the dominant ferromagnetic component with the static magnetic field. In a standard cylindrical bore clinical MRI; the strongest torque is induced in the centre of the bore where the field is uniform and parallel. The implant’s dimensions – principally length and initial angular position relative to the field determine the magnitude of the torque induced, and therefore the device must be tested across the full 360° range of angular position for each primary axis.

### 1.3.2 MRI induced heating

There are three dominant potential routes for implant heating which occur when a patient and medical device undergo an active MR scan. These are electromagnetic induction heating, resonant electromagnetic induction heating, and antenna effect heating.

Electromagnetic induction occurs when the MRI induces currents in conductive materials in the implant. This can occur through the pulsed magnetic gradient fields and/or the pulsed RF fields [86]–[88]. Any circulating currents induced by the gradient and RF magnetic fields will result in ohmic heating through power loss, and this was the method that was traditionally assumed to be responsible for MR burns due to medical devices [86], [89]. The electromagnetic induction can be optimised when a circuit is in a resonant condition and therefore the worst case potential heating through induction will occur. An equivalent electric circuit can be modelled for a conducting coil in an MR field where the circuit can be tuned for resonance with the MR. To avoid the resonant phenomenon, closed coils of conductive material have been avoided for any device entering the MRI. Despite the electromagnetic induction effect
being intuitively the means of implant heating in the MRI, it has been demonstrated to be difficult to induce, with standard electromagnetic induction causing minor heating and the resonant condition requiring very specific circumstances [86]. The antenna effect is associated with the most devastating burns from implants in the MR [86]. Any elongated conductive material in the MR can act as an RF antenna, sensitive to the electric component of the pulsing RF field. The antenna can act as a receiver, with the potential to also demonstrate a resonant condition where standing current and voltage waves are established in the implanted wire or elongated structure [86], [87], [90]–[92]. The resonance antenna condition will occur at approximately the half wavelength of the EM field inside the patient [86]–[88], [93], which is 25 cm and 12 cm for the common clinical MR strengths of 1.5T and 3T, respectively. However, for AIMD’s with leads, the effective implant length can be difficult to determine and is not only dependent on the lead length but the layout, position, and the device unit to which the lead attaches [94]–[96]. Resonant RF antenna heating has been associated with patient injury and severe heating conditions in a range of devices and testing must be undertaken to ensure this does not occur with any new potential device seeking MR conditional approval [83], [88], [89], [91], [94], [95].

Heating induced by the gradient switching fields in the MRI is due to eddy currents developing on the implant surface, as explained by Faraday’s law [99]. The switching gradient fields may also induce visible implant vibration during active scanning or nerve stimulation in exposed lead tips [87], [99]. Gradient field induced effects are of particular concern in exposed electrode leads or highly conductive implants with a large surface area, with heating and vibrations observed in cervical fixation devices [100], large (5 cm x 5cm) orthopaedic plates and frames [101] and metallic rods [101].

RF induced heating of a patient’s tissue around implanted devices is the most complex step in determining implant safety. The distinction between the complexity of potential RF heating for passive and active implants is highlighted in ISO technical specification 10974: Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device. The quantification of RF heating requires a 4-tiered approach incorporating numerical modelling and physical testing [72]. The use of modelling is important in establishing the worst case condition for the difficult to predict RF heating. Testing of existing active implants in clinical MRI has demonstrated heating up to 63 °C at exposed electrode lead tips, which can be avoided by adhering to specific conditions and layout of the implant [84], [91]. External monitoring leads can become safe for use in the MR scanner if the lead is coiled to avoid the
elongated antenna effect [89], [94], [96], [97]. In order to avoid prolonged experimental testing of potential heating conditions, electromagnetic modelling methods can be used to stimulate the MR RF environment and predict conditions to be verified by physical testing in an RF coil or clinical scanner.

1.3.3 Function interference

Currents induced by the pulsing RF and gradient magnetic fields may also cause interference with the electronic circuit and function of implanted active devices. Though it does not pose a risk to the patient, malfunction of an implanted device is an important interaction to be considered and avoided. Some implantable devices contain safe modes that must be activated before entering an MRI to shut down device activity during scanning or safeguard device settings from any undesired induced changes from the MR Fields. Evaluating potential functional interference involves repeatedly exposing the device to a wide range of scan parameters and magnetic fields to determine if any change in function can be induced.

1.3.4 Image artefact

Implanted materials have the potential to disturb the homogeneous magnetic field set up by the static magnet which can result in susceptibility artefacts, signal voids, distortions, and shadowing over tissue regions of interest. Understanding the potential artefacts which can be induced by the device is an important step in investigating and implants interaction with the MRI. Implant location and positioning may have to be targeted to avoid known imaging regions of interest and specific scan parameters used to avoid artefact around the implant. ASTM standard F2119 outlines methods for quantifying the worst case artefact resulting from an implant. Determining the worst case scan parameters is an important step after which pairs of spin echo and gradient echo images containing and not containing the implant are obtained for comparison [82].

Table 1-3 summarises the hazards associated with implants in the MRI, modified from the FDA [67]:

19
### MR Environment’s Effect on Medical Device

<table>
<thead>
<tr>
<th>Component of MR Environment</th>
<th>Medical Device Concern</th>
<th>Potential Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static Magnetic Field $B_0$ (always on)</td>
<td>Rotational force (torque) on object</td>
<td>Tearing of tissues Rotation of object in order to align with field</td>
</tr>
<tr>
<td>Static Magnetic Field Spatial Gradient (always on)</td>
<td>Translational force on object</td>
<td>Tearing of tissues Acceleration of object into bore of magnet &quot;missile effect&quot;</td>
</tr>
<tr>
<td>Gradient Magnetic Field $B_1$ (pulsed during imaging)</td>
<td>Induced currents due to dB/dt</td>
<td>Device malfunction or failure</td>
</tr>
<tr>
<td>Radio Frequency Field (pulsed during imaging)</td>
<td>RF induced currents resulting in heating</td>
<td>Patient burns (thermal and electrical)</td>
</tr>
<tr>
<td>Radio Frequency Field (pulsed during imaging)</td>
<td>Electromagnetic Interference-active device</td>
<td>Device malfunctions Induced noise (monitoring devices)</td>
</tr>
</tbody>
</table>

### Effect of Medical Device on MR Scanner

<table>
<thead>
<tr>
<th>Electromagnetic emission from medical device</th>
<th>Poor quality images, low signal to noise ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical device in or near imaging field of view</td>
<td>Image degradation, signal voids.</td>
</tr>
</tbody>
</table>

Table 1-3: Summary of cause and effect of hazards associated with implants in the MRI.

### 1.4. Objective and scope

The object of this project is to develop and test key aspects of an implantable pressure monitoring device targeting lifetime clinical applications, specifically for the monitoring of
ICP in hydrocephalus patients. The key aspects with lifetime monitoring of ICP have been identified as sensor stability, device longevity and MRI compatibility. Consequently, this thesis includes an investigation into the long term pressure sensor’s stability, the development of a ferrite-less inductive power pickup for the implant’s power supply, small and large animal testing, and an analysis of the MRI interactions with the device to determine patient risk in the clinical setting.

The subsequent Chapters of this thesis are organised as follows:

Chapter 2 outlines bench top experimentation and quantification of the performance of a pressure sensor. This includes the development of a long term drift rig to monitor the sensor stability over a running period of one year. A ferrite-less inductive power pickup is developed as the device’s main power source in anticipation of future MRI compatibility work.

Chapter 3 describes *in-vivo* experimentation and performance of the implantable pressure sensing device. Chronic measurements of the demanding left ventricular pressure signal in a rat heart are conducted along with acute experiments in sheep brain ventricles.

Chapter 4 covers the development of a numerical model of the 128 MHz RF birdcage of a 3T MRI. The model is validated against a clinical 3T scanner system and model approximations of the components of an ICP device are investigated.

Chapter 5 is a comprehensive investigation into interactions of the implantable device in an MRI system including force, torque, function, heating and artefact. RF heating critical components of the device are investigated using the numerical model from Chapter 4 to guide device design from its prototype stage towards MR conditional approval.

Chapter 6 provides a summary of conclusions and contributions made in this thesis. Direction for future work is provided.
2. ICP Device: Sensor performance and power source

Key requirements of a clinical ICP monitor are outlined in the American National Standard: *Intracranial pressure monitoring devices* developed by the Association for the Advancement of Medical Instrumentation [104]. The device and readout display must range from 0 to 100 mmHg. This allows for a generous margin above the “normal” limit in the supine position of 20 mmHg where hypertension occurs and treatment is generally required, and an absolute upper limit of 50 mmHg in a severe condition [105]. The accuracy of the entire system must be ± 2 mmHg in the standard clinical range of 0-20 mmHg, with a 10% error for 20-100 mmHg, and stable across a temperature range from 20 – 39 °C [104]. These standard values have been constructed around the use of acute monitors in the hospital setting where a patient is generally in the supine position. When standing vertically, ICP is negative with a mean of approximately -10 mmHg, and not exceeding -15 mmHg [106]. For chronic monitoring, it is appropriate to expand the implantable device requirements to include the negative pressure range. The pressure monitoring device and readout display must also be fully characterised including frequency response, slew rates, pressure range, accuracy, size of implanted portion and associated skull burr hole, pressure stability with temperature and zero drift [104].

As described in Chapter 1, the dominant limitation on acute ICP monitors and previous attempts at implantable ICP devices has been the sensor zero drift. Widely used acute ICP sensors exhibit drift up to 1-3 mmHg/day during a limited implantation period of approximately 5 days [41]. Demonstrating reduced drift in pressure sensors for the fully implanted absolute pressure sensor application is a significant challenge. Raumedic Neurovent-P-tel reports a drift within ±2 mmHg/year, the ability to provide reliable data for up to 18 months in-vivo, and has CE approval for 3 months of implantation in humans [58], [107]. Based on the American National Standard and the clinical acceptance of the Raumedic device, a drift specification of the order of ± 2 mmHg is an appropriate benchmark for ICP device performance required in the clinical application.
Millar Inc. produce a telemetry based pressure measuring system with many of the desired features of a lifetime ICP monitor. It uses a piezo-resistive pressure sensor of a similar construction to the Raumedic device. These devices are designed for chronic animal monitoring experiments of up to 3 months for physiological variables such as blood pressure. The device consist of the pressure sensor at the end of a catheter connected to the telemeter unit which contains an inductive power transfer (IPT) pick up coil, implantable rechargeable battery, 2.4 GHz Nordic antenna, and related sensing amplification, power management, and communications signal circuitry. Adequate encapsulation for the 3 month intended duration of use is provided by Parylene and polymer coatings. Figure 2-1 shows the commercially available animal monitoring implant.

![Millar implantable device model TRM54P for monitoring pressure in laboratory animals](image)

However, the drift specification for the Millar 2 Fr device is 4 mmHg per month [108]. The absolute pressure sensor device is a piezo-resistive type sensing element embedded in a 2 Fr catheter, utilising similar technology as the Raumedic 5 Fr piezo-resistive sensing catheter. Data on longer term drift performance of the Millar sensors was not available, and an experiment was constructed to obtain this important performance data.

The viability of an implantable device was tested against an expected operating pressure range of -15 to 50 mmHg. The Millar 2 Fr pressure sensor has a documented accuracy of ± 2 mmHg in the temperature range from 23 – 38 °C across a measurement range of -20 to 300 mmHg [108], which makes it at the outset well suited to the clinical ICP application. Understanding the long term (> 3 month) drift characteristics was the first step in determining if the sensor had potential for the implantable ICP device solution.

Electrical power is a key consideration for a long term implantable medical device. Implanted power sources, such as batteries, contain a finite amount of energy and will eventually require surgery for replacement. The ICP application is relatively low power, however size constraints
on implants on the head are significant. IPT can be utilised to achieve transcutaneous energy transfer in a medical device where power is transferred wirelessly across the skin barrier. IPT would negate the need to include a battery, and negate the need to periodically replace that battery surgically.

In the clinical application, a transcutaneous transformer is implemented where the primary, external coil produces an electromagnetic field which induces a voltage in the secondary, implanted coil which powers the medical device. IPT is an ideal solution for implanted electronics designed for lifetime function as power supply is infinite. It is anticipated that powering of the ICP device will be achieved through IPT, either as the sole power source or in conjunction with on board power storage such as rechargeable implantable battery or super capacitor. The clinical implanted device will require the development of a ferrite-less secondary coil to reduce the volume of magnetic material for MRI safety. A working coil set was developed as the sole power source for a small animal telemeter with the goal of carrying out large animal acute experiments with the 2 Fr sensor and ferrite-less pickup coil.

2.1. The solid state pressure sensing catheter

The fundamental component of the ICP device is the pressure sensor. The performance of the 2 Fr Millar sealed pressure sensing catheter is investigated for potential in the clinical application, shown in Figure 2-2.

Figure 2-2: Close up of piezoresistive sensing element in the 2 Fr Millar pressure sensing catheter.

The sensor is of piezoresistive type, where the catheter Titanium encased tip contains a silicone microchip with diffused piezoresistive strain gauges. The piezoresistors are configured in a Wheatstone bridge connected by wires in the 1.5 Fr nylon catheter to the telemeter unit. When an excitation voltage is applied across the bridge and the silicone membrane of the pressure sensing tip deflects under an applied pressure, the embedded piezoresistors undergo a resistance change which can be measured through the bridge as a change in voltage. The sealed
sensor, designed for implantation, measures absolute pressure against a sealed reference vacuum pressure behind the sensing element. Key specifications of the piezoresistive pressure sensor are summarised in Table 2-1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum</th>
<th>Typical</th>
<th>Maximum</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>12</td>
<td>12.5</td>
<td>35</td>
<td>µV/V/mmHg</td>
</tr>
<tr>
<td>Operating pressure</td>
<td>710</td>
<td>1060</td>
<td></td>
<td>mmHg</td>
</tr>
<tr>
<td>Excitation</td>
<td>1</td>
<td>10</td>
<td></td>
<td>V</td>
</tr>
<tr>
<td>Operating temperature</td>
<td>15</td>
<td>40</td>
<td></td>
<td>°C</td>
</tr>
<tr>
<td>Physical dimensions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>870</td>
<td>890</td>
<td></td>
<td>µm</td>
</tr>
<tr>
<td>Width</td>
<td>370</td>
<td>390</td>
<td></td>
<td>µm</td>
</tr>
<tr>
<td>Thickness</td>
<td>115</td>
<td>130</td>
<td></td>
<td>µm</td>
</tr>
</tbody>
</table>

Table 2-1: Key specifications of the piezoresistive sensing element in the 2 Fr pressure sensing catheter.

The Wheatstone bridge which forms the basis of the sensing circuitry typically requires two 820 Ω completion resistors. The sensors demonstrate some light sensitivity which is not of concern once implanted but has important implications during calibration and must be considered during testing.

2.2. Quantification of sensor drift

Based on the relatively small scale of the ICP signal and the intended duration of monitoring, drift has been identified as a critical device requirement (Section 1.2) with a target drift performance of ±2 mmHg per year. An experimental set up was required to measure drift over a period of 12 months to an accuracy of 1 mmHg.

2.2.1 Drift rig design

A drift rig was constructed to monitor static performance of a sample of the proposed ICP pressure sensors (P_{ICP}). To replicate the implanted environment the sensors were maintained hydrated, in the dark, at a stable temperature of 37 °C throughout the test period. To ensure this condition, individual P_{ICP} sensors were contained in test tubes containing saline (0.9 % NaCl) exposed to the atmosphere through a hydrophobic filter (to avoid evaporation) with the P_{ICP} catheter entering the test tube through a tuohy-borst sealable adapter. The tubes where inserted
in an aluminium block of a dry heater maintained at 37 degrees, with an associated temperature accuracy and spatial uniformity of ± 0.2 °C (GENIUS single block, Major Science). Figure 2-3 shows the sensor test tube set-up.

The pressure sensor is inserted with sufficient saline to cover the sensor to maintain its hydrated status while avoiding an additional head of pressure.

A total of eight P_{ICP} catheters were included in the rig. Individual circuit boards completed each bridge circuit and were cumulatively powered by a bench top power supply (HP U8002A). The individual circuit boards used two voltage regulators (MAX6018, Maxim Integrated and REF3312, Texas Instruments) to supply a 1.25 V bridge excitation source to the sensors. An instrumentation amplifier (INA333, Texas Instruments) was used to amplify the bridge signal and the amplifier output for each of the eight sensors was monitored using a stand-alone digital data logger (GL220, Graphtec). The data logger contained 10 input channels and a thermocouple was included in the rig to monitor temperature in an additional saline filled test tube following the set up illustrated in Figure 2-3. The final channel was used to monitor the bridge excitation voltage across the individual boards to monitor the stability of the conditioning circuitry. The heater block containing test tubes and the circuit boards with individual amplifiers were contained inside black boxes to shield from light and avoid any light sensitive changes in signals.
A digital absolute pressure transducer (Model CPT 6100, Mensor, TX, USA), with a total uncertainty of 0.010 % across the full measurement scale (calibration traceable to NIST) and accuracy of at least 0.03 mmHg, was used to compensate for atmospheric pressure against the P_{ICP}’s. The drift rig set up is summarised in Figure 2-4.

2.2.2 Data Acquisition

Prior to inclusion in the rig, all P_{ICP}’s underwent calibration testing to determine the individual coefficients for the voltage-pressure conversion. Calibration was carried out against the same high precision digital Mensor pressure sensor used to monitor atmospheric pressure in the rig (Model CPT 6100, Mensor, TX, USA). The Mensor pressure sensor and the P_{ICP} being tested were placed inside a sealed pressure chamber. All P_{ICP} sensors were hydrated for at least 48 hours prior to calibration. A pump attached through a valve to the chamber was used to apply both a positive and negative pressure, spanning -25 to + 75 mmHg relative to atmosphere. The valve was partially opened to allow the chamber to slowly de-pressurise (over approximately 20 minutes) while sampling the voltage output from P_{ICP} and the corresponding reference pressure from the Mensor sensor every 30 seconds through a LabView data acquisition program. Calibration coefficients were determined from a linear fit of the Mensor pressure and P_{ICP} voltage values. The process was repeated three times to obtain the final calibration coefficients. All tested P_{ICP}’s had a highly linear repeatable response with all coefficients repeatable to within two decimal places having an R^2 of at least 0.99.

The atmospheric pressure signal was sampled by the Mensor pressure sensor and transferred by RS-323 to a dedicated computer which recorded the sampled pressure via a LabView data acquisition program. Data was sampled continuously every ten minutes. This pressure sensor
and computer set up was located in an adjoining room to the drift rig with the txt file accessible on the local server.

The Graphtec data logger was set to obtain a sample from each $P_{ICP}$ every ten minutes and stored on USB. Approximately once every 3 weeks data was taken from the USB and transferred to computer for analysis. Graphtech software was used to read the logged data and convert to CSV for processing in MATLAB. During processing the calibration coefficients for voltage-to-pressure conversion were applied, and adjusted for atmospheric pressure to obtain a value for each $P_{ICP}$ of zero drift. The MATLAB output updated a log file of each channel’s raw voltage, associated pressure, and the corresponding time matched atmospheric pressure. The current drift in each sensor was also displayed on screen as a plot against time to allow for instant feedback on the progress of the rig. This process was carried out for a total of 397 days to determine the long term drift in the proposed ICP sensors.

### 2.2.3 Results

The pressure sensors varied in drift over the total 397 day test period. The rig provided a stable environment, with minor fluctuations in temperature and excitation voltage during the experiment. The test tube pressure sensor set up was effective at maintaining hydration while exposing the sensors to atmospheric pressure. Two periods of signal drop out occurred due to power outage causing a reset of the Graphtech logger and temporary loss of data. Despite the record of drift being lost during this time the sensors were continuously operating (excluding the <12 hour power shortage). A time course of the sensor pressure output is shown in Figure 2-5.

After 397 days, the average drift across the 8 sensors was 5.56 mmHg. Five out of the eight sensors had a final drift of less than 2 mmHg on day 397; the remaining three had a final drift more than 5 mmHg. The most stable sensor drifted a maximum of 1.8 mmHg over the 397 days, with a final day offset of only 0.05 mmHg. The most unstable sensor drifted a maximum of -19.7 mmHg with a final day drift of -18.1 mmHg. Three of the low drift sensors experienced a maximum drift above 2 mmHg at some stage during the experiment time course, however returned to under 2 mmHg by day 397. The final and maximum drift measured in the eight sensors is summarised in Table 2-2.
Chapter 2. ICP Device: Sensor performance and power source

<table>
<thead>
<tr>
<th>Pressure Sensor</th>
<th>Final drift on day 397 (mmHg)</th>
<th>Max drift seen (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.1958</td>
<td>-2.4</td>
</tr>
<tr>
<td>2</td>
<td><strong>-18.116</strong></td>
<td>-19.7</td>
</tr>
<tr>
<td>3</td>
<td>-0.4463</td>
<td>-1.9</td>
</tr>
<tr>
<td>4</td>
<td><strong>-14.589</strong></td>
<td>-14.9</td>
</tr>
<tr>
<td>5</td>
<td>-1.8523</td>
<td>-5.4</td>
</tr>
<tr>
<td>6</td>
<td><strong>-7.2005</strong></td>
<td>-8.2</td>
</tr>
<tr>
<td>7</td>
<td>0.0469</td>
<td>1.8</td>
</tr>
<tr>
<td>8</td>
<td>-1.8696</td>
<td>-3.3</td>
</tr>
</tbody>
</table>

Table 2-2: Summary of final and maximum drift seen in the eight sensors. Bold values demonstrate significant drift (> 2 mmHg).

Figure 2-5: Time course of the zero-drift across eight Millar 2 Fr pressure sensors testing in the dark at 37 °C for 397 days.

The drift was inconsistent and variable in both the negative and positive direction across the sensors and in individual sensors. The graph in Figure 2-6 demonstrates this through the non-accumulative drift per month for each sensor.
The dry bath temperature and excitation voltage remained stable during the experiment, with the fluctuations seen in the $P_{ICP}$’s independent of any temperature, voltage or atmospheric pressure fluctuations. Changes in environmental parameters over a four day period are shown in Figure 2-7. Over this interval, pressure measurements from the sensors fluctuated...
independently from the stable controlled parameters and without correlation to the ambient atmospheric pressure.

![Figure 2-7: Graph across four days of monitoring demonstrating drift in pressure sensor signals (blue), excitation voltage drift (red), dry bath temperature (black) and absolute atmospheric pressure (green).](image)

### 2.2.4 Discussion

Eight 2 Fr pressure sensing catheters were continuously run and sampled over a 397 day period. Two sensors revealed highly stable characteristics with a final and maximum drift of less than 2 mmHg, with a further two sensors drifting up to a maximum of 3.3 mmHg. The performance of these sensors indicate potential for long term monitoring of intracranial pressure, and significantly outperform the current expectations of acute ICP sensor drift which have been demonstrated to experience approximately 2 mmHg drift per week [41]. Two sensors performed particularly poorly, with final drift values approaching the maximum healthy ICP measurement range of 20 mmHg. However, evidence of this instability was clear in the initial 4 weeks of experimentation with both sensors drifting over 2 mmHg in the first month (Figure 2-5). This is encouraging due to the potential for a screening protocol to be used to eliminate sensors due to poor drift characteristics. The development of a sensor selection screening protocol for the chronic ICP application has the potential to improve the average long term drift of the proposed solid state pressure sensing catheter to within the precedent set by Raumedic.

Figure 2-7 demonstrates the rig provided a stable environment throughout the 397 day experiment period. There was no correlation of pressure catheter fluctuations with atmospheric pressure measurements, indicating the span calibration was accurate and stable. The difference
in the P_{ICP} sensors compared with the Mensor digital pressure sensor during the experiment can therefore be attributed to sensor zero drift.

Further work is required in order to determine if the 2 Fr Millar pressure sensor is appropriate for the long term ICP application. It is important that investigation is carried out into the origins of the sensor drift and particularly for evidence of physical discrepancies between sensors with significantly different drift characteristics. Examination of the catheters on day 397 revealed some condensation in the poorly performing sensors, which may indicate the drift is due to water ingress at the sensor tip. The highly stable sensors provide confidence that the Millar 2 Fr catheter could be a potential candidate for the long term implantable ICP device however further testing with a larger sensor sample size is required to establish confidence in the drift characteristics of the sensor and investigate the application of a short term (approximately one month) drift screening protocol to identify stable sensors.

2.3. Sensor sampling rate

The mean ICP value provides an indication of intracranial hypertension and is a key determinant of patient health, however further information can be gained through analysis of the ICP waveform which includes perturbations from the body’s respiratory and circulation systems. Waveform analysis requires the extraction of the amplitude and frequency of the distinct wave oscillations present in the ICP signal. An implantable ICP device with the potential to provide high fidelity signals for continuous waveform data display and analysis would give additional information to the clinician. Variations in pulse amplitude can provide crucial indications on the severity of intracranial hypertension, brain compliance and predict patient outcome [109]. Frequency domain analysis of the ICP waveform can be carried out on low sampling rates such as 25 Hz and the pulse, respiratory, and slow wave dynamics of the ICP signal can be extracted [32], [109]. However, recent work in time domain signal analysis reveals further information can be gathered by the fine structure of the ICP signal. The time domain analysis is more dependent on accurate reproduction of critical peaks in the ICP waveform than the frequency domain method and requires data sampled ideally at 100 Hz, with 50 Hz as a minimum and anything less requiring significant interpolation, risking loss of information [110]. The effect of the Millar 2 Fr pressure sensing catheter’s frequency response on accurately representing biological pressure signals was investigated using a theoretical assessment.
The maximum rate of change of the pressure signal (dP/dt max) depends on the amplitude and shape of the ICP waveform. In the intracranial hypertension or hydrocephalus condition, the ICP amplitude varies with pressure and brain health— with a low compliant brain under high ICP, waveform dynamics can reach up to 2.7 times the amplitude of normal arterial pulsations [7], [111]. The exponential craniospinal volume-pressure relationship dictates the CSF pulse pressure outlined by Avezaat et al and illustrated in Figure 2-8 [112]. The slope of the curve depends on the compliance of the brain, and thus the health of the patient. With the hydrocephalus condition and associated complications such as slit ventricle syndrome, severe pressure volume relationships are seen.

Traditional implantable pressure sensing catheters used throughout the literature in laboratory testing rely on a fluid filled catheter implanted in the region of interest coupled to a pressure sensor on the telemeter board. The frequency response of these fluid filled catheter telemetry solutions has previously been measured [113] and this method applied to the 2 Fr Millar catheter revealed a -3 dB frequency of 470 Hz [114]. This indicates the proposed sensor will be capable of accurately measuring the ICP signal at a sampling rate of 100 Hz without significant loss of information. The very high frequency response (-3dB 470 Hz) will provide
sufficient information for accurate time domain analysis of the fine structure of the waveform dynamics without loss of information or signal dampening.

A theoretical assessment of the ability of the pressure sensor to measure physiological pressures was made to investigate the limitations of the sensor and compare against available laboratory devices. The point at which an error will be introduced to an oscillating pressure signal was investigated to determine the limitations of the sensor. The frequency response of the 2 Fr Millar catheter based telemetry unit TRM54P (3 dB point 470 Hz) was compared against the Data Sciences International (DSI) C40 (3 dB point 40 Hz), C10 (3 dB point 57 Hz), HD-S21 (3 dB point 100 Hz) and the frequency response associated error for a pressure signal with a rate of change (dP/dt) up to 25,000 mmHg/s was modelled.

**2.3.1 Frequency response associated error**

MATLAB was used to generate fourth order Bessel filters with a frequency response corresponding to 1.5 times the -3 dB frequency for each sensor. A discrete series of ramp functions were simulated each representing an increasing transient peak in dP/dt (dP/dt max) and passed through each filter representing the four sensors for comparison. The dP/dt max of the resulting sensor/filter output was compared against the original input function to determine the frequency response associated error in the signal.

The effect of sensor frequency response on ability to accurately measure a step input is shown in Figure 2-9 for the three sensors.

![Figure 2-9: Frequency response effect on a step input (black) with the theoretical sensor output based off the -3 dB frequency for the 2 Fr Millar sensor (blue), DSI C10 (green) and DSI C40 (red).](image)
The dampening effect for specific rates of pressure change $dP/dt$ is shown in Figure 2-10. The 2 Fr Millar sensor based catheter TRM54P maintains an accurate representation of the test input signal through the range tested, and extends up to 50,000 mmHg/s before any drop off is seen. In contrast, the three remaining simulated telemeters introduce a dampening effect such that they begin underestimating the signal rate of change at 8,000 mmHg/s.

Figure 2-10: Frequency response dampening on a signal input of varying rate of change ($dP/dt$) for three pressure sensors; Millar 2 Fr sensor (●), DSI C40 (▼) and DSI C10 (○).

Results from the Bessel filter MATLAB model show that the solid-state telemeters have a sufficiently high frequency response to represent a high $dP/dt$ with a low predicted frequency response error without dampening the signal until well above 50,000 mmHg/s. The results provided the motivation behind performing chronic measurements of rat left ventricular pressure (LVP) for high accuracy recordings of LVP rate of change (LV $dP/dt$) during long term monitoring and drug interventions, which can reach above 20,000 mmHg/s described in Section 3.1.
2.4. Inductive power coil development

The animal monitoring telemeter shown in Figure 2-1 contains an implantable battery which is recharged through IPT where the secondary, implanted coil contains a ferrite core. By definition this structure is highly magnetic and acts to improve magnetic coupling between the primary and secondary coil. This is important in the animal laboratory application where animals are free to move and power is transferred from a large coil underneath the cage to the implanted device. However, this is an obvious obstruction to developing a clinical device to be MRI conditional. The highly magnetic ferrite structure would cause a significant static magnet induced force on the device introducing risk to the patient of injury through implant dislodgement. A ferrite-less IPT coil system was developed and tested in-vitro in anticipation of MR requirements in the clinical device. The coil was developed in anticipation of large animal experiments (Chapter 3) and testing the MRI interactions of the device (Chapter 5).

2.4.1 Specifications

Four key requirements were outlined for the ferrite-less inductive power based device to be developed. This stage of device development was assuming complete reliance on the IPT system, with no on board power storage. The system was developed with the aim of eventually testing in-vivo in an acute large animal study.

1. Sampling rate: Power consumption of the device would be highly dependent on the data sampling rate. In order to allow for waveform analysis (See 2.3) a minimum of 50 Hz and a target of 100 Hz was set.

2. Size constraints: Standard shunt and shunt accessory dimensions were used as limitations to the ICP device. In accordance with commercially available hydrocephalus shunt systems, the battery-less device was designed with the constraints of maximum implant height: 4.5 mm, and diameter: 14 mm, in accordance with these dimensions, limitations on the secondary coil were set at 12 mm diameter and 2 mm thickness.

3. Coil separation: As the secondary coil would be implanted in a relatively stable implant location directly under the skin, above the skull, coupling variation will be minimal. A worst case power transfer distance of 20 mm was targeted; this has been specified by Aschoff et al to be sufficient in 95% of cases, allowing for swelling and hematoma [19].

4. Communication method: Data transfer in the medical device industry is highly regulated with allocated bandwidths for vital, life dependent devices (Class III). The
ICP device will not be life dependent and at this stage the communications method used for the animal monitoring system will remain. This telemeter uses a commercially available Nordic 2.4 GHz wireless data transceiver, operating in the Industrial, Scientific and Medical (ISM) band.

2.4.2 Coil design

A ferrite-based inductive power coil was designed as the exclusive power source for a battery less implantable mouse telemeter as developed by Daniel McCormick et al [115], [116]. This device was considered similar in function to what would be required of a stand-alone ICP device and forms the technology platform which would be further adapted for the ICP application. The telemeter contains the rectifier and power management circuitry required to convert the received AC power to DC and provide a stable supply to the pressure sensor conditioning and Nordic antenna circuits. The ferrite-less secondary coil was designed as a planar spiral “pancake” coil, a low profile design for implantation outside the skull. An appropriate primary coil was also constructed. Based on a sample rate of 100 Hz, and the power requirements of the Nordic 2.4 GHz antenna, the electrical current budget for the device was determined. The Nordic transceiver and microprocessor would utilise approximately 4 mA when actively transmitting data sampled at 100 Hz. Allowing for additional circuit losses (mostly in the secondary coil) and an average component circuit requirement of 4 V, the power output requirement of the secondary implanted coil was set to 40 mW.

The coil system was designed to power the small animal telemeter during future acute experiments. For this application, the primary coil power supply would come from a bench top system utilising a commercially available half bridge inverter and bench top signal generator to drive the coil. This placed little restriction on the primary side and work focussed on establishing a ferrite-less secondary coil to fit within the restraints of a potential ICP device. The coil was required to supply adequate power to operate the telemeter via the lightly restricted primary source. The design process utilised established protocols for basic IPT systems. A brief overview of the fundamentals of IPT is given.

2.4.3 Background

An equivalent circuit diagram of IPT is shown in Figure 2-11. In IPT systems, electrical energy is transferred between two magnetically coupled coils (represented by their inductance; $L_1$, $L_2$). IPT achieves near field wireless transmission of electrical energy between two circuits without
physical contact, and can be used to provide power to devices implanted near the skin surface, as in the ICP application.

![Figure 2-11: IPT equivalent circuit](image)

For the ICP application resonant IPT was used, with appropriate capacitors added to the primary ($C_1$) and secondary ($C_2$) coils to form resonant $RLC$ circuits in order to cancel their imaginary impedance such that power transfer was enhanced [117]. Parallel tuning of the secondary was used to boost the potential induced in the secondary such that a design with an achievable number of turns was created. Figure 2-11 shows a loosely coupled IPT system where mutual inductance has been replaced with a current controlled voltage source. When the systems act in resonance, $L_2$ and $C_2$ cancel each other out leaving only the resistive elements.

The coupling coefficient, $k$, defines the ratio between mutual ($M$) and self-inductances of the primary and secondary coils. In a perfect transformer, the coupling coefficient is one and all magnetic flux from the primary is linked to the secondary. For a small implanted device, $k \ll 1$ as only a small fraction of the total primary induced flux passes through the secondary. The coupling coefficient is defined by:

$$ k \equiv \frac{M}{\sqrt{L_1L_2}} \quad (2.1) $$

Optimum power pickup can be achieved through impedance matching of the pickup coil loses $R_2$ to the load resistance. The coil impedance can be controlled through the number of turns in the coil, $N_2$. The quality factor $Q$ of a coil provides an indication of its efficiency through a ratio of its imaginary to real impedance and is given by:

$$ Q \equiv \frac{\omega L}{R} \quad (2.2) $$

Where $R$ is the frequency dependent equivalent series resistance (ESR) of the coil. With increasing frequency, $Q$ rises, however when parasitic capacitance is involved the effective $Q$: $Q'$, will decrease when approaching its self-resonant frequency [117].
Optimisation of IPT systems involves maximising the $k$ within the constraints of the device and power supply system through consideration of $N$, the number of turns in each coil, the operating frequency, and the load resistance. Specific to the application, optimisation may include a trade-off for improved adaptation to coupling variations. For this stage of development, a set of coils was developed to supply sufficient power for acute large animal experiments and provide a guide for MRI investigations, without completing an optimisation analysis.

2.4.2.2 Method

For the ICP application, the primary coil was developed given the constraints on the secondary size. A starting point of the individual coil geometries was given by the $k$ optimisation carried out by Harrison et al [118]. The method considered Soma’s exact expression for mutual inductance of two aligned circular filaments [119] and Lyles method for approximation of spiral coils as circular filaments from 1902 [120] to determine coil set design parameters based on the expected limitations of implanted biomedical systems – the distance required to transmit power; the minimum coil-to-coil spacing distance ($z$), and the size of the implanted pick up coil; maximum outer diameter of the secondary coil ($d_{2\text{out}}$). For the ICP application, $z = 20 \text{ mm}$, $d_{2\text{out}} = 12 \text{ mm}$. Harrison et al found for a given ratio of $\frac{z}{d_{2\text{out}}}$ it is possible to determine the outer diameter of the external primary coil ($d_{1\text{out}}$), the inner diameter of the external primary coil ($d_{1\text{in}}$), and the ratio of implanted secondary coil inner and outer diameter ($\frac{d_{2\text{in}}}{d_{2\text{out}}}$) that maximise the coupling coefficient, $k$. For the ICP application, using an estimated $\frac{z}{d_{2\text{out}}}$ of 1.67, initial design values were obtained for the ICP ferrite-less IPT system where $z = 20 \text{ mm}$, $d_{2\text{out}} = 12 \text{ mm}$, $d_{2\text{in}} = 9 \text{ mm}$, $d_{1\text{out}} = 60 \text{ mm}$, $d_{1\text{in}} = 11 \text{ mm}$.

The initial design values were used as a starting point to construct a set of coils which were iteratively adapted to achieve the desired power transfer for implantable telemeter. Both the primary and secondary coils were constructed of Litz wire where multiple, individually insulated, thin copper wires are twisted together in a uniform pattern. Litz wire minimises power losses due to the skin and proximity effect through increasing the surface area with minimal increase in conductor size and achieving approximately equal strand currents, respectively. The skin effect is also dependent on the frequency acting through the wire, and wire gauge thicknesses are recommended for a given operating frequency. A strand diameter of 0.1 mm was used in the coil construction, to allow for an operating frequency of
approximately 200 kHz [121], as used in the existing Millar animal telemetry monitoring system [108]. Type 2 Litz wire was used for construction of the primary coil [122]. For the secondary coil, the Litz wire was deconstructed for the desired strand number and thickness.

During the iterative process, the coils were constructed and the inductance and series resistance determined using a RCL meter (Fluke PM6306). The resonant frequency of an LC circuit in Hz can be determined approximately by (ignoring parasitic capacitance and the loading of the implant):

\[ f_0 = \frac{1}{2\pi \sqrt{LC}} \]  

(2.3)

Appropriate capacitors were used to tune and match the primary and secondary RLC circuits to an initial operating frequency of 200 kHz as according to the above equation. Once the operating coil set was constructed, the system operating frequency and secondary coil were refined by considering the figure of merit, \( X \), as in Lenaerts et al’s Inductive Link Design [117].

The method defines a system figure of merit, \( X \) [117]:

\[ X = k^2 Q_1 Q_2 \]  

(2.4)

This can be expressed in single turn equivalencies of the primary and secondary circuits:

\[ X = \frac{\omega^2 M_0^2}{R_{10} R_{20}} \]  

(2.5)

Where \( R_{10} \) and \( R_{20} \) are the single turn ESR values of the primary and secondary coils respectively, \( M_0 \) is their mutual inductance, and \( \omega \) is the operating frequency of the IPT system. McCormick applied the system of merit theory to loosely coupled systems, such as implantable devices, where the secondary pickup coil is typically of much smaller size than the external primary coil and the coupling between the two is very small. The system figure of merit can then be expressed in terms of the primary single turn field strength (\( B_0 \)) and resistance (\( R_{10} \)) and the secondary coil area (\( A_c \)) and resistance (\( R_{20} \)) [115]:

\[ X = \omega^2 X_1 X_2 = \frac{\omega^2 B_0^2 A_c^2}{R_{10} R_{20}} \]  

(2.6)
Given the constructed coil set’s variables were fixed, the system figure of merit was considered proportional to $\frac{\omega^2}{R_{10}R_{20}}$. The final operating frequency was determined by performing a frequency sweep of the coil parameters ($L, R$) from 150 – 520 kHz on the RCL meter. This data was used to determine the frequency that provided highest effective figure of merit.

2.4.2.3 Results

Throughout the iterative process design was guided by the ability of the coil systems to provide adequate power to the telemeter over the required distance. The final coil set provided steady 40 mW across 20 mm to the telemeter off a bench top supply of on average 1 W (depending on coil alignment) corresponding to an overall efficiency of 5%.

Design of the primary coil was unrestrained as it was driven by a bench top power supply (Agilent HP E3610A) and commercially available half bridge inverter circuit (Efficient power conversion, EPC9001). This supply was used for the bench top development and subsequent acute animal experiments with the ferrite-less IPT system (Section 3.2). The final design consisted of a double layer coil of 14 total turns of Type 2 440 strand 40 AWG Litz wire with 1 m leads to allow for powering off the bench top supply during acute surgery. The coil’s parameters were $L_{1°} = 8 \mu H$, $d_{1°\text{out}} = 52 \text{ mm}$, $d_{1°\text{in}} = 12 \text{ mm}$, and an equivalent series resistance (ESR) at 200 kHz of $R_{1°} = 34 \text{ m}\Omega$. This corresponded to a series tuning capacitance $C_{1°} = 98 \text{ nF}$. The secondary coil was constructed beginning with the initial k optimised design values and then iteratively testing and tuning combinations of wire bundle size and turn number for performance with the primary. A coil constructed with 15 strands of individual Litz wire and 22 turns was selected with associated parameters of $d_{2°\text{out}} = 12 \text{ mm}$, $d_{2°\text{in}} = 8 \text{ mm}$, $L_{2°} = 5.62 \mu H$, $R_{2°} = 242 \text{ m}\Omega$. Based on the frequency sweep and analysis of the system figure of merit, the coils were re-tuned to ultimately operate at 320 kHz. The final coil set is shown in Figure 2-12.
2. ICP Device: Sensor performance and power source

Figure 2-12: Ferrite-less inductive power coil set. Secondary coil of 12 mm outer diameter shown on left hand side.

The coil systems were designed off basic optimisation methods and theory, however the iterative physical coil construction and outcome of power testing was the main design guidance. This solution is adequate for the initial application of acute large animal testing, but is far from optimised, as evident in the low efficiency. Future development is required to investigate heating associated with the miniature ferrite-less IPT system. If necessary, losses in the secondary coil generating heat can be reduced, but this may impact the size of the coil. There is plenty of scope, and fewer constraints, for improving the design of the primary system. It is expected that an overall efficiency in the range of 10-20% is achievable for similar implanted devices [118]. This will be useful to advance in-vivo testing from acute, laboratory controlled experimentation to freely moving animals where a portable primary system will be required.

2.5. Implications for lifetime ICP monitoring

The in-vitro testing described throughout this chapter investigated the 2 Fr implantable pressure sensor’s performance and developed a ferrite-less inductive power coil set for future in-vivo testing. The sensor stability results demonstrate a variation in performance across a sensor sample size of eight. Sensors with high drift demonstrated this in the initial month of testing providing evidence that a sensor screening protocol may be able to identify sensors unsuitable for use in the implantable device through a short term drift monitoring period. The analysis of sensor drift is on-going and will be a key determinant of the ICP device; however these initial results provide confidence in the Millar 2 Fr catheter as a potential candidate. The frequency response of the sensor exceeds basic requirements for the ICP application and provides the potential for clinicians or researchers to perform full time domain ICP wave form analysis. In
Chapter 2. ICP Device: Sensor performance and power source

anticipation of the clinical device targeting MRI conditional approval, a ferrite-less inductive power pickup was developed to provide power to the established laboratory animal telemeters developed by Millar.

By using the animal monitoring telemetry platform, in-vivo performance of the sensor can now be investigated with an implant containing key technologies for an implantable clinical device. Large animal studies will be a key stage in demonstrating the future clinical devices performance. This will be carried out in sheep with three stages; initial acute experimentation to develop surgical techniques and test the technology in-vivo, recovery chronic (approximately 3 week) testing where the animals are housed in the laboratory, and a final long term (approximately 3 month) experiment where animals are released on a farm with the implant to perform normal daily activities with periodic ICP measurements taken. Initial acute experiments are described in Chapter 3. Further development of the device is required before progressing to chronic implantation including optimisation of the inductive power system, external reader development and investigation into alternative encapsulation and communication techniques specific to the clinical application.
3. In-vivo Monitoring

The work in Chapter 2 developed and demonstrated that the pressure sensing and implanted telemetry technology has potential for long term implantation. The next step was to investigate the performance and stability of the technology while implanted in animal models.

The rat model is widely used in physiology, particularly for cardiac studies. Left ventricular pressure (LVP) provides valuable information about cardiac health, and the high fidelity of the Millar pressure sensor makes it particularly suitable for the novel application of making chronic recordings of rat LVP and its first derivative, LVP dP/dt, an indicator of contractility. This pressure signal has a much higher amplitude (from 0 – 200 mmHg maximum) and frequency (order of 300 bpm) than the ICP signal the device is targeting. This provides a challenging environment to test the in-vivo sensor performance and will provide confidence in the technology moving forward. The signal is also well characterised and understood, with comprehensively studied drug interventions using acute monitors throughout the literature. The implant was tested for up to 3 months in a rat model to monitor LVP.

Acute sheep in vivo studies were also carried out to demonstrate the sensor and technology’s ability to measure ICP specifically. The sheep brain is of comparable size to human with a similar pressure range. This acute experiment provides the opportunity to develop the surgical techniques required to locate the ventricles and test the telemetry ICP signal against a simultaneously measured gold standard acute transcutaneous pressure sensor. The new, ferrite-less inductive power coil system developed for the ICP device in anticipation of MRI compatibility (Chapter 2) was used to test its ability to adequately power the device through skin. These acute experiments were seen as the first step before the final ICP device could be chronically implanted in a large animal model for long term testing.

3.1. Chronic rat LVP

The devices used in the chronic rat LVP experiment were from the TRM54 series telemeter (Millar Inc., Auckland). The telemetry system is well established with the technology used for freely moving laboratory animal monitoring of arterial pressure and alternative sensors used
for additional measurements such as bio potential and oxygen. The series used throughout the LVP experiments all utilised the 2 Fr pressure sensor investigated in Chapter 2. The technology platform and animal model allowed for the performance of the pressure sensing catheter itself to be isolated for investigating its potential as a sensor for chronic ICP monitoring.

Measurement of rat LVP provides a well understood signal which can be used as an indicator for general cardiovascular health and performance through to assessing the safety of therapeutic compounds. An important index of contractility, the first derivative of ventricular pressure (dP/dt), can be obtained by directly inserting a sensor into the left ventricle (LV) [123]. Prior to this study, the measurement was commonplace in anesthetised rodents however there was little literature in the freely moving, chronic condition [124]–[126]. The traditional approach of placing a sensor in the LV through the carotid and aortic valve is not suitable for chronic experimentation due to potential valve damage [127].

A previously described surgical approach through the diaphragm and apex of the LV was refined and adapted for long term implantation [124], [126]. The high frequency response for the pressure sensor (3 dB point 470 Hz) compared to existing fluid filled telemetry options (3dB point 30-100 Hz) demonstrated its suitability for providing accurate measurements of dP/dt (see Chapter 2). Previous attempts have reported a wide range between 5000 – 13000 mmHg/s, suggesting an error may be introduced with traditional gel-filled catheter pressure sensors and their associated lower frequency response [128], [129].

The solid state pressure sensor was tested while implanted for up to 3 months in 14 rats. Drug interventions demonstrated the sensor’s ability to adapt to a wider range of pressures and continue to provide stable measurements over time. The biocompatibility of the sensor in the implantation environment was assessed by inspection of tissue growth and visualisation of cardiac function (via ultrasound) pre- and post-implantation.

3.1.1 Technology and data acquisition

The telemetry unit consists of the 2 Fr pressure sensor, a rechargeable battery, 2.4 GHz wireless communications antenna, a ferrite core inductive power coil, and associated signal conditioning circuitry. Three configurations of telemeter were used, the single pressure sensor TRM54P, dual pressure (for simultaneous LVP and BP) TRM54PP, or pressure and bio potential (for simultaneous LVP and ECG) TRM54PB.
The battery was charged by an inductive pad (TR180 SmartPad, Millar Inc., Auckland, New Zealand) placed under the individual animal’s cage [130]. The pad doubled as a receiver for the LVP signals which were sampled at 1 kHz using a PowerLab data acquisition unit and LabChart software (v7.3.5, ADInstruments, Sydney, Australia).

3.1.2 LVP sensor implantation
Two groups of male Wistar rats were used to a) develop the surgical methods and test the sensor’s response to drug induced changes in cardiac function (Group A) and b) to test the long term performance of the sensor using the established surgical method (Group B). Group A contained 11 rats with initial weights of 300-320 g, and Group B contained 12 rats with initial weights of 281-385 g. All animals were approved by the University of Auckland Ethics Committee. The animals were housed individually in a room with stable temperature (22 °C), a 12hr-12hr dark-light cycle, and had free access to food and water.

The sensor implantation surgery used a trans-diaphragmatic approach. Animals were initially anaesthetized by inhalation of 4% isoflurane in 2L/min O₂, followed by intubation, mechanical ventilation and maintenance with 2% isoflurane. Antibiotic (Groups A & B: Baytril, enrofloxacin; Bayer, Auckland, NZ; Group C: Penject, penicillin G procaine; Butler Animal Health Supply, US) and analgesia (Temgesic, Buprenorphine; Reckitt Benckiser, US) were given subcutaneously before the beginning of surgery. The telemeter body was implanted in the abdomen with the pressure sensor in the LV. A 2.5 cm abdominal midline incision was made in the skin from the xyphoid process and between the underlying abdominal muscles. A piece of saline-soaked gauze was used to protect exposed organs in the abdomen. A suture though the xyphoid process allowed for gentle retraction to give a better view of the diaphragm. An incision was made in the diaphragm exposing the apex of the heart. A shallow suture was made in the apex of the heart to gently retract and stabilize the heart. A 23 G needle was used to form a hole in the apex of the heart through which the pressure sensor was inserted into the left ventricle. At this point the telemeter was turned on and the signal observed on a nearby computer while manoeuvring the catheter tip to ensure the pressure sensing element of the catheter was inside the ventricular chamber and measuring a typical LVP waveform.

In order to stabilise the pressure sensor in the heart and avoid it being retracted as the heart beats over time and falling out, a variety of surgical techniques were investigated in Group A. A combination of a suture cuff and purse string was found to be the most reliable and used for all animals in Group B. The suture cuff involves wrapping the suture thread around the catheter
several times 10 mm from the tip of the catheter and gluing it in place prior to surgery. This marked the insertion depth of the catheter which placed the pressure sensor in the wide, base region of the LV and the cuff acted as a stopper once secured in the heart. The purse string helped secure the catheter by using a series of shallow stitches in the myocardium surrounding the catheter which were gently tightened to restrict movement.

Once the pressure sensor was in place, the diaphragm was sutured closed around the catheter. Before the final suture was pulled tight the exhaust of the ventilator was temporarily blocked to inflate the lungs. The stitch was closed while simultaneously withdrawing and suctioning excess air using an empty syringe in the remaining hole. A mesh pouch was used to surround the telemeter body and secure it in place in the abdominal muscle wall. The muscle layer incision was then sutured closed and the skin incision closed with staples.

Animals were left in a heated recovery box overnight before being placed in their cage for recordings. Treatment with analgesia (Buprenorphine) was continued for 2 days post-surgery. A subset of Group A animals (n = 6) underwent cardiac ultrasonography (Sonosite MicroMaxx (USA) with 12 MHz sector transducer) prior to surgery, and at least 4 weeks post-surgery to determine fractional shortening (from m-mode) and fractional area change (from short axis images). Ultrasonography results were used to investigate the surgery/implant’s effect on cardiac function.

3.1.3 Experimental protocol

3.1.3.1. Drug induced changes in LVP – Group A

The sensitivity of the sensor to changes in dP/dt was tested by administering the Ca\textsuperscript{2+} channel blocker verapamil (10 mg/kg s.c.) or the β-adrenergic-agonist isoproterenol (10 µg/kg s.c.). Drug induced changes were carried out a minimum of 2 weeks following implantation surgery. The drugs were selected to induce a short-term, less than 2 hour, change in heart function. Continuous recordings were made during drug interventions for 30 minutes prior, and 90 minutes post administration. There was a rest period of at least 2 days in between any drug doses for an individual animal. For analysis, an average of 10 minutes of continuous data for each variable was taken from the baseline period and a steady-state maximum change period after administration. Data from the same 10 minute periods were used to plot beat-by-beat data for each drug. The second cardiac ultrasonography from 6 animals in Group A was obtained a
minimum of 4 weeks following surgery and 2 days following administration of the short term drugs.

During standard recording times (i.e., no drugs being administered) 5 minutes of data were collected every hour for up to 28 days when the animals were euthanized by sodium pentobarbital overdose (150 mg i.p). Telemeters were explanted, cleaned in enzymatic detergents and sterilised for re-implantation. During any drug interventions, the data were continuously collected. It had been previously demonstrated that scheduled acquisition accurately reflected mean arterial pressure and other cardiovascular variables through blood pressure monitoring [131]. However, Group A revealed some problems with non-physiological noise and spikes on the LVP pressure signal coinciding with the 5 minute sampling periods (described further in results).

3.1.3.2. Chronic LVP recordings – Group B

Animals in Group B were monitored continuously throughout the implantation period. Data from animals from Group B were used to investigate the sensor’s stability in the implanted environment (with no drug interactions) and to investigate chronic measurements of dP/dt with the high fidelity sensor for accurate reporting of circadian variation.

After 28-40 days of implantation, Group B animals underwent a second round of isoflurane anaesthesia, such that a 2 Fr acute Millar catheter could also be inserted into the LV via the right carotid artery (SPR-671, Millar Instruments). This allowed for simultaneous LVP recordings to be made under anaesthesia allowing for direct comparison of the telemeter pressure signal’s performance against the acute gold standard. After several minutes of recording, the rats were euthanized by overdose of pentobarbitone (150 mg i.p.).

3.1.4 Chronic LVP results

3.1.4.1 Signal quality

Cardiac ultrasonography results from 6 of the Group A rodents showed the LVP surgery or presence of the sensor in the heart did not significantly affect cardiac function. The average fractional shortening before LVP surgery was 49.2 ±4.2% and 3-4 weeks post-surgery, 47.9 ±2.5 (mean ± SEM, P>0.05). The average fractional area change was 67.9 ±2.5% before surgery and 66.4 ±2.1% (P>0.05) post-surgery. At explantation of the telemeters the hearts looked normal with no obvious external abnormalities. Of the 26 rats that underwent LVP
sensor implantation for this study, only one animal (from group A) was euthanized due to poor health. This was two days post-surgery and the cause of the problem could not be identified.

Despite viewing the LVP signal during the surgery it was observed across all groups that in some animals the signal displayed unusual waveforms. It appeared that the pressure sensor placement had a significant effect on the quality of the waveform obtained. Figure 3-1 demonstrates the range of the waveforms observed.

![Figure 3-1: Four patterns of LVP waveforms (upper trace) observed during the study and their corresponding LV dP/dt (lower trace). Dotted lined indicate where the maximum dP/dt occurred on the LVP waveform.](image)

The "normal" LVP, shown in Figure 3-1 panel a), has a waveform that is almost square and the maximum point on dP/dt occurs on the upstroke of the LVP waveform. Figure 3-1 panels b), c) and d) contain abnormal “spikes” which are assumed to be from the heart muscle contracting against the pressure sensing element. At least one of these waveform variations was occasionally observed in each animal. Different LVP waveforms could be seen in single animals if the catheter had not been fully secured in place and it moved over the course of the study. This was particularly evident in the first few surgeries performed where tissue adhesive was used to secure the catheter. In some cases, non-ideal LVP waveforms could still be used...
for measuring the $dP/dt$ max which was often unaffected by the "spike" in the waveform during systole. Whether or not a non-ideal LVP waveform influenced $dP/dt$ max depended on the timing of $dP/dt$ max relative to the LVP shape.

Data were excluded from further analysis if the abnormal waveform influenced the $dP/dt$ max. Panel b) shows an LVP waveform with a spike occurring on the LVP down-stroke. This does not influence $dP/dt$ max, and contractility data from these waveforms was considered valid. In panels c) and d) the $dP/dt$ max occurs during the spike, typically giving abnormally large values of $dP/dt$ max. Therefore, periods of data with these waveform types were excluded. In general, if there was an abnormal “spike” in a LVP waveform which caused a $dP/dt$ value greater than the physiological $dP/dt$ max (occurring during LVP upstroke), data would be excluded.

At post-mortem of the rats in Group B, the heart tissue was carefully dissected away to allow visualisation of the pressure sensor tip. Of the 12 rats implanted in this group, 2 had the tips completely buried in the LV wall and 2 were held against the wall by tissue. The LVP waveforms from these rats were found to have the most frequent unusual shapes of Group B including spikes as shown in Figure 3-1 and also periods when the whole waveform was offset by up to 20mmHg. Data from these 4 rats were excluded from further analysis. Two further animals had small bumps of tissue visible on the LV wall suggesting that the tip of the catheter may have been hitting the LV wall. From the included 8 rats from Group B, no difference was found between the telemeter and acute catheter measurements of EDP ($7.8 ± 1.4$ vs. $8.2 ± 0.9$ mmHg, $P=0.74$), LVP max ($104.0 ± 3.1$ vs. $101.5 ± 2.2$ mmHg, $P=0.29$) and minimum LVP ($0.0 ± 1.8$ vs. $0.2 ± 0.7$ mmHg, $P=0.86$). In group A, drug response data was included for animals who displayed none of the unusual waveforms as seen in Figure 3-1 during the drug response data recording period. Out of the 14 animals in Group A, 6 provided sufficiently stable drug response waveforms resulting in 4 animals per drug (see 3.1.4.3).

### 3.1.4.2 Chronic Data

For Group B animals, 7 out of a total of 12 LVP surgeries were considered successful based on post-mortem position of the pressure sensor tip and providing stable LVP signals throughout the majority of the implantation periods (28 to 40 days). LVP max, EDP, HR and $dP/dt$ max were monitored in each animal. From the 7 successful preparations, an average (mean ±SEM) LVP max of $118 ±2$ mmHg, EDP of $8.2 ±1.4$ mmHg, HR of $303 ±4$ bpm, $dP/dt$ max of $9444 ±363$ mmHg/s and $dP/dt$ min of $-7793 ±182$ mmHg/s was measured in the day time data in this group.
The variation in these parameters over 28 days in one animal is shown in Figure 3-2.

From this single animal recording it is clear that a circadian variation in contractility parameter dP/dt max and heart rate is fully established approximately 10 days following surgery. The mean dP/dt max, dP/dt min, heart rate, EDP and LVP max for this animal over the course of implantation (28 days) was 10516 mmHg/s, -8611 mmHg/s, 344 bpm, 6 mmHg and 117 mmHg respectively.
In each animal there was evidence of a circadian variation in \( \frac{d\text{P}}{dt} \) max, HR, and EDP, emerging between 3-7 days after surgery (\( P<0.05 \) by paired T-test). Figure 3-3 shows the circadian variation seen across the 7 animals over 24 hours.

There was visible peak in the circadian data at 9-10 am, which is the time the lab technician cleaned the cages and weighed the animals each day. The 9 and 10 am data points were therefore excluded from the light to dark differences. The average difference of the dark period

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**Figure 3-3:** Circadian variation in LVP max (a), EDP (b), \( \frac{d\text{P}}{dt} \) max (c), \( \frac{d\text{P}}{dt} \) min (d) and HR (e) across 24 hours. Each point is the mean ± SEM per hour across 5 days in 7 animals.
to the light period was $+918 \pm 84\text{mmHg/s}$ for LV dP/dt max, $-675 \pm 85 \text{mmHg/s}$ for LV dP/dt min, $+38 \pm 3 \text{bpm}$ for heart rate. There was no circadian influence on LVP max and EDP.

### 3.1.4.3. Drug induced changes in LVP

For Group A, 8 of the 11 surgeries were considered successful giving good LVP signals throughout the majority of the implantation periods (28 to 44 days). One of the 3 animals with unsuccessful surgery had a consistently bad signal, attributed to poor placement of the catheter in the heart and was euthanized 12 days after surgery. The remaining two animals’ catheters pulled out of the heart early after 9 and 13 days of implantation. These animals were both early in the model development with only tissue adhesive used to secure the catheter.

In subsequent analysis the data were included only if the waveform shape was deemed to be acceptable. In Group A, the maximum effect of the drugs was observed 30-60 minutes after drug administration. The typical response from a single animal to the different compounds administered is shown in Figure 3-4.
Figure 3-4: Bowditch plots of an individual animal’s response to subcutaneous injection of a) 10 mg/kg verapamil and b) 10 µg/kg isoproterenol. HR and dP/dt were measured from 10 min of control data prior to injection (closed circles) and 10 min of post injection drug data (open circles) when the maximum effect was observed.

The average effect on the 8 animals included in Group A’s drug induced changes analysis is shown in Figure 3-5. Verapamil increased heart rate from 285 ±8 to 340 ±4 bpm ($P<0.05$ by paired T-Test), with a decrease in the dP/dt max from 10107 ±550 to 6102 ±899 mmHg/s ($P<0.05$). Isoproterenol increased both heart rate (320 ±16 to 498 ±23 bpm) and dP/dt max (9380 ±923 to 16110 ±2283 mmHg/s) ($P<0.05$).
Figure 3-5: Response to subcutaneous injection of a) verapamil (10 mg/kg, n = 4) and b) isoproterenol (10 µg/kg, n = 4) as measured by the pressure sensor implanted in the LV. Data is the mean across n animals from 10 minutes of data prior to injection (closed circle) and post injection when the maximum effect was observed (open circle).

3.1.5 Rat LVP discussion

This study tested the performance of the pressure sensor in the highly demanding, reasonably long-term implanted environment. The blood implant environment is likely to be more challenging than CSF due to the additional risk of clots causing biocompatibility complications.

A reliable surgical approach for the chronic implantation of a pressure sensor in the rat LV was established using a 2 Fr implantable pressure sensor. Stable LVP signals were recorded for the duration of the study (up to 40 days), with accurate measurements of dP/dt made due to the high frequency response of the sensor. This revealed a strong circadian variation in dP/dt. Pronounced changes in the contractility index dP/dt max were measured (from -6,000 to
+13,000 mmHg/s) by drug induced changes. The validation of the surgery and technology confirms use of the high-fidelity pressure sensing telemetry for chronically, and accurately, monitoring cardiac function in the conscious, freely moving rat.

While there have been previous reports of LVP measurement [124]–[126], [128], [129], [132]–[134], few include data from conscious, unrestrained rodents and the dP/dt values reported (up to 13,000 mmHg/s) could be significantly underestimated, possibly by up to 60%, due to the fluid filled catheter approach. Sato et al. monitored LVP in the conscious rat for up to two weeks using DSI C40 pressure transmitters with a reported circadian variation from light to dark in dP/dt max of approximately 500 mmHg/s and in heart rate variation of +54 bpm [126]. Our results showed a mean value of LV dP/dt max of 9443 mmHg/s and 10361 mmHg/s for light and dark phases and a difference in heart rate of +38 bpm. While the circadian variation in heart rate in our study is less than that of Sato the circadian variation in dP/dt max of 918 mmHg/s is larger and the dP/dt max is consistently larger in both the light and dark periods. From our analysis of frequency-response associated error in the different pressure transmitters (Section 2.3.1) we propose that the pressure telemeter used by Sato et al. may potentially have an error of >1370 mmHg/s at a dP/dt max of 10,000 mmHg/s (>14%). It is expected this would have significantly damped the circadian variation recorded during the higher-intensity dark phase. In comparison, the high-fidelity sensor used in our study has a frequency response associated error of 80 mmHg/s (<1%) at dP/dt levels of 10,000 mmHg/s (Section 2.3.1). The high frequency response of the solid-state telemeter allows for a more accurate measure of the circadian variation in dP/dt max to be obtained. Our results show a circadian variation in the contractility parameter LV dP/dt max much greater than that which has previously been reported.

A recent study by Adeyemi et al. examined the use of the QA interval (interval between the Q wave derived from the ECG and the onset of the arterial pressure waveform) as a measure of cardiac contractility by comparing how the QA interval changed in response to drug administration against how LV dP/dt max changed [124]. Fluid-filled catheter based pressure telemetry was used to measure LVP (DSI C10) in a separate group of animals to those implanted with aortic pressure and ECG telemetry. Due to the nature of the increasing frequency response error with increasing contractility, baseline measures of dP/dt max in that study are likely to be accurate, but when drugs were used to increase dP/dt max up to 12,000 mmHg/s there is an estimated corresponding error of 800 mmHg/s for the C10 transmitter. As a result, there may have been some dampening of the drug’s effect on dP/dt max which could...
introduce error in the correlation between changes in $dP/dt$ being reflected in changes in the QA interval. This would have significant consequences when using such results to provide an estimate of $dP/dt$.

In conclusion, this study has demonstrated the ability of a new solid-state pressure sensor to chronically and accurately measure LVP and LV $dP/dt$ in conscious, freely moving rats over long periods of time. Combined with a further third group of animals from another research institute, results from this study was published as “Chronic Measurement of Left Ventricular Pressure in Freely Moving Rats” in the Journal of Applied Physiology [135]. The circadian variation and drug induced changes have been measured to a resolution finer than the frequency response associated error in fluid-filled catheter based pressure sensor telemeters. The surgical approach did not influence contractility and was refined to ensure interference free, LVP waveforms could be obtained for extended periods. We propose this technique, and associated data provides the basis for examining cardiac function in a variety of research paradigms including drug evaluation and basic research with disease models. No adverse reactions were seen due to the implantation; the sensor was stable and accurately measured the demanding LVP signal. This demonstrates the sensor has potential for ICP measurement.

### 3.2. Acute sheep ICP

The rat LVP study utilised Millar’s established animal implant monitoring technology platform to rigorously test the performance of the pressure sensing catheter in the in-vivo environment. The performance of the sensor alone was able to be isolated and results support the bench top experiments (Chapter 2) in demonstrating the capability of the sensor for the chronic ICP application.

The next step was to use the sensor and telemetry system for measuring ICP in a large animal model. This experiment used the 2 Fr sensor which has been extensively tested throughout Chapter 2 and in the rat LVP model. It also tested the ability of the ferrite-less inductive power coil developed in Chapter 2 to transfer adequate power through the sheep’s skin to run the device. Remaining components of the implantable electronics unit were based on a battery-less mouse telemeter – 2.4 GHz Nordic communications antenna, IPT power only signal conditioning and solid state sensor amplification circuitry.

Methods for ICP implantation and ventricular catheter insertion were carried out following procedures developed for chronic testing in the literature [46], [57], [136] in order to establish
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the procedure for future, recoverable experiments. The sheep model was chosen due to its comparable size and ICP range with the human brain and potential for future chronic experiments including kaolin-induced hydrocephalus in the sheep [137].

3.2.1 Experimental protocol

The aims of this experiment were to develop the surgical method for implanting an ICP sensor in the sheep brain, locate the lateral ventricles for insertion of a ventricular catheter to allow acute changes in ICP to be induced by infusion or withdrawal of cerebral spinal fluid (CSF), test the ferrite-less ICP coil developed in Chapter 2, and demonstrate the system’s ability to measure ICP across the average range in a human suffering hydrocephalus (-15 to 50 mmHg).

ICP was measured by two means; the telemeter-based measurement (ICP_T), and a gold standard tethered acute 3.5 Fr pressure catheter (ICP_A) with a transcutaneous lead (SPR-524, Millar Instruments). The SmartPad receiver/charger used for 3.1: Chronic Rat LVP (TR180 SmartPad, Millar Inc., Auckland, New Zealand) received the ICP_T signal. Both ICP measurements were sampled at 1 kHz using a PowerLab data acquisition unit and LabChart software (v7.3.5, ADInstruments, Sydney, Australia).

Three ewes weighing between 44-69 kg were used in this study. Four telemeters were developed using the ICP coils, and 2 Fr pressure sensors. The telemeters were calibrated against a digital absolute Mensor pressure transducer (CPT 6100, Mensor, TX, USA) with accuracy of at least 0.03 mmHg and total uncertainty of 0.010%. Calibration was carried out with the catheters continuously hydrated (at least 24 hours in saline prior to calibration), in the dark, at room temperature within 24 hours of the experiment.

At the time of surgery the ewes were weighed and left front brachial vein cannulated with a 20g intravenous cannula. The ewes were then anaesthetised initially with injection of 2% Propofol (5 mg/kg, Diprivan, AstraZeneca, UK) and intubated, ventilated at 14 breaths per minute, and anaesthesia maintained through 2-3% isoflurane in O2. The head was shaved and cleaned using Hibitane and Betadine. The surgical procedure was led by a clinical neurosurgeon.

Implantation of the ICP_T and ICP_A catheters into the brain parenchyma was the first step. A semi-circular incision 2 cm anterior to the coronal suture towards the parietal margin was made and muscles retracted to expose the frontal parietal cranium. A 4mm diameter burr hole was drilled in the frontal bone. After inspection of bone thickness, the catheters were marked to
indicate insertion depth for the sensor to sit 20 mm into the brain parenchyma. The ICP$_T$ catheter was inserted, and the ICP$_T$ telemeter body was tunnelled under the skin, above the skull. The ICP$_A$ catheter was inserted into the same hole to ensure the same pressure was being measured from both devices. The incision was partially closed, leaving the ICP$_A$ transcutaneous lead running out of the incision.

Once the pressure sensors were implanted and recording, the ventricular catheter procedure began. Location of the sheep ventricles was determined through correspondence with laboratories conducting experiments requiring sheep ventricles, and the guidance of the clinical neurosurgeon. A semi-circular incision was made to reveal the posterior fontanelle and coronal suture. A 4 mm diameter burr hold was drilled 1.5 cm anterior and 1.5 cm lateral to the posterior fontanelle at an angle of 10° from the sagittal plane. From this point, a variety of techniques were investigated across the three animals to locate the ventricles:

- 14 G needle used to form tract through burr hole 20 mm deep into parenchyma. The needle was removed and a polyvinyl catheter (SV65 1.52 mm OD, Dural Plastics) advanced through tract until fluid flow was seen through the catheter
- Catheter (SV65 1.52 mm OD, Dural Plastics) attached to a syringe filled with saline slowly advanced through burr hole, drop in syringe saline volume used to indicate ventricle location
- Needle guide-wire with catheter inserted through burr hole, fluid flow used to indicate ventricle
- 16 G needle used with attached catheter to syringe infusion pump (Pump 22, Harvard Apparatus catalogue #55-2226) operating at 16 mL/hour, needle advanced through burr hole while monitoring infusion pressure. A drop in pressure indicated catheter tip was in the ventricle

Once the respective technique’s indicator signified the ventricle had been located, the ventricular catheter was secured by suture and a three way tap was added to the catheter line for syringe attachments. Simultaneous ICP measurements were made for a direct comparison of ICP$_T$ and ICP$_A$. The ventricular catheter was used to induce and measure changes in ICP. Changes in ICP were used to verify the dynamic response of the telemetry sensor through CSF withdrawal (5 mL maximum) and saline injection (5 mL maximum) into the cistern magna, jugular vein compression, and hyper-ventilation (increase in mechanical respiratory up to 25
breaths/min). A flow chart demonstrating the procedures to induce changes in ICP is shown in Figure 3-6.

![Flow chart demonstrating the procedures to induce changes in ICP](image)

Figure 3-6: Flow chart demonstrating the procedures used during the acute experiment to induce and measure changes in ICP.

After approximately one hour of recording time, including a range of induced changes, the ventricular catheter and ICP pressure sensors were removed and animals euthanized by overdose with pentobarbitone anaesthetic.

### 3.2.2 Results

The infusion pump technique was the most successful at locating the ventricles. This technique was used on the latter two of the three animals, with the ventricle located and confirmed with a distinct drop in infusion pump pressure at an insertion depth of 18 and 20 mm. In the first animal, the guide-wire technique was deemed successful after fluid flow was observed at a depth of 20 mm. This however was not repeatable across later experiments or during the same experiment after fluid flow in the ventricular catheter could no longer be achieved and the catheter appeared to have moved out of the ventricle. Both techniques were unstable and despite securing the catheters by suture at the set depth after observed fluid flow, over the course of the experiments the ability to increase the fluid in the ventricles or withdraw CSF diminished. The ICP telemeter body with inductive power coil was implanted under 5-6 mm of sheep skin and power successfully transferred to the implant throughout the experiments. Both ICP<sub>A</sub> and ICP<sub>T</sub> showed a clear respiratory and heart rate frequency in the otherwise stable ICP signal. The power transfer method was susceptible to periods of drop out and signal noise when coupling was inconsistent. Significant noise (> 2 mmHg) was introduced to the pressure signal when the primary coil centred over the telemetry unit rather than above the secondary coil. These coupling sensitivity issues were overcome by securing the secondary coil with clips.
to the surrounding sheep’s wool, allowing for the ideal coupling to be maintained throughout the acute experiment where a standard noise level of approximately 1 mmHg was seen on the telemeter signal. An example of 5 seconds of data sampled at 1 kHz during a period of offset coupling and during ideal coupling (ICP\textsubscript{T}) is shown in Figure 3-7 along with the corresponding acute pressure signal (ICP\textsubscript{A}).

![Graph showing pressure measurements](image)

**Figure 3-7**: Five seconds of data sampled at 1 kHz for the implantable telemeter device (ICP\textsubscript{T}, red) and the transcutaneous gold standard sensor (ICP\textsubscript{A}, blue) during periods of offset coupling induced noise (upper trace) and stable signal with ideal coupling (lower trace).

The ICP\textsubscript{T} recorded accurate dynamic ICP measurements demonstrated by its correlation with ICP\textsubscript{A}. Induced increases in ICP measurements were successful, ranging from 1.5 – 15 mmHg. Induced changes by jugular vein compression ranged from 2.0 to 4.5 mmHg, saline injection from 2.0 (1 mL injected) to 15 mmHg (5 mL injected). The response across animals varied. Efforts to reduce ICP by ventilation rate manipulation saw no change and attempts to withdraw CSF through the ventricular catheter were unsuccessful.

An observable offset error was present in all tested telemeters, which developed in the (less than) 48 hours between calibration and surgery. An example of the entire experimental period for animal one is shown in Figure 3-8 demonstrating the multiple induced changes in ICP.
across the 65 minutes of measurement time. There is a short signal drop out from ICP\textsubscript{T} after 32 minutes. The ICP\textsubscript{T} offset is unstable and changed with both time and pressure over the course of the experiment and with sudden changes in ICP, as measured by ICP\textsubscript{A}.

Due to the large offset seen in animal 1, two telemeters were used which had been calibrated within 12 hours of surgery for animal 2. The experimental time course for this animal measured through the acute pressure catheter and two telemeters is shown in Figure 3-9. A sudden shift in offset for both telemeter devices occurs at 15 minutes, immediately before a series of ventricular catheter saline injections to induce an ICP change. There was a severe offset in both telemeters and order of magnitude above the ICP pressure signal itself.

Table 3-1 outlines the offset seen between ICP\textsubscript{A} and ICP\textsubscript{T} across the three experiments.
Animal | ICP offset (mmHg) during experiment period (40-70 minutes)
---|-------------------
1 | 3.2 | 4.7 | 5.2
2 | 24.6 | 28.3 | 30.5
3 | 10.6 | 14.3 | 16.5

Table 3-1: ICP offset seen during acute experiments measured as ICPT - ICPA. Table shows the unstable offset with the minimum, maximum, and average offset seen.

These offset values were significant and occurred rapidly with calibration carried out a maximum of 24 hours before surgery.

3.2.3 Post-surgery telemeter performance investigation

The acute ICP sheep experiments suffered from severe offset in the telemeters. Though calibrations were carried out within 48 hours of experimentation, there was a clear discrepancy occurring between calibration and surgery environments. The offsets were too significant to be attributed to drift over the short timeframe. It was known the sensors had possible light sensitivity and consequently calibration was carried out in the evenings with no light sources. Post-surgery investigations into telemeter sensitivity revealed significant, inconsistent, light sensitivity across the telemeters. The entire device, telemeter unit only, or sensor only was exposed to room light, or shielded in a black Perspex container. Devices were powered directly by a DC power supply (HP Agilent E3610A) to remove any influence of the IPT system. Sensitivity tests were conducted on four devices – three used during surgery and one spare. Results for the sensor tip exposure are summarised in Table 3-2.

<table>
<thead>
<tr>
<th>Telemeter</th>
<th>Light sensitivity (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>4 (spare)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 3-2: Light sensitivity demonstrated by individual telemeters shift in pressure reading when moved from dark to natural room light. Two devices show the expected magnitude of sensitivity and two demonstrate severe sensitivity.

The four telemeters revealed two distinct sensitivity characteristics. Two telemeters (1, 4) demonstrated light sensitivity levels consistent with those previously seen – approximately 2
mmHg when exposed to room lighting vs. a light shielded box. To account for this level of sensitivity, the standard protocol was to carry out calibration procedures being carried out in the “dark” – all artificial lighting turned off and the sensor covered. However, the remaining two telemeters (2, 3) demonstrated extreme light sensitivity. When exposed to room lighting, shifts in pressure measurement were seen up to 80 mmHg. These telemeters also revealed periods of severe noise when exposed to room lighting which spanned +300 mmHg to –100 mmHg, shown in Figure 3-10. The effects of the periods of light exposure were not repeatable or predictable, and on occasion caused a permanent shift of up to over 100 mmHg at a time when the telemeters were returned to the dark.

![Figure 3-10: Light induced noise seen in telemeter 2 exposed to atmospheric pressure. During light exposure there is severe noise with an overlaying mean pressure of approximately 125 mmHg, when shielded by light (grey bar) noise is instantly reduced.]

### 3.2.4 Discussion

The device offset performance caused a significant error during the experiments. However, protocols for the surgical procedure and ICP induced changes were successfully developed and tested. The ICP$_T$ recordings showed potential during ideal coupling with breathing and heart rate induced undulations in the ICP recordings, as present in ICP$_A$. The induced changes demonstrated a wide range of ICP. The inconsistent response to each intervention is to be expected due to the variance in the animal’s physiology such as brain compliance and surgical effects such as loss of CSF through ventricular catheter insertion surgery.

The ferrite-less IPT coil system successfully transferred power across the sheep skin to operate ICP$_T$. The system did experience some noise with offset coil coupling which became significant at over 2 mmHg. With ideal coupling an average noise of approximately 1 mmHg on the ICP$_T$ signal could be maintained throughout the experiment. Further testing and development to
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desensitise the signal to coupling variations and to reduce the standard 1 mmHg of noise is required for these coils to be utilised in chronic experiments, where the animal will be free to move, and for future work towards a clinical device. This result provides confidence that the power system within the ICP implant will be able to perform electrically and is worthy of assessment for MRI Conditional approval.

Before further large animal studies are conducted the sensor screening and calibration protocols need to be adapted to consider the severe light sensitivity in some sensors. When in use the sensors will be in the dark, and if sensitivity to light is stable, then appropriate handling during calibration will support obtaining accurate ICP measurement. However, in some cases, light exposure induced permanent changes in the sensor’s performance. The sensors were known to have some light sensitive characteristics in the order of 2 mmHg and therefore pre-surgery calibration and desktop testing was carried out with the sensing elements shielded from room light. The severe light sensitivity flaw explained the sudden significant offsets present in devices 2 and 3 which occurred in the 48 hours between calibration and surgery. The nature of this sensitivity, and in particular the extreme permanent changes induced in the sensor characteristics following light exposure, will have to be thoroughly investigated and either screening, or very well controlled handling procedures will be required.

The three acute ICP experiments provided confidence in the surgery required to implant ICP$_T$ and ICP$_A$. However, the methods for locating the sheep ventricle and securing a ventricular catheter provided inconsistent results and ventricular catheter patency was unable to be obtained for the full surgical procedures for all ICP change interventions to be carried out. It appears this was due to the catheter falling out of the ventricle, but there may also be some collapse of the ventricle occurring during the procedure which will require further testing and examination should these methods progress to use in long term chronic experiments. Further acute investigation into the surgical procedure to locate and secure a ventricular catheter is required.

3.3. Towards human trials

In this chapter, the 2 Fr pressure sensing catheter proposed for use in the long term implantable ICP device has been tested in two implanted environments. The LVP experiments demonstrated reliable, accurate, and stable pressure measurements could be made for up to three months in a highly demanding implanted environment. This chronic experiment gives
confidence in the pressure sensing catheter as a candidate for the lifetime ICP device. The sensor was exposed to a higher frequency and magnitude of pressure than would be present in ICP and performed consistently. However, the acute ICP sheep experiments revealed key vulnerabilities within the sensor. The acute sheep experiments were crucial in investigating and developing the surgical techniques to be used in the future. However careful screening, handling and calibration protocols for individual sensors are required to be established in preparation for chronic ICP experiments.

The in vivo experiments demonstrated the pressure sensing catheter has the potential to be used in a chronic clinical environment, but will require more stringent bench top testing and calibration before integration with the device. Success of the ferrite-less IPT coil system gives confidence that the device can be designed with MR conditional approval in mind.

Further acute ICP sheep experiments are required to thoroughly test the complete device and surgical methods. Ethics approval for these experiments contained details of two advanced stages which would need to be achieved before considering the clinical applications of the device. A second stage, chronic four week implantation, would further test the implant for longer term chronic implantation. This experiment would involve the implantation of the proposed ICP device along with two commercially available large animal pressure telemetry devices (Telemetry Research Ltd, Model 84P). The separate devices would provide independent verification of the ICP values obtained while the animals are housed in the lab. This experiment will require robust methods to implant a ventricular catheter which can be exteriorised for the potential induction of Hydrocephalus in the animals using a Kaolin model of induced hydrocephalus [137], [138]. This chronic experiment will demonstrate the safety of the device to be implanted long term while keeping the animals in a controlled, supervised environment. The final stage of animal testing will involve a long term 6 month implantation period where the animals (after a recovery period) are released back on a farm with the implant in place. During this experiment, periodic ICP measurements will be taken from ICP_T up to twice a week using an external wand containing a power supply, the primary IPT coil and telemetry interrogator and receiver.
4. Modelling Heat Generated by Active Implanted Devices in the MRI Environment

Magnetic resonance imaging (MRI) is growing in diagnostic importance due to its lack of ionizing radiation and on-going improvements with soft tissue contrast and resolution. However, the magnetic and radio frequency (RF) fields in the MRI can cause interactions with conductive material in implantable devices, inducing forces and torques, tissue heating, image artefacts and electromagnetic interference [86], [87], [91], [139]–[143]. Passive implantable devices such as aneurysm clips, heart valve prosthesis, coils, stents, orthopaedic implants and vascular access points have widely achieved MR conditional approval through the American Society for Testing and Materials (ASTM) International series of test procedures for implantable passive devices [75], [79]–[82]. MR critical implants, including active implantable medical devices (AIMD’s), semi-active implants (powered from outside the body), elongated metallic structures and implants containing resonant conducting loops, are highly sensitive to the conditions under which testing is performed and have the potential to cause excessive heating [86]–[88], [142], [144]. MR imaging has traditionally been a contraindicated for patients containing active electronics due to their interactions with the MRI system being more difficult to determine and test for. However, recent growing demand for MRI techniques in diagnostic medicine have led to a need for AIMD’s to not exclude patients from access to such technology. In addition, since 1995 a range of publications have demonstrated conditional MRI scanning of AIMD’s within a safe heating range such as partially implanted elongated sensing leads, cochlear implants [145]–[147], implantable infusion pumps [148], deep brain stimulator (DBS) systems [149]–[152], spinal cord or micro-simulators [153]–[155], implantable cardiac defibrillators (ICDs) [156]–[158], and pacemakers [94], [157], [159], [160]. Contradictorily, there have been wide reports of patient injury or severe heating measured in-vitro with AIMD’s, in some cases reported in the same publications. Achenbach et al measured temperatures over 63 °C after 90 seconds of MR exposure in a detached pulse generator lead [94], Konings et al demonstrated heating in guide wires of between 26 °C – 74 °C after 30 seconds [92] and Rezai et al have shown DBS leads causing heating over 25 °C at the electrode tip [150]. These conflicting results lead to changes in terminology where implants were
previously granted MRI compatibility, the need to define the environmental, device, and patient conditions for critical implants lead to the definition of MRI conditional approval [75].

The high dependence of RF heating on MR, patient, and device conditions combined with conflicting results from AIMD’s emphasised the need for AIMD specific testing procedures above that required for passive devices. Understanding the key factors of AIMD heating has grown in importance since the first demonstrations of safe pacemaker scanning in the MRI conflicting with previous reports on severe heating risk [94], [160]. As explained in Section 1.3, the most significant mechanisms for RF heating with conducting MRI on patient’s containing implants is electromagnetic induced heating; where the RF pulses induce voltages in conductive materials resulting in ohmic heating, and resonant heating; the resonant RF waves set up in the implant can lead to a risk of severe heating due to the antenna effect at resonant lengths [86], [92]. Increased risk of elongated metallic implants causing heating has been widely established, with exposed lead tips and electrodes of particular concern [86], [161]. Mattei et al investigated 374 metallic lead configurations in the ASTM torso phantom, showing lead length as a key determinant of maximum heating and worst case heating occurring closest to the edges of the phantom wall and coil [95]. Bassen et al combined numerical and experimental work to determine simulated specific absorption rate (SAR) values provide the most reliable indicator of implant heating, and that the SAR concentrations depend significantly on implant length, insulation, and position in the coil [93]. The effect of modifications to implants on MRI heating has also been investigated, with Gray et al showing minor design changes, such as coil wire pitch, can significantly reduce heating (by more than 10 °C) of implanted leads [102] and Baker et al demonstrating introducing small coiled loops into a deep brain stimulation lead directly influenced heating [162].

In 2012, ISO technical specification 10974: “Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device”, was published to meet and reinforce the demand for controlled testing of AIMD’s in the MRI. ISO/TS 10974 refers to the ASTM test methods throughout the specification, particularly for methods to evaluate static field interactions [72]. The induced heating evaluation is expanded to overcome shortcomings in the testing procedures for passive devices and allowed for improved correlation between the measurements made in the original ASTM gelled phantom standard testing and the actual exposure in patients [72], [163]. ISO/TS 10974 combines both experimental and numerical approaches to evaluate the worst case heating for a given device. Numerical modelling of the RF environment allows for the potential heating effects to be investigated while avoiding
expensive and timely physical scanning. A four-tiered test approach is employed where lower tiers require less intensive numerical modelling methods by applying high overestimation approximations [72]. Should the tested device demonstrate unsafe heating at lower tiers, more complex steps are required to refine and reduce the overestimation errors. The fourth tier contains minimal overestimation; however it is extremely computationally intensive requiring complete anatomical human body multi-tissue/organ population models to be included in the RF MRI coil environment and statistically relevant implant lead path trajectories investigated within potential implantation areas [72]. Cabot et al have reported the tier may be too demanding for complex implants, requiring 12,000 simulations for a fourth tiered analysis of a generic DBS system [72], [163].

For ISO/TS 10974 and ASTM F2182 testing, numerical modelling allows the investigation of RF heating for a range of implant configurations without requiring multiple physical scans. These modelling results can be used to identify critical device configurations to be investigated in a clinical scanner. A model of the RF environment of a 3T scanner was constructed to allow for investigating the potential for RF induced heating of the ICP device in patients undergoing MR scanning.

4.1. Electromagnetic modelling

Modelling the interactions between an implant and the MR RF environment is a large problem domain due to the difference in scale between the MRI’s body birdcage coil (approximately 700 mm in diameter) and the sub mm details of the implant. Maxwell’s equations will be solved to model the electromagnetic (EM) interaction between the MR RF coil, implanted environment, and metallic implant. The resulting electric fields (E-fields) and magnetic fields (H-fields) can be used to calculate the specific absorption rate (SAR) and temperature effect on the body. SAR is a measure of the rate of RF energy absorption by the human body in an EM field and is commonly used to quantify safety levels of an EM environment.

There are three common techniques for solving Maxwell’s equations: the method of moments (MoM), the finite element method (FEM), and the finite-difference time-domain method (FDTD) [164]. MoM, solves for the integral form of Maxwell’s equations and is ideal for handling homogenous highly conductive material or electrically large problems. FEM exploits the differential form of Maxwell’s equations, discretising the computational domain by using elements of different shapes. FEM’s advanced discretisation is well suited to heterogeneous
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volumes of complex geometry. The solution to the differential form of Maxwell’s equations is approximated, requiring a large system of linear equations with a large computational cost. FDTD also utilises the differential form of Maxwell’s equations, solving for the operators by finite difference approximations. A staggered Cartesian grid is established across the computational volume, with the E- and H-fields solved for in a leap frog scheme, as developed by Yee [165] and illustrated as a Yee cell in Figure 4-1.

![Yee Cell](image)

Figure 4-1: Yee Cell

The Cartesian grid result in complex geometries and curved surfaces requiring highly discretised large computational domains, however FDTD is well suited to heterogeneous media and easily parallelised for GPU hardware acceleration.

For the MRI RF coil, human tissue, and detailed implantable device problem, EM simulation platform SEMCAD (SEMCAD X v14.8.5) was chosen to model the problem [166]. SEMCAD solves for a 3D full-wave FDTD E- and H-field solution. The SEMCAD solver utilises Accelware to interface with GPU acceleration which can result in improvements in simulation speeds of up to 100 times [166]. The software is particularly well suited to simulating implants in the MR environment as it includes a built it Huygen’s box excitation method. The Huygen’s box method allows for a two stage simulation where a primary simulation with a relatively coarse grid, and associated large time step, establishes the incident field distributed about a smaller volume defined by the Huygen’s box. The resulting E- and H-fields distributed about the Huygen’s box become the source of a secondary simulation within the small defined volume, containing a fine grid and requiring a small time step. This method is ideal for the implant-patient-MR RF field computational problem as the primary simulation can be used to solve for the EM fields in the simulated human tissue about the region of interest without the
implant present, before adding the detailed implant model to the secondary Huygen’s box simulation.

4.2. Thermal simulation

The software package SEMCAD also includes a thermal solver utilising Penne’s bio-heat equations for simulation of temperature fields resulting from the EM solution. Using this built in solver, based on non-uniform FDTD, allows for EM and thermal simulations to be based on the same gridding information minimising error introduction from interpolation. To ensure numerical stability the von Neumann stability analysis is applied for the thermal time step, where the thermal conductivity becomes an important dependent factor. With an active implant with small metallic structures, the high conductivity and small grid resolution can result in prohibitively long simulation times, requiring multiple weeks for convergence. Approximations to the conductivity of metallic solids can be made where the properties of the surrounding tissue/phantom gel are applied to the solid, allowing for a larger time step and greatly reduced simulation time. This has been demonstrated to result in an error of approximately 10-20% [166]. There are also two built in solver alternatives to the explicit Penne’s solution – the Discrete Vascular culture (DIVA) solver, and the steady state solver. The DIVA solver allows for pseudo 1D boundary conditions applied to thin, highly thermal conductive structures. The approach is used for modelling complex vessel pathways but can also be applied for analysis of thin wire-like structures, which would standardly require extremely long simulations with high resolution and small time step. DIVA allows for a reduction in resolution and a larger time step with accurate solutions. Voxels near the surface of the thin structure are used to estimate flux through the boundary of the object with interactions between the thin structure and the surroundings updated after each time step. The steady state solver provides an alternative to solving in the time domain where a direct matrix solver is used to find the steady state temperature distribution. Convective boundary conditions are required to provide heat sinks in the simulation to ensure steady state is reached. The steady state solution generates a significantly faster solution to the explicit Penne’s, but provides no transient information.

Throughout this chapter either the explicit Penne’s solution, conductivity approximated explicit Penne’s solution, DIVA, or steady-state solver will be applied where appropriate to generate temperature results. All modelling results are based on assumptions and approximations, in this case, the results are often used to understand implications of relative
changes of device features and always lead to a device and physical experiment in a MR machine. This goes someway to alleviate risk associated with approximations used.

4.3. RF birdcage development

The 3T MRI RF body coil was modelled as it exposes the full phantom to RF energy and is considered worst case for RF heating with a whole body average SAR limit of 4 W/kg in first level operating mode [72], [81]. Following methods outlined by Liu et al [167], a non-physical coil was modelled, shown in Figure 4-2.

![Figure 4-2: SEMCAD generic birdcage model showing eight rungs (red) and end rings as tuning capacitors (blue).](image)

The non-physical model method was chosen to substantially reduce the long computational times associated with modelling the exact geometries of the birdcage, the tuning capacitors and quadrature excitation while effectively establishing equivalent E- and H-fields as present in a physical scanner [163], [167], [168]. The non-physical model enforces current sources along the individual rungs connected by tuning capacitors in the end rings. An outer shield surrounds the RF coil, replicating a physical clinical scanner and allowing for weaker enforcement of boundary layers and a faster simulation time. Development of the model can be broken down into 5 key steps:
1. Tuning the birdcage coil to the 3T frequency of 128 MHz
2. Primary simulation verification a) Simulating the empty coil and inspecting the E- and H-field results
3. Primary simulation verification b) Loading the coil with the ASTM phantom model and inspecting SAR distribution
4. Huygen’s box simulation verification: Simulating an implant with a known response in a 128 MHz RF coil
5. Clinical scanner verification: Generating experimental results in a clinical scanner for comparison against model

Once completed, the model will then be ready for use to understand interactions between the MR RF field and the ICP device.

4.3.1 Tuning the birdcage coil

The non-physical coil consists of SEMCAD current sources used to represent and act as the body coil’s rungs, with capacitors as the coil rings, illustrated in Figure 4-2. The coil’s diameter was 630 mm and height 650 mm. Eight sources were used in the 3T/128 MHz model and activated with a progressive delay moving clockwise around the coil –i.e. current source 1 delay: 0, current source 2 delay: 0.125 periods, current source 3 delay: 0.25 periods. This activation scheme is used to simulate quadrature fed coil excitation most commonly used in physical scanners. End ring capacitors were tuned to match the 3T clinical scanner resonance of 128 MHz.

Using methods outlined by SEMCAD and previously used by Liu et al, the loaded RF coil was tuned to 128 MHz to simulate a 3T MR RF environment [166], [167]. A series of broadband simulations are used where one rung source is activated with the remaining rungs set as perfect conductors. The ring capacitor values are iteratively adjusted until resonance is reached at 128 MHz. For the modelled coil, this was achieved with a ring capacitance of 1.3 pF.

The non-physical coil model does not account for the potential of the ICP device to interact and change the characteristics of the body coil. Due to the small size of the ICP device relative to the body RF coil, this assumption is acceptable and has been used throughout the literature on numerical analysis of implants in the MRI [167], [169]. The non-physical coil greatly reduces simulation time and gridding complexity required for modelling the exact geometries.
of a clinical RF coil. The simplified RF coil model was chosen to allow for reasonable simulation times when the complex active implants are added to the simulation domain.

4.3.2 Empty coil simulation

All sources were activated with a progressive phase delay to approximate quadrature fed excitation and generate a circularly polarised E-field within the coil. The harmonic simulation at 128 MHz was run and the resulting E and H fields inspected. The fields generated by the generic coil model represent those occurring in a clinical scanner. The centro-symmetric E-field demonstrates the progressive phase delay of the current sources is effective at replicating quadrature excitation with the B-field uniform across the centre of the coil where the patient will be placed. These features are required in a clinical scanner to produce accurate images. The pulsing B₁-field produced by the RF coil activates tissues of interest (depending on the scan sequence) while not disrupting the uniform static B₀-field set up by the super conducting magnet.

4.3.3 Coil simulation with ASTM phantom

The RF coil was then loaded with a model of the ASTM phantom gel. The ASTM torso is a rectangular phantom 650 x 420 x 90 mm in dimension [81]. The SAR distribution within the phantom in the common clinical scanner strengths of 1.5 and 3T have been well tested and established throughout the literature allowing for verification of the SEMCAD RF MRI coil [72], [81], [170], [171]. The phantom gel and outer container were assigned the following linear material properties: The ASTM gel was modelled as a dielectric with a relative permittivity (\(\varepsilon_r\)) of 80.38, relative permeability (\(\mu_r\)) of 1 and electrical conductivity (\(\sigma\)) of 0.47 S/m, as specified [81]. The Phantom’s casing was also modelled, with \(\varepsilon_r\) of 3.7, \(\mu_r\) of 1, \(\sigma\) of 0 S/m.

The ASTM phantom and the expected SAR distribution inside a 128 MHz RF body coil is shown in Figure 4-3. The phantom average SAR is 0.63 W/kg at 128 MHz for a B₁ average across \(z = 0\) of 1\(\mu\)T.
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Figure 4-3: ASTM (head)/torso phantom and associated SAR distribution for a 128 MHz B1 field of 1 µT [81].

The phantom was voxelled and the simulation run until convergence met. The resulting E-field and SAR distribution when normalised for a $B_1 = 1 \, \mu T$ is shown in Figure 4-4.

Figure 4-4: SAR distribution results for empty ASTM phantom in SEMCAD showing asymmetric distribution and concentration at the phantom edges.
The SAR distribution normalised for a B\textsubscript{1} average across z = 0 of 1\mu T for the birdcage coil agrees with previously established results. A sensor set up to encapsulate the gel phantom verified the average SAR as 0.63 W/kg, providing confidence in the primary, empty phantom, simulation set up.

### 4.3.4 Standard implant Huygen’s box simulation

In order to verify the results of the Huygen’s box simulation step, a standard implant was used with a highly characterised response in the MRI. ISO/TS 10974 outlines two “standard active implantable medical devices” (S-AIMD) [72]:

1. S-AIMD 1: Straight stainless steel wire of 1.5 mm diameter, 200 mm length, with 0.5 mm thick plastic insulation and 10 mm at both ends of the wire left un insulated [72].
2. S-AIMD 2: Straight grade 5 Titanium rod of 3.175 mm diameter, 100 mm length, with 1 mm diameter holes drilled transverse to the axis 1 mm from each end of the rod [72].

For this work, S-AIMD 2 was selected to be used for verification due to its simplicity for modelling and to construct for physical experiment verification. The ICP device would also not have exposed leads such as in the more complex and electrode lead specific S-AIMD 1. The implant was modelled and positioned along the left-hand side of the ASTM torso, 20 mm from the phantom edge and surface, longitudinally centred along the y-axis. The material parameters outlined in Table 4-1 were applied.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S-AIMD 2</th>
<th>Tissue simulant/phantom gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative permittivity</td>
<td>-</td>
<td>78</td>
</tr>
<tr>
<td>Electrical conductivity</td>
<td>Infinity</td>
<td>0.47 S/m</td>
</tr>
<tr>
<td>Heat capacitance</td>
<td>560 J/kg/K</td>
<td>3200 J/kg/K</td>
</tr>
<tr>
<td>Thermal conductivity</td>
<td>7.2 W/m/K</td>
<td>0.42 W/m/K</td>
</tr>
<tr>
<td>Density</td>
<td>4420 kg/m\textsuperscript{3}</td>
<td>1000 kg/m\textsuperscript{3}</td>
</tr>
</tbody>
</table>

Table 4-1: Solid region material parameters for S-AIMD 2 electromagnetic and thermal simulations.

This set up has a well characterise temperature response. For S-AIMD 2 in a 128 MHz birdcage coil producing a uniform tangential background electric field resulting in a local (over 10g of tissue [81]) SAR of 1W/kg, after 360 s of field application, there is a 1.45 °C temperature rise in the 1 mm holes at either end of the device.
The current source rung amplitude was adjusted to 0.7845 V to achieve a local SAR about S-AIMD 2 of 1 W/kg. The EM model was then fed into SEMCAD’s thermal solver. Due to S-AIMD 2’s structure and high thermal conductivity, the Discrete Vasculature (DIVA) solver model was used. This solver uses a 1D vessel approximation to significantly decrease the large simulation times associated with highly conductive materials, while still allowing the real metallic parameters to be applied to the model [166]. The DIVA model operates in the time domain, allowing for the explicit solution to Penne’s bio heat equations to be found, providing transient heating results. SEMCAD’s vessel model function was used to approximate S-AIMD 2 with thermo-point sensors positioned in the centre of the device’s holes. The three simulations (0.7845 V primary rung source, S-AIMD 2 Huygen’s source, DIVA thermal simulation) were run with a resulting $T_{360} = 1.45211$ and temperature response shown in Figure 4-5.
Figure 4-5: S-AIMD 2 model results from SEMCAD for an EM field simulation producing a local SAR about S-AIMD 2 of 1 W/kg.

These results match the characterisation of S-AIMD 2 to within 0.01 °C and provided confidence in the model to proceed with investigating the RF heating of an ICP device. Before moving on to ICP device modelling, S-AIMD 2 was used to correlate physical scanner results for characterisation of scan parameters to allow future use of the model to be comparable to the clinical 3T scanner environment.
4.4. Clinical scanner validation with S-AIMD 2

For the initial physical experiments with S-AIMD 2, the ASTM phantom was downsized to consider only the head portion. This allowed for significant reduction in simulation and experimental set up time while further testing the flexibility of the model. The 270 x 150 x 90 mm head rectangular phantom was modelled in the centre of the RF birdcage coil. S-AIMD 2 was positioned 20 mm from the top corner of the phantom generating a non-uniform SAR generated across the region in which S-AIMD 2 would be positioned, as shown Figure 4-6.

![Figure 4-6: ASTM head phantom with S-AIMD 2 positioned for worst case heating 20 mm from the phantom corner exposing the S-AIMD 2 to non-uniform SAR conditions.](image)

This non-symmetric SAR distribution allows for a disparate temperature change to be monitored at each monitoring end of S-AIMD 2. The two stage EM simulations and DIVA thermal simulations were carried out as in Section 4.3.4.

For the experimental set up, the head portion of the ASTM phantom and S-AIMD 2 were constructed. The phantom solution was prepared as specified in ASTM F2181, and the gelled saline solution’s (1.32 g/L NaCl, 10 g/L polyacrylic acid) conductivity was measured as 0.47 S/m. All air bubbles were removed under a vacuum and S-AIMD 2 was positioned 20 mm from the left hand side phantom wall, top corner and gel surface (as modelled in SEMCAD). The phantom set up was allowed to equilibrate with the MRI scanner room for 2 hours prior to scan time. Clinical scanner Siemens SKYRA 3T (MAGNETOM Skyra 3T, Siemens, Munich, Germany) was used.
Opsens MPK4 fibre optic temperature sensors and signal conditioner Tempsens (Opsens Inc., Quebec, Canada) were used to measure changes in gel temperature while in the MR. The 0.51 mm diameter fibre optic temperature sensors were calibrated before scans against a high precision fluke digital thermometer (Model 1504, Fluke Corporation, UT, USA). Two probes were placed in the holes of S-AIMD 2 and two in reference positions replicating the simulated temperature point sensors. Five minutes of baseline recordings were taken before each scan sequence, during which a 10 second localiser scan sequence was run as required by the MR software for image optimisation. During scanning, the patient comfort fan was turned off.

The scan sequence outlined in Table 4-2 was used to maximise RF energy deposition.

<table>
<thead>
<tr>
<th>MRI Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>Turbo spin echo</td>
</tr>
<tr>
<td>TR</td>
<td>619 ms</td>
</tr>
<tr>
<td>TE</td>
<td>13 ms</td>
</tr>
<tr>
<td>Turbo Factor</td>
<td>4</td>
</tr>
<tr>
<td>Plane</td>
<td>Transversal</td>
</tr>
<tr>
<td>Flip angle</td>
<td>90°</td>
</tr>
<tr>
<td>Bandwidth</td>
<td>130 Hz/Px</td>
</tr>
<tr>
<td>Field of view</td>
<td>400 mm</td>
</tr>
<tr>
<td>Matrix</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Section thickness</td>
<td>10 mm</td>
</tr>
<tr>
<td>Total slices</td>
<td>40</td>
</tr>
<tr>
<td>Transmitter gain</td>
<td>(gain: high)</td>
</tr>
<tr>
<td>Scan time</td>
<td>15:55 (TA, acquisition time)</td>
</tr>
</tbody>
</table>

Table 4-2: Scan sequence used in Siemens SKYRA 3T MRI with the RF head coil for S-AIMD 2 implant heating and numerical model correlation testing.

For the 12 kg head phantom, this sequence generated a whole-body system reported SAR of 0.4 W/kg in normal control mode. Two scans were conducted, with S-AIMD 2 present and with the empty phantom. The empty scan temperature rise was used to calculate the SAR in the phantom according to \( \text{SAR} = \frac{c \Delta T}{\Delta t} \) c. The average fibre optic temperature rise of 0.084 °C corresponds to a calculated SAR of 0.39 W/kg which supports the MR’s system reported value.
The EM and thermal simulations were then adjusted to represent the power deposited by the physical machine.

Figure 4-7 shows the temperature rise recorded in the ends (T1, T2) of S-AIMD 2 in the clinical scanner, and by the thermo point sensors (T1, T2) for the vessel approximation of S-AIMD 2 in SEMCAD.

![Figure 4-7: Numerical modelling and physical experiment time course of temperature rise in the S-AIMD 2 in a 3T MRI with the device positioned asymmetrically in a head phantom.](image)

The model appears to perform well in estimating the temperature rise at either ends of an asymmetrically implanted S-AIMD 2. The experimental results appear to approach a steady state temperature after approximately 500s of exposure; however the model outcome appears to continue to rise after 900s, particularly for the high exposure site of T2. This may be due to the approximations in the explicit thermal DIVA solver used and errors introduced in material parameters. Future work will use the 900 s test point as per ASTM F2182 and ISO/TS 10974 [72], [81] however this demonstrates the risk of over-assumption of model predicted heating with the model in steady-state solver mode.

These experimental and modelled results demonstrate the model’s flexibility in representing simulation changes and verify the model as an accurate representation of the RF environment of the Skyra Magnetom 3T clinical scanner. This step completed the RF birdcage model.
development, with results demonstrating the 128 MHz RF body coil’s ability to generate appropriate E- and H-fields, induce established SAR distribution in the ASTM head-torso phantom, and accurately simulate heating of standard implants.

4.5. Model sensitivity to environment conductivity

With the simulation validated, numerical investigation was carried out to determine the sensitivity of the SEMCAD generic RF birdcage and ASTM phantom environment. In this investigation, the phantom gel conductivity was altered across a range of human tissue values to provide an indication of how the implantation location not only effects the RF heating due to spatial location in the MRI’s EM field, but how the influence of the surrounding tissue about the implant determines the heating response. Prior to the current ASTM F2182 and ISO/TS 10974 standards for biomedical implant testing in an MRI, the sensitivity of temperature results from gelled and liquid saline phantoms was demonstrated by Park et al by comparing results for a deep brain stimulation system across four phantoms of varying viscosity and conductivities of 0.22 – 0.26 S/m [172]. The study confirmed the need for a highly viscous gel to avoid significant underestimations of heating risk due to convection influencing temperature measurements in liquid saline phantoms [172]. These results reshaped the standard testing methods phantom requirements and explained previous discrepancies in thermal risk reported of the same implant by independent groups generating heating of 2.1 °C in a liquid phantom [173], and up to 25.3 °C in a gelled phantom where thermal transport was limited [31]. The current edition of standard ASTM F2182 requires a gelled phantom of 0.47 ± 10 % S/m conductivity [20], with the lower tiered testing in ISO/TS 10974 pointing to this phantom. Higher tiered testing in ISO/TS 10974 includes human specific models (rather than homogeneous phantoms) to be used during numerical investigations such that accurate tissue properties are considered given the implant’s location in the body. In 2012, Langman et al demonstrated the variation in pacemaker lead tip heating in three experimental phantoms ranging from 0 – 3 S/m, corresponding to a heating variation of 12.5 – 50.4 °C [174]. This investigation was to determine the sensitivity of numerical results in the homogeneous phantom across a range of human tissue conductivity values as an approximation to tissue-specific implantation testing. S-AIMD 2 was used as the implant across all simulations, following the methods and settings verified in sections 4.4-4.5.

The generic RF body coil containing an ASTM head phantom positioned in the centre of the coil was used. The head phantom reduced the size of the problem domain, providing fast
simulation times. S-AIMD 2 was positioned along the left-hand side of the head, 20 mm from the phantom edge and surface, longitudinally centred along the y-axis. The material parameters for S-AIMD 2 were consistent with Table 4-1, with the conductivity of the ASTM gel varied about the prescribed standard 0.47 S/m [81] in seven simulations to span simulated tissue conductivities from 0.05 – 0.7 S/m. The simulated conductivities were selected based on results by Gabriel; “Compilation of the dielectric properties of body tissues at RF and microwave frequencies” where over 25 tissue types were characterised for conductivity and permeability in the frequency range of 1 MHz to 20 GHz [175]. The initial, phantom-only EM model was run using rung source amplitudes of 1 V. Field sensor results were used to drive the secondary Huygens’s source simulation containing S-AIMD 2. Thermal simulations driven by the Huygens’s results utilised the DIVA approximation solver for the highly conductive S-AIMD 2 as in Section 4.4.4.

Temperature results were analysed after 900s of field exposure. Results were extracted along the length of S-AIMD 2, with peak temperatures occurring at the ends of the titanium rod. Figure 4-8 shows the temperature along the z-axis of S-AIMD 2 across the 7 simulated conductivities.

![Temperature profile](image)

**Figure 4-8**: Temperature along z-axis aligned with S-AIMD 2 in ASTM head phantom of conductivities ranging from 0.05 – 0.7 S/m.
The global maximum temperature for each simulation was also plotted against gel conductivity, showing a maximum temperature response at approximately 0.2 S/m. After this point the maximums gradually decrease with increasing gel conductivity. These results are summarised in Figure 4-9, with the conductivities of significant tissues highlighted based on results by Gabriel at 200 MHz [175].

![Figure 4-9: Global maximum temperatures for 128 MHz RF coil simulations containing ASTM head phantom of varying conductivity gel containing S-AIMD 2 compared with human tissue conductivities at 200 MHz.](image)

Maximum temperature increases for S-AIMD 2 simulated in gels ranging from 0.5 – 0.7 S/m were in the range of 0.92 – 2.46 °C. The most significant temperature rise occurred with a phantom gel conductivity of 0.2 S/m, approximately 1 °C higher than in the prescribed 0.47 S/m, for an RF body coil operating at 128 MHz. These results are in agreement with Nyenhuis et al who demonstrated the discrepancy in simulating an orthopaedic implant in the standard phantom conductivity, conductivity specific to bone (0.16 S/m), and in a human model [176]. By using the implant bone specific conductivity in the in-vitro homogeneous simulation, a greater heating was predicted closer to the in-vivo predicted temperature rise [176]. The numerical results also support those of Langman et al [174] who determined the conductivity of the solution at the implant should be considered for in-vitro experiments.
It has been identified that the conductivity of the surrounding simulated tissue is a key parameter influencing heating. It is proposed that testing in homogeneous phantoms of conductivity specific to the target implantation environment (if that information is known) may be of benefit as an intermediate step in assessing heating in MRI critical implants. This step requires little increase in modelling complexity and can provide a greater understanding of the potential for heating before simulating the highly complex inhomogeneous human body models required in high tiered RF testing specified in ISO/TS 10974.

4.6. Numerical and experimental RF heating of components of the ICP device

In order to determine RF heating of the ICP device, individual device components were modelled and experimentally tested in the ASTM head phantom. This step determined whether significant approximations could be made in the modelling process, specifically to the PCB as a blank dielectric-PEC alternating solid containing no components, and to the inductive power coil as a solid copper disc representative of the copper volume in the coiled Litz wire. The model approximation results were then compared against experimental tests in a 3T clinical scanner, using the actual populated PCB and inductive power coil as developed in Chapter 2.

The ASTM head phantom was used throughout the numerical modelling and experimental testing as a human tissue simulated medium maintaining the standard testing conductivity of 0.47 S/m. All simulations were run in the same generic 128 MHz 3T MRI RF body coil, scaled to the experimental clinical scanner as in 4.4. The two –stage Huygen’s Box method was used with the primary simulation consisting of the 0.47 S/m gelled saline phantom centred in the RF coil and a component-specific sized field sensor. This field sensor was used to drive a Huygen’s source for the secondary simulation containing the component voxelled over a fine grid. Components included a standard encapsulation of 1 mm thickness modelled with silicone material properties. Components were simulated in an implantation location where the SAR in the ASTM phantom is at a maximum and considering ASTM standard specifications on separation of device and phantom walls [81]; 20 mm from each the left hand side of the phantom and surface of the phantom gel, central on the z-axis.

4.6.1 The numerical models

The device PCB was modelled as a 20 x 25 x 1.6 mm solid 6 layer board, with perfect electric conductor (PEC) material attributed to the 0.035 mm copper layers and the corresponding 0.226
mm FR-4 epoxy layers modelled as a dielectric. The device inductive coil was modelled as a solid copper disc of 5 mm inner diameter and 12 mm outer diameter, PEC material properties were attributed as for the PCB PEC layers. The solid material properties are summarised in Table 4-3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCB PEC/Cu Coil</th>
<th>PCB Dielectric</th>
<th>Tissue simulant/phantom gel</th>
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</thead>
<tbody>
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<td>Relative permittivity</td>
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<td>4</td>
<td>78</td>
</tr>
<tr>
<td>Electrical conductivity</td>
<td>Infinity</td>
<td>0.002 S/m</td>
<td>0.47 S/m</td>
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<tr>
<td>Heat capacitance</td>
<td>560 J/kg/K</td>
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<td>3200 J/kg/K</td>
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<td>Thermal conductivity</td>
<td>385 W/m/K</td>
<td>0.14 W/m/K</td>
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</tbody>
</table>

Table 4-3: Solid region material parameters for PCB electromagnetic and steady-state thermal simulations.

The grid for the Huygen’s source simulation was highly refined in the y-axis to achieve accurate voxels of the fine PCB layers, verified by inspection of the voxel model representation. An explicit Penne’s solver was run for the thermal simulation, exposing the device to 900s of EM field results. Thermal point sensors were included about the outside of the PCB, in positions that could be replicated in the clinical scanner experiments with fibre optic temperature probes. Properties as in Table 4-3 were applied to the model.

The EM simulation results showed E-field and SAR concentrations about the edges of the PCB and copper disc. The maximum temperature rise in the phantom was in proximity of the PCB “implant” with a maximum temperature rise of 0.34 °C for the silicone encapsulated blank PCB, and 0.28 °C for the inductive coil approximated as a solid copper disc.

4.6.2 Experimental testing

The clinical 3T clinical scanner, Siemens SKYRA (MAGNETOM Skyra 3T, Siemens, Munich, Germany), with the ASTM head phantom constructed for 4.4 was used to determine whether the approximations made to the PCB and inductive coil in 4.6.1 were suitable for numerical investigations into the RF heating of the ICP device. The physical components were
tested as the fully populated PCB, which contained no inductors, and the ferrite-less inductive power coil developed for the acute sheep experiments in Section 2.4.

The temperature monitoring set up and scan parameters were used as for S-AIMD 2 testing in Section 4.4. Opsens MPK4 fibre optic (FO) temperature sensors and signal conditioner Tempsens (Opsens Inc., Quebec, Canada) were used to measure changes in gel temperature, positioned to replicate thermos-point monitoring in the numerical models to within 1 mm. The 0.51 mm diameter FO temperature sensors were calibrated before scans against a high precision fluke digital thermometer (Model 1504, Fluke Corporation, UT, USA) and positioned using Perspex clamps and guided with vitrotubes™ 1.8 mm glass round capillaries (Vitrotubes, VitroCom Inc.) to allow for accurate and repeatable positioning through the gelled saline. Five minutes of baseline recordings were taken before each scan sequence, during which a 10 second localiser scan sequence was run as required by the MR software for image optimisation. During scanning, the patient comfort fan was turned off. The scan sequence outlined in Table 4-2 was applied for approximately 15 minutes of scan time. The test set up of the two head phantoms (individually scanned) containing the components and FO temperature probes (FO T1 through to FO T4) is outlined in Figure 4-10.

![Figure 4-10](image)

*Figure 4-10: Experimental set up for individual component testing of ICP device in clinical MRI using ASTM head phantoms, demonstrating the a) PCB and b) Coil with associated fibre optic temperature probe locations (FO T1 - FO T4).*

A comparison of the heating measured by FO temperature probes and the associated thermal maximum from the approximated numerical simulations are summarised in Table 4-4.
Experiment | T1 °C | T2 °C | T3 °C | Simulated Temperature Max °C
--- | --- | --- | --- | ---
Blank telemeter | 0.33 | 0.27 | 0.25 | 0.33
Coil | 0.34 | 0.18 | 0.28 | 0.28

Table 4-4: Comparison between temperature increase experimentally measured and numerically modelled for individual components.

These results give confidence that the ICP populated PCB containing specific surface mount components and associated copper tracks can be approximated as a block containing alternating layers of solid copper and dielectric. Similarly, the inductive coil approximation as a solid copper disc is appropriate for this specific design. This allows for greatly reduced simulation times for future modelling of the ICP device to investigate RF heating with significant reductions in model complexity. It is important to specify these approximations have only been shown to be appropriate for the given device components, in an ASTM phantom of homogeneous conductivity, in the Siemens SKYRA 3T clinical scanner operating as the scan sequence in Table 4-2 specifies.

4.7. Developing the ICP device for MR conditional approval

The potential for safe MRI scanning of patients implanted with the ICP device is considered a critical feature of the device development. In order to ensure the device is developed to achieve this goal, further numerical investigations into the limitations of the device will be carried out. Modelled device component approximations verified in this chapter will greatly reduce the complexity and simulation time required to determine RF heating design limitations. It is anticipated that the length of the sensing catheter will be a key consideration, though it’s insulated sensor lead tip should avoid severe heating as seen in electrode leads.

Further work will establish the dependence of MRI induced heating on catheter lead length and configuration. Full static magnetic field, RF heating, artefact and device function interference tests will be carried out on a prototype ICP device to identify device features that have the potential to conflict with MRI conditional approval and guide future device design.
5. MRI Interactions of an ICP Device: Measurements and simulations

To test MRI compatibility, a prototype implantable device was assembled containing the critical elements of a long term ICP monitor; sensor, catheter and electronic module (sensor interfacing, radio, power transfer).

The prototype device uses the 2 Fr piezoresistive sensor tested in Chapters 2 and 3. The sensor is able to be placed in the brain parenchyma, with the catheter containing wires from the sensor to the electronic unit implanted outside the skull, underneath the skin. The electronic unit consists of all components used in the acute sheep experiment in Chapter 3; an inductive power coil for transcutaneous energy transfer, a 2.4 GHz wireless data antenna link, and associated signal conditioning and amplification circuitry. The fully implantable device is designed to sit dormant in the patient until interrogated by an external reader wand. This wand will transfer energy through IPT which will run the device and receive a measurement of ICP. A battery is included in the prototype to support the potential clinical need for periods of prolonged continuous monitoring, overnight or during daily activities, without the external wand present. This may be of interest for ICP wave time domain analysis, where the device can measure at over 100 Hz for complete ICP wave information (refer to Section 2.3), or for further investigation into the patient’s brain compliance from ICP reactions to events such as standing, coughing or during sleep cycles [25], [177]. For the purpose of technology assessment, the device is encapsulated in a silicone jacket to allow for RF transparency. Encapsulation techniques for clinical implants are well established and widely implemented in existing medical devices using materials such as titanium, glass and ceramics. Hermeticity is a fundamental element of encapsulation, and is a function of bulk material permeability, fabrication process, external environment and seal design. Ceramic-metal feed through technologies are implemented in pacemakers, cardio defibrillators, neuromuscular stimulators and cochlear implants, and are available from specialised manufacturers. Analysis of the complete ICP monitor will need to account for the final encapsulation method, at this stage it
is assumed if the internal parts can be demonstrated as MR Conditional, then appropriate encapsulation will be technically feasible.

Simulations containing device component assumptions verified in Chapter 4 were used to predict heating in different device configurations, using the ASTM torso phantom approximation to predict patient E-fields and SAR for given scan sequences. The sensitivity of the simulated heating was investigated by varying the critical device feature – catheter length.

Test methods investigated the MRI induced force, torque, RF heating, artefact and device function. Methods were developed with guidance from the International Organisation for Standardisation (ISO) technical specification on active implants in MRI (ISO/TS 1052 [72]), associated American Society for Testing and Materials (ASTM standards F2502, F2213, F2182, F2119 [79]–[82]), and widely utilised and published methods from Frank Shellock, author of the annual Reference Manual for Magnetic Resonance Safety, Implants and Devices [83]. [84].

The device was tested for a range of configurations to investigate the limitations of the implant and to guide future design decisions towards an MR Conditional product.

5.1. Numerical modelling of catheter length effect

Numerical investigations into the RF heating of the device were carried out using the RF coil model and device model approximations developed and validated in Chapter 4. The ASTM head-torso phantom was used, with standardised gel conductivity of 0.47 S/m. The device was modelled, with the populated PCB approximated as a blank PCB of solid alternating perfectly electrically conducting (PEC) and FR4 dielectric layers, and the Litz wire inductive coil approximated as a solid copper disc of equivalent volume. These approximations were validated in Section 4.6. The battery was represented as a solid homogeneous block. The pressure sensing catheter model was simplified as a straight wire lead, using SEMCAD’s wire solid feature with a resistive element tip and the 2 Fr silicone casing extending 0.5 mm from the resistive element tip such that the entire lead was insulated. The catheters wires were continuous with a PCB PEC layer. A summary of the solid material properties applied to the model is in Table 5-1.
### Table 5-1: Solid region material parameters for implanted pressure sensing device simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phantom gel</th>
<th>PEC/coil disc</th>
<th>PCB FR4</th>
<th>battery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative permittivity</td>
<td>78</td>
<td>-</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Electrical conductivity (S/m)</td>
<td>0.47</td>
<td>Infinity</td>
<td>0.002</td>
<td>0.5</td>
</tr>
<tr>
<td>Heat capacitance (J/kg/K)</td>
<td>3200</td>
<td>560</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>Thermal conductivity (W/m/K)</td>
<td>0.42</td>
<td>385</td>
<td>0.14</td>
<td>0.3</td>
</tr>
</tbody>
</table>

In order to overcome the complications of a large overall body coil simulation environment with the sub-mm detailed implant model, the Huygen’s source driven (see Section 4.3.2), two stage electromagnetic simulation method was used as throughout Chapter 4 [166], [178]. The SEMCAD thermal solver utilised the Penne’s Bio heat equation for which the steady state solution was applied as an indication of heating levels. The potential for overestimation using this solver was considered acceptable due to the results being used primarily to guide experimental procedures and as a relative comparison. Material property approximations were used for the highly conductive components of the implant to overcome long simulation times associated with the complex model.

The MRI induced RF heating dependence of implants on lead length, configuration and location has been widely documented [86], [87], [93], [95], [102], [150], [179], [180]. These have been specific to partially insulated electrode leads where the tip is exposed, however the effect of the elongated wires within the fully insulated pressure sensing catheter of the ICP device is predicted to also be a key determinant of device heating. A series of simulations were carried out with the length of the catheter varied from 50 to 600 mm long. The complete model environment is demonstrated in Figure 5-1 with all implants centralised in the ASTM torso z-axis, 20 mm from the edge and surface of the phantom gel, for implantation in the high SAR region. Simulations for each individual implant were run independently based off individualised Huygen’s box sources (outlined in red).
Figure 5-1: SEMCAD model environment for the investigation into catheter length effect on RF heating showing the series of ICP implant models with sensing catheter lengths ranging from 50 - 600 mm.

EM simulations showed peak E-field and SAR occurring at the distal tip of the catheter for all device lengths. This is consistent with the theory of elongated leads picking up RF energy along their lengths with the energy being deposited at the tip. The EM simulations showed peak SAR’s occurring at 150 mm and 420 mm lead lengths. Steady state thermal simulations were run based of uniform amplitude rung sources in the EM simulations in order to compare the effect of sensing catheter length on device heating across the 50 – 600 mm test range. Figure 5-2 shows the relationship between catheter length and maximum temperature.
Figure 5-2: ICP device steady-state simulated maximum RF heating (red) and maximum RMS E-field (blue) for sensing catheter lengths ranging from 50 – 600 mm long.

From the minimum length simulated (50 mm) to 250 mm the RF induced heating increases with increasing catheter length. The heating then shows a decreasing heating trend with catheter length, with a peak occurring with lengths 380-425 mm. All maximum temperature, E-field, and associated SAR values, occurred at the catheter sensor tip. The absolute temperature values are expected to contain some overestimation error through the steady state solver, however they provide important information about the relevant effect of changing catheter length on temperature for the ICP device. From these results, further numerical testing and physical testing of prototype devices were carried out at lengths of 150 and 420 mm. The 150 mm length is determined to be a large overestimation of catheter length required for the ICP application with the sensor tip implanted at a depth of 20 mm into the brain parenchyma and catheter tunnelled to the implant unit on the skull. As a comparison, Raumedic’s Neurovent-P-tel implantable ICP monitors range from 30-65 mm in catheter length [59]. The 420 mm length will allow for investigation into the simulation results peak, while providing information about pressure sensing applications requiring long length catheter and allow for the effect of coiling the long catheter device to also be investigated (Section 5.3.3).
5.2. The implantable pressure monitor

The ICP prototype incorporated all significant components having the potential to cause risk when in the MRI environment, or are unique to the implantable pressure sensing application. Numerical modelling results indicated the catheter length would be a key determinant of resulting RF induced heating for the device, which is consistent with published work on partially insulated leads for pacemakers, cardio defibrillators and neurostimulators [102], [103], [179]. Two versions of the device were built and investigated for RF induced heating, identical other than in catheter length; a short catheter device (SC) with the sensor 150 mm from the electronic unit, and an elongated long catheter device (LC) with the sensor 420 mm from the electronic unit. These variations are representative over estimations of potential target applications. The SC device, suitable for full implantation in the head of the patient, specifically targets the ICP application. While the LC device has the potential to accommodate the implant for more general pressure sensing applications, or for the electronic unit requiring distal implantation in the ICP application, and allows investigation of the temperature peak seen in numerical modelling results (Section 5.1).

5.3. The ICP device in a 3T clinical MRI

All experimental testing was carried out in Siemens 3T SKYRA clinical scanner (MAGNETOM Skyra 3T, Siemens, Munich, Germany).

5.3.1 Static field testing

MRI static magnetic attraction is proportional to the implant’s volume and geometry of ferromagnetic material, overall geometry and mass, and the strength and spatial gradients of the applied static field. For investigating safety of implanted devices, the deflection angle test was used as developed by New et al [85] and recommended in ASTM F2052 [79].

The test specifies that the translational force experienced by a device that is deflected by less than 45° when placed in the region of the highest spatial magnetic field gradient, is less than the attractive force owing to gravity [79]. Therefore any risk associated with force induced by the 3T magnetic field would be no worse than that experienced by normal daily activity [79]. The test fixture was a rigid structure with a protractor at the top attachment point with 1 degree graduated markings. A string weighing less than 1% of device weight was used to suspend the device from the 0 degree marking on the protractor [79]. The fixture and device was placed at
the off-axis position, where the static magnetic gradient was a maximum of 720 gauss/cm, as defined by manufacturer gauss line plots and empirically determined to cause the worst-case deflection [83], [181]. With the scanner inactive and just the static magnetic force of the magnetic bore influencing the device, the maximum deflection angle from the vertical direction was measured for each LC and SC versions of the device three times, and the mean deflection calculated.

The device may also experience a static field induced torque due to magnetisation of ferromagnetic materials which, if large enough, will attempt to align the long axis of the dominant ferromagnetic component with the field [87], [141]. A qualitative assessment of torque, as developed and extensively used by Frank Shellock [83], [84], [141], [148], [182] was used to assess the device safety. This method has been comprehensively used throughout the literature on a wide variety of implantable passive and active devices in the MRI environment and demonstrates an initial indication of induced torque. The SC and LC device configurations were tested individually, positioned on a flat plastic sheet with a millimetre grid. The device was orientated at a 45 degree angle to the static field and placed in the centre of the bore where the field is uniform and at its largest, ensuring that the worst-case effect is investigated. The device was visually inspected to determine whether any rotation owing to the presence of the magnetic field occurred. The device’s orientation with respect to the magnetic field was increased in 45° increments to encompass 360° of rotation and repeated for each 3 primary axis to fit in the bore for the short and long device. A qualitative scale was used to assess the torque where 0 = no torque, +1 = low torque, the device shifted slightly but did not align to the magnetic field, +2 = moderate torque, the device gradually aligned to the magnetic field, +3 = strong torque, the device showed rapid and forceful alignment to the magnetic field, +4 = very strong torque, the device showed very rapid and very forceful alignment to the magnetic field, as defined by Shellock et al [141].

For both the short and long catheter configurations of the device the average deflection angle was 15° and the qualitative torque was 0 – no torque.

5.3.2 Scan sequence SAR quantification

The clinical MRI system reported whole-body averaged SAR (WB-SAR) is known to be a conservative estimate for patients in the MR machine. This reported WB-SAR has been demonstrated to underestimate the heating for scaling the heating results of implants by up to a factor of 7 [183]. To avoid this underestimation, the calorimetry method outlined in ASTM
F2182 was used to quantify the RF energy deposited in the phantom during a physical MRI scan such that the numerical results could be accurately scaled [81], [139], [184]. This was required in order to quantify the RF environment in which the ICP device's heating is being tested to avoid both scanner system reported SAR in-accuracy and discrepancies between scanners for a given set of parameters [139], [180].

The body RF coil was used to transmit RF energy as it exposes a large area to RF power during scanning and is considered worst case with respect to RF heating [142], [185]. Table 5-2 describes the 15 minute scan sequence designed to maximise the RF energy deposited by the body birdcage coil used for testing the interactions of the ICP device. Landmark positioning was consistent across the centreline of the longitudinal y-axis of the phantom torso for all scans.

<table>
<thead>
<tr>
<th>MRI Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>Turbo spin echo</td>
</tr>
<tr>
<td>TR</td>
<td>5760 ms</td>
</tr>
<tr>
<td>TE</td>
<td>124 ms</td>
</tr>
<tr>
<td>Turbo Factor</td>
<td>23</td>
</tr>
<tr>
<td>Plane</td>
<td>Transversal</td>
</tr>
<tr>
<td>Flip angle</td>
<td>180°</td>
</tr>
<tr>
<td>Bandwidth</td>
<td>130 Hz/Px</td>
</tr>
<tr>
<td>Field of view</td>
<td>400 mm</td>
</tr>
<tr>
<td>Matrix</td>
<td>512 x 512</td>
</tr>
<tr>
<td>Section thickness</td>
<td>10 mm</td>
</tr>
<tr>
<td>Total slices</td>
<td>40</td>
</tr>
<tr>
<td>Transmitter gain</td>
<td>(gain: high)</td>
</tr>
<tr>
<td>Scan time</td>
<td>15:00 (TA, acquisition time)</td>
</tr>
</tbody>
</table>

Table 5-2: Scan sequence parameters used to expose the ICP device to MRI RF energy using the RF body coil.

The ASTM torso-head phantom was constructed with Perspex (poly-methyl methacrylate) lined on all sides with 25 mm thick polystyrene insulating sheet, ensuring conductance of less than 0.029 W/m·K to the external environment. The phantom was filled to 9cm depth with 2.5 g/L NaCl dissolved in deionised water, with a measured conductivity of 0.47 S/m. The saline phantom was allowed to equilibrate in the scan room for 2 hours prior to scan time.
Opsens MPK4 fibre optic temperature sensors and TempSens signal conditioner (TempSens, Opsens Inc., Quebec, Canada) were used to measure changes in gel temperature while in the MRI, as in Chapter 4. The probes were positioned in the centre of the phantom, the phantom was moved to the centre of the MRI bore and the scan initiated. Upon completion, the phantom was immediately removed from the MRI, saline stirred without removing the insulation layers and the peak temperature change recorded. Temperature measurement was continuous throughout the scan allowing for the peak temperature to be recorded once stirring diffused the temperature concentrations throughout the phantom. Whole body average SAR was calculated from this temperature change, where \( \text{SAR} = \frac{c \Delta T}{\Delta t} \) [81].

The MRI system reported whole body (WB) SAR scaled for the 28 kg phantom was 3.5 W/kg, where the calorimetry determined value was 3.2 W/kg. This slight overestimation by the MRI system is consistent with other published experience and is due to manufacture proprietary methods of calculating SAR, validating the need to perform calorimetry [81], [139]. The SAR values are consistent with the system requiring to be run in First Level Mode, indicating an RF power deposition of greater than 2 W/kg. These results confirm the scan sequence is exposing the phantom/implant system to significant SAR for testing the upper limits of the potential for patient risk through heating. The calorimetry measured SAR value was used to scale numerical simulations of RF heating.

5.3.3 RF heating of ICP device

The RF induced heating for the ICP device was initially assessed by numerical models selected from the outcomes of Section 5.1 and scaled to the SAR measured in Section 5.3.2. Three implant positions were subsequently tested for RF induced heating in the 3 T clinical MRI.

5.3.3.1. Test specific simulation results

Following the scan sequence SAR quantification experiment, the simulations carried out in 5.1 were normalised to the measured SAR and repeated for the test specific, SC and LC devices.

The effect of coiling on the LC device has also been investigated by adding a simulation where the elongated 420 mm catheter length was coiled into 50 mm coils starting 80 mm from the catheter distal tip. This specification was to replicate that prescribed by the Codman acute partially implanted sensing catheter for safe use in the MRI which outlines: “leave a straight segment approximately 8 cm in length, as measured from the tip of the implanted sensor. Coil
the remaining CODMAN MicroSensor near the base of the connector into 5 or 6 loops approximately 5 cm in diameter...Do not perform MRI with the CODMAN MicroSensor in a “straight line” configuration. Failure to follow this guideline can result in serious injury to the patient.” [97]. The simulation model environment and temperature distribution for the short and long catheter device is shown in Figure 5-3.

![Figure 5-3: Model environment and steady-state temperature distribution for the short and long catheter devices. Temperature distributions are log scale, normalised for the maximum temperature for each device (1.8 °C and 9.2 °C).](image)

For the short catheter device and coiled catheter configurations, peak E-fields and temperatures around the body of the telemeter and tip of the sensor were of a similar magnitude, with the large localised temperature and E-field concentrations seen for the long catheter device no longer occurring. Less than 2 °C steady state heating was reached in all short and coiled catheter configurations, with the 150 mm model reaching a steady state temperature of 1.8 °C, and the 420 mm catheter coiled around a 50 mm diameter reaching 1.7 °C. The 420 mm, long catheter device reached a maximum steady state temperature of 9.2 °C.

5.3.3.2. Clinical MRI experiments

Physical MRI experiments were carried out in a Siemens SKYRA 3T/128 MHz using the RF body transmit/receive coil. The 15 minute scan, as characterised in the scan sequence SAR quantification, used was designed to maximise RF energy deposition.

For the ICP device, heating was assessed for both the short and long configuration at 128 MHz/3T. Numerical simulations were used to investigate E-field distributions in the phantom with the device present in order to verify worst case device positioning was being targeted [72], [184]. Results from these simulations determined the experimental test protocols. The experiment set up demonstrates a likely overestimation of localised heating due to a lack of tissue perfusion. Three implant configurations were investigated, shown in Figure 5-4.
Figure 5-4: The three implant locations tested for the prototype ICP device showing device and catheter layout with associated fibre optic temperature sensor positioning (+).

Implantation location 1, with the elongated lead positioned in the area of highest SAR/heating, was expected to cause the highest heating results as determined by numerical models of the ASTM phantom. This configuration would be considered for applications outside of ICP, or when the patient requires distal implantation of the electronic unit. The short catheter device, which represents the configuration expected to be most commonly used for the ICP application, was also tested in this high SAR region (Implant location 2). Implant location 3 replicates conditions from acute ICP sensing catheter device manufacturer Codman to ensure patient safety when undergoing MRI with an acute ICP sensing catheter implanted. The long lead of the acute ICP catheter is specified to be coiled in a circle approximately 5 cm in diameter after leaving a straight segment of 8 cm from the sensor tip [97]. This set up was tested with the long catheter device, allowing 8 cm from sensor tip to coil, 2.25 turns, and 3 cm from coil to electronic unit.

The ASTM head torso phantom was filled with a gelled saline solution (1.32 g/L NaCl, 10g/L polyacrylic acid) which had a verified conductivity of 0.47 S/m. The gelled saline phantom was allowed to equilibrate in the scan room for two hours prior to scan time. The device was positioned in the phantom in the three implantation locations of interest were investigated.

For all configurations a fibre optic temperature sensor was located at the catheter lead tip, as numerical models predicted this point to be where maximum temperature rise would occur. A temperature sensor was also positioned at the opposite, telemetry unit end of the device, and at the junction between device and catheter or a sharp bend in the catheter. For all heating
experiments, the landmark positioning was consistent with the SAR calorimetry method, at the centre of the phantom torso.

The fibre optic probes were positioned using Perspex clamps and guided with vitrotubes™ 1.8 mm glass round capillaries (Vitrotubes, VitroCom Inc.) to allow for accurate and repeatable positioning through the gelled saline. Baseline temperatures were recorded for 2 minutes, before recording throughout the scan and for 2 minutes post scan. The highest temperature change seen was recorded. Temperature sensor positioning was inspected post scan to ensure no movement had occurred. Each experiment was repeated with the implant removed and the temperature sensors set in position to record background temperature changes for the given scan set up.

The highest temperature change seen was for the long catheter device torso experiment, consistent with the predictions from the modelling results. The temperature change at the sensor tip was 7.2 °C, where the short catheter device caused a temperature change of 1.7 °C, after 15 minutes of scan time. Reference temperature measurements ranged from 0.7-0.8 °C in the phantom.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Maximum heating measured (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device present</td>
</tr>
<tr>
<td>Long device torso</td>
<td>7.2</td>
</tr>
<tr>
<td>Short device torso</td>
<td>1.7</td>
</tr>
<tr>
<td>Long device coiled torso</td>
<td>0.8</td>
</tr>
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</table>

Table 5-3: Summary of RF induced temperature change for the three tested device configurations and their associated temperature change with no device present.

The time course heating during the 15 minute MRI scan for the short and long device implanted in the phantom region of high SAR is shown in Figure 5-5.
5.3.4 Device function testing

The device was finally subjected to a wide variety of scan parameters to determine if the MRI machine could interfere with the device’s operation. The potential for induced currents from the MRI’s pulsing RF and gradient fields to alter device function is extremely difficult to characterise and predict. Testing requires exposing the device to a large variety of potential scan and MRI environment conditions. A series of 8 scans were selected based of previously reported results on effects of MRI on function. The device was also exposed to the static field multiple times in each orthogonal axis while passing in and out of the bore ten times. The basic function and calibration of the device was tested by checking its response to a step pressure increase prior and post exposure to the range of MRI conditions outlined in Table 5-4. The pressure increase was generated by inserting the catheter tip to a syringe via a tuohy-borst adapter and monitoring the pressure measurement through the Millar configurator receiver (TR190, Millar Inc, Auckland New Zealand) and software (Configsoft 2.0, Millar Inc, Auckland, New Zealand).
Chapter 5. MRI Interactions of an ICP Device: Measurement and simulations

<table>
<thead>
<tr>
<th>Sequence</th>
<th>T1-SE</th>
<th>T2-SE</th>
<th>T1-FSE</th>
<th>T2-FSE</th>
<th>GRE, 3D</th>
<th>FGRE, 3D</th>
<th>GRE, MTC</th>
<th>EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (ms)</td>
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<td>3000</td>
<td>700</td>
<td>5010</td>
<td>20</td>
<td>9</td>
<td>628</td>
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</tr>
<tr>
<td>TE (ms)</td>
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<td>105</td>
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<td>180</td>
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<td>Field of view (mm)</td>
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<tr>
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<td>256x256</td>
<td>256x256</td>
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<td>256x256</td>
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<tr>
<td>Slice thickness (mm)</td>
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<td>10</td>
<td>10</td>
<td>3</td>
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<tr>
<td>Imaging plane</td>
<td>Transverse</td>
<td>Transverse</td>
<td>Transverse</td>
<td>Transverse</td>
<td>Volume</td>
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<td>Exposure time</td>
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</tbody>
</table>

Table 5-4: Eight scan sequences used to expose the ICP device to a range of 3T MRI conditions.

Exposure to the 3T static field and multiple scan sequences did not induce any interference with the prototype device function, response to the step pressure increase prior and post exposure was within 1 mmHg.

5.3.5 Device induced artefacts

ICP device induced artefacts were evaluated for the 3T/128 MHz Siemens’s scanner for the prototype device and the pressure sensing catheter alone. The device and catheter were positioned in separate rectangular Perspex containers containing a Perspex grid. Nylon cylinders were included around the device/catheter to act as reference objects in the scans. The containers were filled with a 1.5 g/L copper sulphate solution. The transmit-receive head coil was used with the following scan sequences designed to induce significant artefacts. The sequences, given below, have been well tested throughout the literature on similar head implants [84], [185] for representing induced artefact while maintaining imaging geometries:

1. **T1 weighted spin echo sequence:**
   
   TR 500 ms, TE 20 ms, 10 mm slice thickness, 280 mm field of view, 256 x 256 matrix size, 2 averages, 250 Hz/Px bandwidth

2. **Gradient echo pulse sequence:**
   
   TR 100 ms, TE 15 ms, 30° flip angle, 10 mm slice thickness, 280 mm field of view, 256 x 256 matrix size, 2 averages, 200 Hz/Px bandwidth
Imaging planes were orientated perpendicular and parallel to the short and long axis of the device. Multiple section locations were tested to determine those which showed the largest artefacts. The area of the artefact was determined by analysis of the void size and reference objects through use of Siemens scanner image processing software (Syngo FastView, Siemens, Munich, Germany).

The device caused large artefacts relative to its size. The gradient echo pulse sequence caused the most severe artefacts with a circular signal void in the transverse orientation about the device’s telemetry unit with a diameter of over 100 mm and a loss of signal intensity and geometric distortions seen extending over 110 mm from the unit. The pressure sensing catheter and tip caused minor distortions of a maximum 5 mm. The largest artefact slice observed for both the gradient and spin echo sequences is shown in Figure 5-6.

![Figure 5-6: Image of artefact test set up (left) with SC device in phantom with the worst artefact slice observed for the (left to right) gradient echo coronal plane, gradient echo transverse plane, spin echo coronal plane, spin echo transverse plane.](image)

The largest artefacts were produced using the gradient echo pulse sequence. Although there are a large variety of scan parameters to be investigated to ensure absolute worst case is demonstrated, this sequence allows for comparison against multiple published previously investigated devices. The large artefact is consistent with similar active implants at 3T [148], [186] and could potentially inhibit visualisation of key areas of interest in the brain or near the implanted device. However, these experiments use a scan designed to demonstrate the ultimate potential of a device to generate image artefact using techniques such as large slice thickness, which are unlikely to be used in the clinical setting when obtaining high quality diagnostic images. Scan parameter optimisation techniques have been developed and demonstrated to avoid image quality concerns where metallic implants are present and could be used to reduce the artefact produce by the ICP device [187], [188].
5.3.6 Artefact breakdown

Results from the investigation into MRI-device-patient interactions using a prototype implantable pressure sensing monitor indicate the device has the potential to achieve MRI conditional approval with minor MRI induced force and torques, and safe RF heating levels achievable through device feature design. The image artefact caused by the device is significant relative to device size and demonstrates the potential to reduce the diagnostic quality of the MR images. An investigation into the source of the artefact was carried out to determine if design changes to the prototype could reduce such image distortions.

The device was broken down into significant components which were thought to be a potential source of the artefact – the inductive power coil, implantable lithium ion battery, and the electronic PCB. The PCB was further broken down to two separate versions; 1) original complete stand-alone PCB encapsulated in silicone (no battery, coil or sensing catheter), 2) best-case stand-alone PCB. For the “best-case” PCB, surface mount components were removed which were identified as ferromagnetic using a rare earth magnet. This revealed the clock crystal as a significant contributor to the static-field induced torque and this component was removed from the “best-case” PCB. When the battery was tested alone, the terminal tags were removed which displayed weak magnetic attraction to the hand held rare earth magnet. Due to the RF heating results in Section 5.3.3, the effect of coiling the long catheter on artefact was also investigated, using the 420 mm catheter length coiled in 50 mm diameter. The procedure used for the full device prototype was repeated for seven component variations:

1. Prototype device excluding battery
2. Prototype device excluding battery and IPT coil
3. Prototype device using “best-case” PCB
4. “Best-case” PCB alone
5. Implantable rechargeable battery alone
6. IPT coil alone
7. Long catheter coiled

Each component/device was centred in the head phantom containers filled with a 1.5 g/L copper sulphate solution. The transmit-receive head coil was used with the same scan sequences from 5.3.6 to investigate worst case artefacts.
The images revealed minor artefacts (< 5mm) for the IPT coil alone, but significant artefacts, approximately equivalent to the full prototype device for each configuration containing the PCB (1., 2., 3. and 4.). The battery alone also caused significant artefact, with only a slight reduction on the signal void caused with the device PCB variations. The long catheter coiled developed a pronounced signal distortion and void about the coiled region, not seen in the preliminary testing of the short catheter alone.

Examples of the image slices showing the largest artefact generated by the gradient echo pulse sequence in the coronal and transverse plane for the prototype device excluding battery, “Best-case” PCB alone, battery alone, and long catheter coiled are shown in Figure 5-7.

Figure 5-7: Gradient echo pulse images for the (left to right) prototype device excluding implantable battery, "best-case" PCB alone, battery alone and long coiled catheter. Artefacts are shown for the coronal plane (above) and transverse plane (below).

These results indicate that both the battery and PCB have an equivalent effect on image artefact approximating that seen using the full PCB prototype. It is useful to see the artefact of the battery because there are multiple options that could be considered to reduce artefact generation. These options include different battery technologies (e.g. lithium polymer versus
lithium ion) and eliminating the batter in favour of only providing IPT for powering the device. The PCB itself causing an equivalent artefact is of concern as it forms an integral part of the device which cannot be eliminated. It is hypothesised that the copper ground planes of the PCB may be significant in the artefact observed. The ground planes serve a useful purpose in eliminating electrical noise and form part of the radio antennae design. Further work is justified in understanding the contribution of the way the PCB is designed and the trade-off between electrical performance and artefact generation.

The coiling of the long catheter introducing image distortions is not unexpected due to the resulting concentration of the sensing wires. This finding may influence the location of such coiling to avoid both heating and artefact with the implant configuration. These experiments investigated the source of the artefact using a scan designed to produce significant image distortions while maintaining geometries. It is unlikely that such scan parameters will be used in the imaging of a patient and the investigation and development of optimised scan sequences for imaging in proximity of implantable active devices may be required to reduce artefacts induced by the implantable pressure monitoring device.

5.4. ICP device safety in MRI

MRI interactions of the prototype pressure sensing device indicate the potential to achieve 3T MR Conditional approval based on MR induced force, torque or RF heating. RF heating of short catheter configurations indicate safe scanning can be achieved, even at high (> 3 W/kg) whole-body averaged SAR producing scans. Elongated sensing catheter configurations introduce significant heating risk with temperature increases over 7 °C recorded in the 3T clinical scanner. The device implantation location and prospective MR scan parameters will have to be considered to avoid adverse effects on image quality due to the significant artefact produced on images relative to device size.

In order to establish the conditions behind safe use of the ICP device in the MRI, the final clinical device must be tested as carried out in this chapter and towards the full ISO/TS 1052 methods, including consideration of the 4-tier combined numerical and experimental procedure for RF heating. These results provide confidence that the device will achieve conditional approval (provided catheter lengths are limited) during the final product design process. Experimental testing show at a catheter length of 150 mm, 1.7 °C of heating is experienced during a 15 minute scan sequence producing high WB-SAR (> 3 W/kg), as measured by
calorimetry. This catheter length was chosen as a generous overestimation of the length required for ICP measurements [59]. Based on numerical model results, it is expected that catheter lengths shorter than 150 mm will induce considerably less heating. Furthermore, considering the head SAR limit of 3.2 W/kg for an MRI operating in Normal or 1st Level Controlled mode, the MRI heating experiments carried out in this chapter include significant overestimation of the clinical requirement [78]. It is anticipated that the future final configuration of the ICP device will be able to demonstrate MR Conditional safety through low tiered ISO/TS 10974 testing. These low tiers include significant overestimation to allow demonstration of device safety for small, low risk devices without extensive numerical modelling work incorporating anatomical models (as required in tiers 3-4).

Should an implantable device be considered for clinical application with a long catheter, significant further investigation into the conditional safety of the device will be required given the high heating observed in the ASTM phantom at 3.2 W/kg WB-SAR. It is expected that higher tiered testing, as per ISO/TS 10974 would be necessary to define the conditions for safe operation in the MRI. Gradient field induced heating was not included in this investigation into device-MRI interactions. The ability of the RF coil model to predict clinical scanner heating provides confidence that the RF field is the main source of heat generation, as expected for an implant of small size and limited conductive material where gradient interference is minimal [87], [99]. However the final clinical device will require formal analysis of gradient switching field induced heating and device vibration.

Due to the wide range of current medical devices with MR Conditional approval utilising titanium and ceramic encapsulation technologies, it is expected that the change in encapsulation will not incur significant heating risk, and the dominant MRI heating factor will continue to be the configuration of the sensing catheter.

All testing was carried out with use of a 3T clinical MRI scanner. Static magnetic interactions will show the device will be safe in magnetic field strengths of 3T or less. However, RF heating results and device function interference are specific to the MR system tested. Results from such interactions cannot be extrapolated to lower (or higher) strength machines, and are dependent on RF frequency, transmit/receive coils, specific dimensions and geometry [87], [171].
This MR testing programme for the prototype pressure sensing device has given us confidence that a clinical ICP monitoring device, based on the technologies presented, could qualify as MR conditional for 3T MRI machines.
6. Conclusions and Future Work

The aim of this work was to develop and test an implantable pressure sensing device towards a clinical application. Monitoring ICP to improve the management of patients suffering hydrocephalus was the proposed target clinical condition, with a resulting emphasis on sensor stability, signal quality and MRI safety.

Chapter 1 outlined the motivation behind the device; the hydrocephalus condition and its characteristics, current treatment practices, and associated complications. The clear need for a long term ICP monitor was described, supported by multiple prior attempts towards a device solution since the 1970’s with common failure traits, often related to sensor drift. The most successful technology from Raumedic targeting chronic ICP measurements was also presented. The importance of MRI safety with the implanted device was introduced, of particular concern for the hydrocephalus application due to a reliance on imaging techniques for determining patient health. An overview of patient-device-MRI machine interactions was given, with reference to specific testing standards used to establish implanted device safety with MR imaging.

Chapter 2 described bench top testing of a sensor technology identified as a potential candidate for clinical use. The long term stability of a 2 Fr pressure sensing catheter was investigated, through the development of a pressure drift test rig. Eight sensors continuously operating and monitored for over 1 year were used to determine the feasibility of the sensors being used for chronic ICP monitoring. Results showed a wide variation in sensor performance, with two sensors emerging as good candidates drifting less than the target ±2 mmHg/year. Sensors with poor performance showed evidence of high instability within one month of testing, providing confidence a screening protocol may be successful in identifying sensors unsuitable for the long term application. The sensor’s frequency response was also investigated against
physiological signals showing the potential to monitor high fidelity signals with high accuracy. The inductive power pickup of the laboratory device was altered to a ferrite-less coil in anticipation of improving susceptibility to MRI interactions.

Chapter 3 involved the \textit{in-vivo} testing of the pressure monitoring device. Devices appropriate for monitoring laboratory animals, based on the 2 Fr pressure sensing catheter were used to make chronic measurements of rat LVP. The first derivative of LVP, LV dP/dt was extracted as a contractility index, providing the first accurate measurements of this signal up to 25,000 mmHg/s in both the chronic and drug induced condition. The device modified to include the ferrite-less pickup developed in Chapter 2 was used in an acute investigation into monitoring sheep ICP. Surgical methods for implanting the sensor and ventricular catheter were investigated. An acute, gold-standard ICP catheter was used in conjunction with the implanted, telemetry based measurement. Changes in ICP were induced via the ventricular catheter and mechanical means showing the ability of the sensor to measure across the ICP range. Significant sensor light sensitivities were revealed.

MRI induced RF heating of the device was identified as a key complication in MR Conditional approval for AIMD’s. In Chapter 4, FDTD simulation software SEMCAD was used to develop and verify an EM model of the RF body coil of a 3T MRI. A standard implant was used to compare and scale the model against a clinical scanner high RF energy scan sequence, with the model predicted heating accurate to within 0.1 °C. Approximations towards modelling key components of the ICP implant were investigated and validated, including the printed circuit board and pick up coil.

In Chapter 5, the ICP device in its prototype stage was tested against standard test methods for MRI safety. The numerical model developed in Chapter 4 was used to guide physical scanner tests and to investigate the dependence of RF heating on the length of the sensing catheter. The MRI induce force, torque, function, heating and artefact were tested with the clinical 3T scanner. Force and torque effects were well within safety limits, and the device did not alter in function in response to MRI exposure. Heating could be controlled depending on catheter length to safe limits; however artefacts were significant relative to the device size. A breakdown of the components causing artefact revealed the device PCB a central cause.
6.1. Contributions of this thesis

The main contributions of this thesis include:

- Demonstrating the long term stability of implantable pressure sensing catheters over one year of operation.
- Design of ferrite-less IPT pickup coil for use in *in-vivo* ICP measurements and to guide MRI interaction modelling and experiments.
- Demonstrating sensor performance *in-vivo* including high accuracy chronic LVP and LV dP/dt measurements in the rat heart.
- Development of surgical methods during acute ICP measurements in a sheep model.
- Development and validation of a 128 MHz RF coil model against a 3T clinical scanner and scanner sequence.
- Validation of individual AIMD component model approximations for RF heating analysis.
- Demonstrated the catheter length dependence and length-temperature relationship of MRI RF heating for the prototype implantable pressure sensing device.
- Demonstrated MRI device interactions including force, torque, RF heating, function and artefact with the implantable pressure sensing device in its prototype stage.

While a great deal of evidence has been gathered to support the viability of a fully implantable pressure monitoring system appropriate for chronic measurement of ICP, there remain substantial risks. Although some sensors were found to be suitable and showed good drift characteristics, a reliable method of identifying unsuitable sensors needs to be validated. In this thesis, multiple methods have been developed and documented on how sensors, telemetry elements and telemetry systems can be designed and tested. These methods can be used in future device evaluation programmes which may adopt new technologies including new sensor candidates.
Chapter 6. Conclusions and Future Work

6.2. Publications

The work from this thesis has been published in the following:

Journal papers


E. Stehlin, D. McCormick, S. C. Malpas, B. P. Pontré, P. Heppner, D. M. Budgett, “MRI interactions of a fully implantable pressure monitoring device”, *Journal of Magnetic Resonance Imaging*. 2015 (provisionally accepted for publication subject to reviewer’s recommended changes)

Conference proceedings


6.3. Future work

The work presented in this thesis has initiated the development of a long term implantable ICP device to improve hydrocephalus patient management. An implantable laboratory animal monitoring system with promising pressure sensor technology and stability was used as the device development platform. Testing and development focused on the pressure sensing catheter, power source, and MRI interactions to adapt the existing device towards the clinical application. This research provides confidence that a long term implantable clinical ICP monitor can arise from the presented technology, however there are several key aspects requiring further investigation in progressing towards a medical implant.
Chapter 6. Conclusions and Future Work

Sensor stability screening

The sensor stability analysis outlined in Section 2.2 revealed long term drift characteristics of eight sensors. The variance in individual sensor performance was apparent in the early stages of the test timeline (within one month) providing confidence that a short term stability sensor screening protocol may be successful in excluding sensors not suitable for the long term implantation application. A larger long term test sample of sensors will be required to develop and define a successful protocol. This work also exposed the need to determine the source of the sensor drift, particularly for the poorly performing sensors (> 10 mmHg/year). An investigation into the source or cause of sensor drift may include physical discrepancies between sensing elements, encapsulation techniques and sensor handling.

Designing an accelerated test

The year-long stability investigation carried out in this initial research into chronic pressure sensor zero-drift was important for the feasibility investigation but required significant time demand. An investigation into accelerated life testing for sensor stability and encapsulation hermeticity will allow for the long term characteristics to be predicted through short term testing in a highly demanding environment. This has the potential to greatly reduce the timeline for evaluation of future prototype developments.

External reader wand development

The ferrite-less IPT pick up and primary coil were developed (Section 2.4) as a working coil set for acute experimentation and to provide design indication for MRI modelling and experimentation. However, an optimisation of the coil system was not carried out. In order to further develop the power system, the development of the external reader wand is required to determine the limits on the portable primary coil. With the external reader wand defined, the IPT system will be able to go through optimisation analysis to improve link efficiency over required coupling conditions.

Device encapsulation and data communication

Throughout this research, the encapsulation used in the laboratory animal implant (Parylene and silicone) remained. In development towards a chronic clinical device, long term encapsulation methods and materials with established safety approval will be implemented for the ICP implant. It is anticipated this will involve the use of titanium with glass feed-throughs
for IPT and sensor connections, or ceramic encapsulation methods. Similarly, established specific implantable medical device wireless communication methods, such as data transfer in the Medical Implant Communication Service (MICS), will require investigation for use with the ICP implant, which currently utilises the 2.4 GHz ISM radio band. The data communication method will also have to be incorporated into the external reader wand.

**Chronic large animal ICP experiments**

To provide confidence in the ability to measure ICP long term in human patients, chronic animal experimentation will be required. It is anticipated that the next stage will involve implanting the device in the brain of sheep, allowing it to fully recover and return to the field. Measurements of ICP will be taken periodically over at least three months. This will require the external reader wand to be in operation and implementation of the appropriate communication band and robust encapsulation. These studies are also crucial for the purpose of understanding the biological response (at least in sheep) to the presence of the devices which may influence the accuracy of the pressure measurement in representing the true ICP. This can be assessed at the end of the experiment when acute measurements can be obtained to verify the ICP against the test device, and then the test device can be recalibrated on explantation.

**MRI safety testing towards ISO/TS 10974**

The work carried out in this thesis demonstrated the value in MRI testing in the prototype stage to provide an indication of device-patient safety in the 3T MRI and aid device design. Incorporation of significant overestimation of heating conditions provides confidence the final device configuration will qualify as MR Conditional. However, these methods will have to be repeated for the final device configuration with a full analysis of testing conditions and uncertainties as required for ISO/TS 10974 to define the conditions of safe operation of the ICP device in the MRI environment. This thesis provides guidance on how to implement these tests.
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