Movement Correction and Clinical Implementation of Wearable Magnetoencephalography (MEG)

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I, Stephanie Mellor, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

This project has been carried out by Stephanie Mellor at the Wellcome Centre for Human Neuroimaging, Institute of Neurology, UCL under the supervision of Prof. Gareth Barnes and Prof. Matthew Walker.
Abstract

Magnetoencephalography (MEG) is the non-invasive measurement of magnetic fields due to neuronal current flow. The magnitude of the magnetic fields (10 fT to 1000 fT) is millions of times smaller than the Earth’s static field. Consequently, highly sensitive magnetic sensors are required for MEG. Until recently, MEG systems have been based on sensors requiring cryogenic cooling. Hardware limitations from this cooling have made MEG systems large, immobile and expensive. In recent years, Optically Pumped Magnetometers (OPMs) have become viable sensors with which to measure neuromagnetic fields. These can be placed directly on the scalp. This wearability means that the participant is no longer required to remain still and the cost of the system, both financial and in terms of space, is generally lower. The freedom of movement opens up new neuroscientific and clinical applications. However, this new system is not without limitations. Movement in particular leads to artefacts unlike those previously seen in MEG; the OPM properties (gain, sensitive axis orientation, phase) are dependent on the ambient magnetic field at the sensor, which changes with position. In this thesis, we look at the impact of movement on OPM based MEG (OP-MEG) and how it can be reduced.

In Chapter 2, we look into the cause of movement artefacts in OP-MEG, by mapping the spatial variation in the background magnetic field in our OP-MEG system. We show that the field varies both spatially and temporally, and that by modelling it we can reduce the interference in an OP-MEG recording. In Chapters 3 and 4, we correct for this changing field in real-time, first in simulation and then empirically. Based on the simulation results, we updated our empirical method to remove reliance on recording the position of the participant and to minimise time delays in providing the correction. Finally, in Chapters 5 and 6, we record interictal (between seizure) and ictal (seizure) OP-MEG in patients with epilepsy, while considering the impact movement has on the recordings and interictal event detection.
Impact Statement

The freedom of movement in OP-MEG, when compared with previous cryogenic MEG or functional Magnetic Resonance Imaging (fMRI), means that it holds great promise for neuroscience experiments involving natural human behaviour, or application to population groups such as children or people with movement disorders, from whom it has previously been challenging to record.

We demonstrate that real-time feedback to the electromagnetic coils on-board OPMs can be used to actively compensate for subject movement. This has the potential to not only allow a larger range of movements during MEG recordings, but also to reduce some of the dependence on expensive magnetic shielding.

We show some of the earliest OP-MEG recordings of both interictal (between seizure) and ictal (seizure) epileptiform activity. We demonstrate that epileptiform activity can be recorded and localised with OP-MEG, while the patient is comfortably seated and their head movement is unconstrained.

By allowing more comfortable recording, due in large part to greater freedom of movement, it will be possible to increase patient MEG recording times with OP-MEG. This will lead to a higher number of both ictal and interictal events being recorded and has the potential to give rise to more precise surgical planning for more patients.
Research Paper Declaration

This thesis contains work reported in the following manuscripts:


- **Stephanie Mellor**, Tim M. Tierney, Robert A. Seymour, Ryan C. Timms, George C. O’Neill, Nicholas Alexander, Meaghan E. Spedden, Heather Payne, Gareth R. Barnes, 'Real-time, model-based magnetic field correction for moving, wearable MEG', *In Preparation*


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## Contents

1 Introduction
   1.1 Origin of MEG Signals .................................................. 12
   1.2 MEG sensors ............................................................. 14
      1.2.1 Cryogenic MEG ...................................................... 14
      1.2.2 OPMs ............................................................... 16
   1.3 Movement in MEG ....................................................... 20
      1.3.1 Cryogenic MEG ...................................................... 20
      1.3.2 OP-MEG ............................................................ 21
   1.4 Epilepsy and MEG ....................................................... 22
   1.5 MEG analysis methods .................................................. 23
      1.5.1 Data pre-processing .............................................. 23
      1.5.2 Source localisation .............................................. 27

2 Experiment 1: Magnetic Field Mapping and Correction for Moving OP-MEG 35
   2.1 Introduction ............................................................. 35
   2.2 Methods ................................................................. 36
      2.2.1 Theory .............................................................. 36
      2.2.2 Recording Setup .................................................. 39
      2.2.3 Experiments ....................................................... 40
   2.3 Results ................................................................. 42
      2.3.1 Triaxial Recording ................................................ 42
      2.3.2 OP-MEG Recording ............................................... 44
   2.4 Discussion .............................................................. 47
   2.5 Conclusion .............................................................. 50

3 Experiment 2: Optimising OPM feedback based on field models: A simulation study 51
   3.1 Introduction ............................................................. 51
   3.2 Methods ................................................................. 51
   3.3 Results ................................................................. 53
   3.4 Discussion and Conclusions .......................................... 55

4 Experiment 3: Local, real-time magnetic field update for OP-MEG 58
   4.1 Introduction ............................................................. 58
   4.2 Theory: Homogeneous Field Correction ............................. 59
   4.3 Methods ................................................................. 60
      4.3.1 Control Algorithm ............................................... 60
4.3.2 Implementation .......................................................... 60
4.3.3 Validation Experiments .............................................. 61
4.4 Results ............................................................................. 65
  4.4.1 Environmental Noise Recordings ................................. 65
  4.4.2 External Coil Recordings ........................................... 66
  4.4.3 Auditory Evoked Response Paradigm .......................... 72
4.5 Discussion and Conclusions ............................................ 74

5 Experiment 4: OP-MEG and Epilepsy Pilot ......................... 77
  5.1 Introduction .................................................................... 77
  5.2 Methods ......................................................................... 78
    5.2.1 Recordings .............................................................. 78
    5.2.2 Analysis ................................................................. 79
  5.3 Results ............................................................................. 81
  5.4 Discussion ...................................................................... 86

6 Experiment 5: OP-MEG of hippocampal and temporal lobe epilepsies, a case study 89
  6.1 Methods ......................................................................... 89
  6.2 Results ............................................................................. 91
    6.2.1 Interictal ................................................................. 91
    6.2.2 Ictal ........................................................................... 94
  6.3 Discussion and Outlook ................................................... 96

7 Discussion ........................................................................... 97
  7.1 General Discussion ........................................................ 97
  7.2 Outlook .......................................................................... 103

8 Bibliography ....................................................................... 104

List of Figures

  1.1 Zero-field OPM Schematic ............................................. 16
  1.2 OPM Response Function ............................................... 18
  2.1 Triaxial Field Mapping Set Up ...................................... 40
  2.2 Triaxial Field Mapping Sensor Placement ...................... 41
  2.3 Whole-head Field Mapping Sensor Placement ............... 41
  2.4 Background Field Spatial Map ...................................... 43
  2.5 Variance Explained against Model Order ....................... 44
  2.6 Movement PSD ......................................................... 45
  2.7 Example OPM recordings with Movement ..................... 46
  2.8 RMS Noise Reduction ................................................. 46
List of Tables

2.1 Spherical Harmonic Functions and Derivatives ........................................ 38

3.1 Feedback simulation error sources ............................................................... 53

4.1 Movement range in Auditory Experiment .................................................. 72
1 Introduction

Magnetoencephalography (MEG) is a non-invasive, functional neuroimaging technique. Small magnetic fields induced by neural currents are measured and used to infer the underlying activity. MEG measures the same source current flow as electroencephalography (EEG). The key difference is that the induced magnetic field is measured, rather than the electric field. The magnetic field is less influenced by the conductivity of the participant’s head, meaning that, at only a few millimetres, MEG often has a higher spatial resolution than scalp EEG (Englot et al., 2015; Stufflebeam et al., 2009). As a result, it has been shown to have clinical value for presurgical planning in epilepsy (Duez et al., 2016; Rampp et al., 2019). However, it is traditionally large and stationary, motion sensitive and uncomfortable, and so is not widely used clinically. These limitations are largely imposed by the cryogenic sensors typically used to record MEG, known as superconducting quantum interference devices (SQUIDs). However, the magnetic fields induced by neuronal current flow are exceptionally small - on the order of hundreds of femto Tesla - and so there are only a limited number of sensors capable of measuring them. Optically Pumped Magnetometers (OPMs) are relatively new magnetometers with a similar sensitivity to SQUIDs but which are small, self-contained and do not require cooling (Shah and Wakai, 2013). OP-MEG utilises these new sensors to create a wearable MEG system which avoids many of these traditional limitations. This new system is small, relatively comfortable and the participant can sit naturally during a recording (Boto et al., 2018). In this chapter, we will provide further detail on the motivation for OP-MEG, its limitations and the areas which this thesis aims to progress.

1.1 Origin of MEG Signals

The human cerebral cortex contains approximately $10^{10}$ cells, with around $10^{14}$ connections between them (Murre and Sturdy, 1995). At these connections, electrical and chemical signals are passed between neurons. The magnetic fields measured in MEG originate from ion transfer when large populations of neurons communicate. Neurons transmit information through the transfer of charged ions, which gives rise to a small current flow, which in turn induces a small magnetic field. While single neurons do produce magnetic fields from ion transfer, these fields are too small to be measured. It is thought that at least 50 000 neurons must be firing synchronously in the same region of the brain to produce a measurable MEG signal (Murakami and Okada, 2006). We will first examine the electrophysiology of a single neuron, then consider the macroscopic behaviour.

A neuron consists of the soma or cell body, dendrites and the axon. The cell body contains the nucleus of the cell. The dendrites are thread-like structures which receive electrical impulses from other cells and pass them to the cell body. The axon is a single fibre which carries electrical impulses from the cell body to other cells. Electrical signals from other cells are received at synapses along the neuron.

Like other cells, the neuron also has a membrane, controlling what does and does not enter the cell. Which ions can enter the cell is controlled by proteins on the membrane that pump selected ions in a particular direction, as well as passive ion channels. Whether these ion channels are open or closed is either
voltage gated or chemically controlled. Sodium ions (Na$^{+}$), Potassium ions (K$^{+}$) and Chloride ions (Cl$^{-}$) are particularly important to facilitate communication between cells. In an inactive state, there are much higher concentrations of Na$^{+}$ and Cl$^{-}$ outside of neurons than the intracellular concentration, while there is a higher concentration of K$^{+}$ inside of the neuron. This concentration gradient is maintained by sodium-potassium pumps throughout the membrane, which push ions against their concentration gradient. Overall, this leads to a resting potential difference across the membrane of approximately $-70$ mV (Hämäläinen et al., 1993; Goldman, 1943).

If the potential at the start of the axon (the axon hillock) reaches a critical threshold, voltage-gated passive ion channels open. Sodium ion channels open quickly, and so Na$^{+}$ ions rush into the cell due to the imbalance of intracellular and extracellular concentrations. This leads to a positive potential difference across the cell membrane, which in turn triggers ion gates further down the axon to open. At such high potentials, the Na$^{+}$ channels become inactive, until the voltage difference is once again negative. Potassium ion gates also open, although more slowly, and so potassium ions flow out of the cell. This then reduces the potential difference across the cell membrane. The K$^{+}$ ions will over-shoot, causing the cell to hyperpolarise, meaning that the membrane potential is below $-70$ mV. Now that the voltage is low, the sodium and potassium channels close and the concentrations of potassium and sodium are restored via ion pumps. As mentioned, the high potential at the axon hillock opens ion gates further down the axon. These in turn will open ion gates further down the axon, travelling down the axon until reaching the synapse of another neuron at the axon terminal. This is an action potential. As the charge distribution over the membrane is quickly going up and then down, due to the time for the ion gates to open and the signal to travel down the axon, at a snapshot in time, the membrane has an area of low potential followed by an area of high potential. As such, an action potential can be modelled as a current quadrupole travelling down an axon.

As mentioned, an action potential is triggered when the membrane potential at the axon hillock reaches a certain threshold. The potential at the axon hillock is altered by post-synaptic potentials travelling down the dendrites from other neurons. When an action potential from one neuron reaches a synapse at another neuron, it stimulates the release of neurotransmitters. These neurotransmitters diffuse across a small gap to reach the receiving neuron, where they bind with chemically-gated ion channels. This opens these channels which pump ions into the cell’s dendrites. Positive, excitatory ions such as Na$^{+}$ or K$^{+}$ raise the membrane potential and increase the probability of the neuron firing an action potential. Negative, inhibitory ions such as Cl$^{-}$ lower the membrane potential and reduce the probability of the neuron firing. A single post-synaptic potential (PSP) is insufficient to raise the membrane potential enough to trigger an action potential. Multiple excitatory PSPs over time are required to fire an action potential (Murakami and Okada, 2006).

Whether the PSP is excitatory or inhibitory, it creates a current known as the primary current along the dendrite as ions flow towards the cell body. At the cell body, ions are pumped back into the extracellular medium. This then creates a secondary, volume current outside of the cell, travelling in the opposite direction. It is generally accepted that the MEG signal is predominantly caused by the primary current, while EEG measures volume currents (Mondt, 1989).

PSPs usually dominate the MEG signal, rather than action potentials for a number of reasons. A single action potential or PSP is too small to be recorded outside of the head and so around $10^4$ neurons must be active coherently to record MEG (Hämäläinen et al., 1993; Murakami and Okada, 2006). Action potentials are fast, biphasic (i.e. increase and decrease from baseline) and the magnetic field from them decreases as
the inverse of distance cubed. Postsynaptic potentials are comparatively slow, monophasic (either increase or decrease from equilibrium) and the magnetic field from them decreases as the inverse of the square of distance. This means that, if a large population of neurons fire action potentials roughly simultaneously, they are unlikely to overlap well due to their short time. When they do overlap their magnetic fields may cancel because they have opposite phases. Additionally, assuming the MEG sensors are outside of the head, the distance may mean that the signal has attenuated too significantly for the MEG signal to be measured. By comparison, PSPs are slow enough to overlap and when they overlap they are additive. The signal decreases less dramatically with distance so is less strongly attenuated at a couple of centimetres from the head (Hämäläinen et al., 1993).

The arrangement of the neurons is also important to consider when looking at the origin of MEG signals. Neuron populations with aligned dendrites will produce a larger signal as the magnetic fields add constructively. The pyramidal cells of layers II, III and V of the cortex have long dendrites and are reasonably well aligned, meaning that the PSPs are long and broadly synchronous. Consequently, it is generally accepted that pyramidal cells in layers II, III and V of the cerebral cortex most significantly contribute to MEG signals (Hämäläinen et al., 1993).

In this thesis, we will demonstrate OP-MEG recordings from patients with epilepsy. Epilepsy is characterised by seizures, which at a neuronal level are prolonged periods of spontaneous, widespread, sustained synchronous activity (Sabolek et al., 2012). This means that strong MEG signals can be recorded during an epileptogenic seizure (Stufflebeam et al., 2009). Patients with epilepsy also usually experience more frequent but shorter periods of smaller synchronous activity between seizures, often originating from the same source as the seizure activity, known as interictal activity. This interictal activity can take many forms, for example as perhaps more traditional spikes and waves (also called interictal epileptiform discharges (IEDs)) but also as abnormal oscillatory activity or high-frequency oscillations. It has been hypothesised that this interictal (between seizure) and ictal (seizure) activity is initiated by a deficiency of inhibition relative to excitation in these neurons but this is still an area of much research and debate (Sabolek et al., 2012).

1.2 MEG sensors

1.2.1 Cryogenic MEG

MEG signals are non-trivial to measure. The Earth’s magnetic field is of the order of $5 \times 10^{-5}$ T, while neuromagnetic fields generally range between $1 \times 10^{-14}$ T and $1 \times 10^{-10}$ T. As a result, MEG is normally recorded in a magnetically shielded room (MSR). These rooms have walls made of aluminium and mu-metal, which are highly magnetically permeable, and so distort the background magnetic field pattern inside the room, reducing its magnitude. Depending on the MSR, the magnitude and spatial variation of the background magnetic field can be reduced to less than $1 \times 10^{-8}$ T and $5 \times 10^{-9}$ T m$^{-1}$ respectively. In addition to this, sensors for MEG must have a high precision in order to observe these small signals.

The first MEG was recorded by Cohen (1968). He used a 1-million turn copper coil with a ferrite core to record brain activity between 5 Hz and 10 Hz while the participant opened and closed their eyes. Not only was this single magnetometer cumbersome but it also had a low signal-to-noise ratio (SNR) compared with current technology; Cohen averaged 2500 repeats of the eye opening experiment to obtain a clear signal. These magnetometers meant performing MEG for clinical evaluations or neuroscience research was impractical.

The step change in the development of MEG came with the introduction of superconducting quantum
interference devices (SQUIDs). These are highly sensitive magnetometers, with a noise level of around 3 fTHz^{-1/2} (Körber et al., 2016). Consequently, they are capable of measuring fields of only a few femto Tesla strength (Clarke and Braginski, 2005) with only a few trials to achieve the SNR of Cohen’s original experiment. Until recently, SQUIDs were the only magnetometers available which were sensitive enough to perform MEG reliably.

As the name suggests, SQUIDs need superconductors to operate. Details of SQUID operation can be found in the SQUID Handbook (Clarke and Braginski, 2005). A traditional MEG scanner consists of an array of approximately 300 SQUIDs distributed evenly around the top and back of the head. However, unlike EEG where individual electrodes are placed directly onto the participant’s head, SQUID sensors in MEG are fixed into a scanner, into which the participant places their head. This is because superconducting metals only superconduct at temperatures close to absolute zero. As a result, the SQUID array is contained within a large chamber of liquid helium to lower its temperature. To maintain the temperature of this liquid helium and avoid harming the participant, this array is fixed in a vacuum chamber, with the sensors approximately 3 cm to 6 cm from an adult participant’s scalp (Boto et al., 2017).

The main advantage of MEG over EEG is in spatial resolution. Neural volume currents are distorted by the tissue between the source of the field and the electrodes on the participant’s scalp. The distortion depends on the structure and conductivity of the tissue. This limits the accuracy of MEG and EEG source reconstruction. Finite element modelling of individual participants’s heads (Piastra et al., 2018) can reduce this limitation, but requires MRIs for each participant and considerable time for the modelling, which overall makes an expensive and time consuming process, so it is not generally performed. The MEG signal however, is less dominated by volume currents than EEG, and so is less affected by individual anatomy. This gives MEG a maximum spatial resolution of millimetres. It also means that muscle artefacts are less significant since in MEG they are more tightly localised to fewer sensors, while in EEG the artefact spreads out to multiple electrodes.

It is worth noting that the spatial resolution of MEG is not always higher than EEG. EEG is more sensitive to deep neural sources and sources oriented radially to the scalp than MEG (Ahlfors et al., 2010; Hunold et al., 2016; Piastra et al., 2021). EEG also allows the participant to move freely and therefore record for longer in more natural environments than MEG. Therefore, whether MEG or EEG is preferable will depend on the application.

In turn, the advantage of MEG over Functional Magnetic Resonance Imaging (fMRI) is that it has a higher temporal resolution. MEG is a direct measure of brain function, as the magnetic fields are produced at the same time as the neurons communicate and travel to the sensors at the speed of light. fMRI however, measures the decrease in the volume of deoxygenated blood which occurs after neurons in an area of the brain are active. As a result, fMRI is much slower to record changes in activity and cannot record short pulses of activity, such as those you see in patients with epilepsy. Consequently MEG is a good technique to use if you require both high temporally and spatially resolved functional information.

However, the use of SQUIDs limits the practicality of cryogenic MEG. Firstly, the distance between the scalp and the sensors means that the signal is considerably attenuated before it reaches the sensors. Generally, the magnetic field strength from a neuronal source decays as the inverse of the square of distance, meaning that the signal strength of MEG could be greatly improved by moving the sensors closer to the scalp. This is particularly true for children. Most MEG centres only have one MEG scanner due to their cost and, unless it is a specialist centre, they are typically designed for adults. As children typically have smaller heads, this means the sensors are further from their scalp than for adults. Moving the magnetic
sensors closer to the scalp would also be beneficial for neuromagnetic sources deep within the brain, such as the cerebellum or hippocampus, which are typically difficult to measure with MEG (Boto et al., 2017).

Secondly, as previously mentioned, MEG is highly motion sensitive. Since the MEG sensors are fixed, if the participant moves their head, their brain moves relative to the SQUIDs. This changes the mapping between the sensors and the brain, and so changes the sensor recordings. This leads to errors in source reconstruction: the assumption is generally made that the head is stationary. The motion sensitivity of cryogenic MEG limits the experiments which can be performed and the population groups which can be studied. Children and patient groups who struggle to remain still are notoriously difficult to record from with cryogenic MEG (Wehner et al., 2008; Hill et al., 2019).

1.2.2 OPMs

Optically pumped magnetometers or OPMs are a relatively new type of magnetometer which generally have a higher noise floor than SQUIDs but at only approximately $15 \text{ fT Hz}^{-0.5}$, are sensitive enough to measure MEG (Boto et al., 2018). They do not require cryogenic cooling, so are small and self contained. This means an OP-MEG system can be created where they are placed directly on the scalp, theoretically increasing the signal from superficial cortical sources for an adult up to 10-fold from a cryogenic MEG system, and increasing the signal from deep sources such as the hippocampus approximately 2-fold (Boto et al., 2017; Iivanainen et al., 2017). Therefore, despite the higher noise floor the SQUID sensors, OPM based MEG (OP-MEG) may have a higher signal to noise ratio (SNR) than SQUID based MEG, depending on the region of interest within the brain. Additionally, when OPMs are worn on the scalp, movements of 5 cm over 0.5 s have been shown to be possible (Seymour et al., 2021; Boto et al., 2018; Holmes et al., 2021). This thesis focuses on increasing the range of possible movement and minimising its impact, by utilising active magnetic shielding on the individual sensors.

OPMs have their properties because they work on a different principle to SQUIDs, using the atomic properties of alkali metals to measure the local magnetic field. Figure 1.1 shows a schematic representation of the contents of an OPM. There are three primary components: a laser, a vapour and a photodiode. Rubidium or Caesium are often chosen for the vapour because they have a single valence electron in their outer shell. This means that they can be well described mathematically and can be optically pumped. A brief description of OPM operation is given below. Details are given by Tierney et al. (2019), with specific information on optical pumping available from Dumitrescu and Endlich (2007). Here we focus on low-field, Rubidium-87 vector magnetometers produced by QuSpin Inc.. A brief description of other OPM designs is given at the end of this section.

For these QuSpin sensors, the wavelength of the OPM laser is tuned to 795 nm, the D1 transition of Rubidium. It is collimated and right-hand circularly polarized, as required for optical pumping (Dumitrescu and Endlich, 2007). The laser gives energy to the gas, pushing the Rubidium atoms into a higher energy state. In this energy state, the spins of the Rubidium electrons are aligned and so the gas has a polarisation.
When there are no more electrons in the lower energy state in the gas, the laser cannot excite the gas further. The vapour is then transparent to the laser beam, meaning the light intensity recorded at the photodiode is equal to the emitted laser intensity.

If a magnetic field is then applied to the gas with a component perpendicular to the laser beam, the polarisation vector of the Rubidium is perturbed. At the macroscopic level, this causes the polarisation vector of the Rubidium to precess around the laser axis. At an atomic level, this means that the number of Rubidium atoms with spin aligned with the laser beam is no longer maximised. As a result, there are now atoms in the lower energy state, available to be excited by the laser light. The vapour is no longer transparent and the light intensity observed at the photodiode decreases. The observed laser light as a function of the applied perpendicular magnetic field has a Lorentzian distribution, as represented in \( P_x \) in Figure 1.2. Mathematically, the impact of a magnetic field on the polarised gas at the macroscopic level is described by the Bloch Equations (Bloch, 1946):

\[
\frac{dP}{dt} = \gamma (P \times B)
\]

(1.1)

where \( P \) is the polarisation of the Rubidium gas and \( B \) is the magnetic field. Under the assumption that the ambient magnetic field is zero and that there are only small magnetic field variations of interest on the z-axis of the OPM \( (B_z) \), when an oscillatory, modulation magnetic field is applied to the z-axis (discussed further later in this section), it can be shown that the voltage from the photodiode \( (V) \) can be described by

\[
V = A_0 \frac{\gamma B_z \tau}{1 + (\gamma B_z \tau)^2}
\]

(1.2)

where \( A_0 \) is a constant, \( \gamma \) is the gyromagnetic ratio of the Rubidium vapour and \( \tau \) relates to the relaxation time of the Rubidium spins (Tierney et al., 2019; Cohen-Tannoudji et al., 1970).

The OPMs are designed to operate in the so-called spin-exchange relaxation free (SERF) regime (Dang et al., 2010). This is achieved by heating the Rubidium vapour to approximately 150 °C while keeping the background magnetic field close to 0 T. This increases the rate at which the atoms collide. If this is not done, for magnetic fields of the order of femto Tesla, the magnetisation of the Rubidium relaxes back along the laser beam too quickly for any difference to be observed with the photodiode. The reason this SERF regime works is somewhat counter intuitive. The fast relaxation along the laser axis is caused by atoms colliding and exchanging the orientation of their spins. To prevent this being the dominant form of relaxation, the rate of collisions is increased by heating the gas and increasing the velocity of the atoms, while the precession rate of the net magnetisation vector around the laser axis is slowed by reducing the magnetic field. This means that in the SERF regime, the precession rate of the magnetisation vector is much lower than the collision rate of the atoms and so during one precession, there is no average change in the spin distribution of the atoms. This is what makes SERF OPMs sensitive to femto Tesla level magnetic fields and consequently makes them contenders with SQUIDs for MEG.

In order to minimise the magnetic fields at the OPMs to put them into this SERF regime, each OPM has a set of on-board electromagnetic coils which can locally offset any background magnetic field which is not removed by external magnetic shielding in all three directions. They apply a field equal in magnitude and opposite in direction to this remnant field. Additionally, these coils modulate the magnetic field across the vapour with a frequency of 923 Hz. This serves two purposes: firstly, it moves the OPM signal into an area of the frequency spectrum of the photodiode output with little noise. Secondly, it differentiates the OPM response curve, producing the a dispersion curve, shown as ‘\( P_y \)’ in Figure 1.2. Unlike the Lorentzian
Figure 1.2: Representation of the raw and modulated OPM photodiode response. The x-axis is the magnetic field perpendicular to the gas cell, the y-axis is the atomic polarisation. The Lorenzian curve, $P_x$, is the raw photodiode output, the other curve, $P_y$, is the output when the field over the gas is modulated by the OPM on-board coils. Reprinted from Tierney et al. (2019).

curve ($P_x$) in Figure 1.2, which only depends on the magnitude of the magnetic field, not it’s direction, the ‘lock-in output’ varies linearly with magnetic field for fields within ±1.5 nT (Tierney et al., 2019). This means both the field magnitude and direction perpendicular to the Rubidium cell can be inferred from the modulated photodiode output, so long as the field magnitude is below approximately 10 nT. At fields above this turning point, recordings become meaningless as the modulated photodiode output decreases as the field increases. In calculating the perturbing magnetic field from the photodiode voltage, a linear relationship between the two is assumed. However, as is seen in Figure 1.2 and in Tierney et al. (2019), this approximation is only valid at low magnetic fields, less that approximately 1.5 nT. After this point, the linearity assumption leads to a gain error and results in the magnetic field being underestimated. For this reason, the magnetic field at the OPMs is minimised for OP-MEG.

Many different limits for the maximum allowable magnetic field for OP-MEG are quoted. The fundamental limit before which the OPM recordings become meaningless comes from the turning points on the $P_y$ curve in Figure 1.2, as after this point, an increasing field leads to a decreasing signal. For QuSpin OPMs, this point is typically at ±10 nT. However, to increase the precision of the recording (by reducing the magnitude of the least significant bit) and minimise these gain errors and non-linearities, the range of the OPM electronics is usually set to only record between ±1.5 nT or, if greater range is required for an experiment to be feasible and so a compromise with higher gain errors is necessary, ±5.56 nT. We will generally consider the limit ideal of the OPMs to be ±1.5 nT but use the wider range of ±5.56 nT in Chapter 2 and Chapter 6 to allow experiments with a wider range of background magnetic field and consequently a higher range of movement.

These OPMs are generally designed to allow recordings in 2 orthogonal directions (dual axis sensors). This is possible since there are two orthogonal directions to the laser beam. However, recently triaxial OPMs have been developed which will allow recordings of the full magnetic field vector. This is achieved by adding an additional laser beam with a different orientation. All of the empirical data in this thesis was recorded with dual axis sensors, but triaxial sensors are considered in the discussions and simulations.

**Alternative OPM designs**

There are now many different designs of OPM or atomic magnetometer which can be used for MEG and many more which are being developed. The main limitations of the previously described low-field vector magnetometer are that it requires a very low magnetic field to operate and is susceptible to changes in
the background magnetic field. New or alternative designs generally focus on improving or resolving these issues.

In principle, the simplest change which can be made is to use gradiometers rather than magnetometers. The principle here is the same as in cryogenic MEG; one sensing element is placed closer to the brain than another, and so detects more neuromagnetic signal, but the environmental noise is similar at both positions and so the difference is dominated by the neural signal, removing the background noise. Realising this adaptation is more complicated in an OP-MEG system however. In a SQUID system, the difference between the magnetic flux at the two points can be measured by simply creating and joining metal coils at each position. To build an atomic gradiometer, either two gas cells are needed (Nardelli et al., 2020) or multiple laser beams (Pratt et al., 2021). This has the disadvantage of increasing the size of the sensor as more components are required. Additionally, the noise floor of the sensor can potentially be raised, since the noise sources of the gas cells are partially independent of one another (due e.g. to the density of the vapour) and so when the signal from one cell is subtracted from the other, the new noise floor is the sum of the two independent noise floors.

Another increasingly common adaptation to the aforementioned design is to add in a feedback loop. Since SERF magnetometers only operate in low magnetic fields, it can be beneficial to actively shield the OPMs by applying a time-varying magnetic field opposing the remnant background field. This has been done using large external coils (Holmes et al., 2019; Iivanainen et al., 2019; Zhang et al., 2020b) and using small, local nulling coils (Nardelli et al., 2020; Pratt et al., 2021; Robinson et al., 2022). The main disadvantages of such approaches are that the application of such a time varying field may raise the noise floor of the OPMs and, when performed locally, can lead to cross-talk between the sensors. It is also an open question as to how best to control what is fed-back to the OPMs.

Lastly, some recent OPMs rely on different atomic properties to function. This is naturally the largest step away from the previously described system. For example, Kowalczyk et al. (2021) have demonstrated a non-linear OPM based on the non-linear magneto-optical rotation (NMOR) technique (Budker et al., 2002). The basic set up is similar to the previously mentioned OPM design, except that the laser light is detuned from the Rubidium-87 D1 transition by ≈ 480 MHz, is linearly polarised, and is frequency modulated at resonance at twice the Larmor frequency of the Rubidium vapour. A bias field is applied along the sensor. The laser still optically pumps the Rubidium and so the atomic alignment of the Rubidium precesses at the Larmor frequency around the bias field. When a magnetic field is applied orthogonal to the bias field, like a SERF-OPM, the polarisation of the vapour is rotated. The frequency of this rotation is dependent on the magnetic field and so by measuring the rotation frequency, the magnetic field can be measured. NMOR relies on the rotation of the vapour rotating the polarisation of the light, which can then be measured. This constant bias magnetic field is significantly larger than the background field of the environment, which ensures that fluctuations in the background field do not as significantly impact the recordings. Alternatively, Limes et al. (2020) have developed a total field gradiometer which can be used in Earth’s ambient magnetic field, removing the need for magnetic shielding. Whole-head arrays of these new magnetometers are yet to be developed, but their resistance to changes in the ambient magnetic field shows great promise for further development of OP-MEG.
1.3 Movement in MEG

1.3.1 Cryogenic MEG

As cryogenic MEG scanners are fixed in place, participants cannot move outside of the headspace provided. Additionally, it has been well established that head movement within cryogenic MEG leads to errors in source localisation of recorded activity, due to uncertainty on the relative position of the participant’s brain and the MEG sensors (Uutela et al., 2001). This can be mitigated by data processing methods, but is nevertheless particularly problematic for studying children, partly because they move more than adults, but also because the distance between the sensors and their brain is larger, so a small movement leads to a larger distortion in the field at the sensors (Wehner et al., 2008). Larson and Taulu (2017) conclusively showed this. They found localization errors of between approximately 5 mm and 20 mm for simulated cryogenic MEG measurements using real participant head movement measurements. A two-way ANOVA test showed that age group was a significant predictor of both head movement and, consequently, source localisation error.

A number of methods have been suggested for head movement correction in MEG. For MEG recordings with a high degree of movement, electromagnetic coils on the head can be used to measure head position throughout an experiment. This information can then be used to reconstruct the magnetic fields in the participant’s coordinate frame, i.e. relative to their head rather than relative to the sensors. To construct these virtual sensors, either Signal Space Separation (SSS) (Taulu et al., 2004; Medvedovsky et al., 2007) or an adjusted forward model (Uutela et al., 2001) can be used. SSS in particular has been shown to allow movements of approximately 15 mm and head rotations of 40° in cryogenic MEG (Nenonen et al., 2012). Further details on SSS are given in subsection 1.5.1; forward models are introduced in more detail in subsection 1.5.2. The recorded head movement can also be regressed from the MEG data (Messaritaki et al., 2017). Alternatively, head movement can be restricted, with use of either a bite bar (Singh et al., 1997; Adjamian et al., 2004; Heim et al., 2006) or a personalised headcast inside the MEG scanner (Troebinger et al., 2014; Meyer et al., 2017). Many researchers may also remove trials or whole participant datasets which are strongly corrupted with movement. One common limit for the rejection of a trial is movements of over 5 mm (Gross et al., 2013). However, this has been found to be far less than the magnitude of natural movements in many people (Larson and Taulu, 2017). Fundamentally, despite effective correction methods for post-processing cryogenic MEG recordings containing movement, the way that MEG scanners are currently made, it is not possible to stand up during a recording due to the physical constraints of the system.

Electroencephalography (EEG) does not have this limitation in the same way. As the sensors (in this case electrodes) are placed directly on to the scalp, the participant is theoretically free to walk about during an experiment, at least as far as the electrode wires allow. There are motion artefacts, predominantly caused by small movements of the electrodes relative to the scalp over the course of an experiment (Kilicarslan and Contreras Vidal, 2019), but they are significantly smaller than those seen in cryogenic MEG. This has given EEG a distinct advantage over cryogenic MEG for certain tasks and has made it a valuable imaging modality for research into movement dynamics (Lisi and Morimoto, 2015; Nathan and Contreras-Vidal, 2016), as well as for use in virtual reality studies (Tromp et al., 2018; Tauscher et al., 2019). These promise to emulate natural environments, allowing more naturalistic neuroscience experiments. This has also meant that EEG has gained traction for use in real-time brain-computer interfaces, which promise to revolutionise rehabilitation (Luu et al., 2017). However, it remains true that the spatial resolution of EEG
is poor by comparison to MEG, limiting the inference about the underlying brain activity which can be made from these experiments.

### 1.3.2 OP-MEG

There is, therefore, demand for MEG with the motion insensitivity of EEG. It is hoped and largely expected that wearable, OP-MEG will meet this demand. In the wearable system proposed by Boto et al. (2018), the head and sensors move together, as in EEG, avoiding the field distortions seen in cryogenic MEG.

Several groups have been successful in measuring MEG signals with OPMs while both the sensor and participant were stationary. These have generally been proof-of-concept experiments, recording responses from auditory stimulation (Xia et al., 2006; Johnson et al., 2013; Kim et al., 2014; Borna et al., 2017), as well as somatosensory evoked fields from median nerve stimulation (Johnson et al., 2010; Sander et al., 2012; Borna et al., 2017), and high frequency visual gamma band responses (Iivanainen et al., 2020). Alem et al. (2014) also used OPMs to measure epileptiform activity in rats, suggesting that this technology will be clinically useful.

The novelty of the OP-MEG system developed by Boto et al. (2018) is that it is wearable, meaning that sensors are close to the scalp and that the participant is able to move. This does, however, lead to motion artefacts from a different source. The background magnetic field within an MSR is not spatially homogeneous (Holmes et al., 2018), so as an OP-MEG participant moves through it, the field at the head-mounted OPMs changes, leading to an increase or decrease in the observed signal. In an experiment with many trials where the movement and stimulus are unrelated, this could theoretically be averaged out. However, the change in background field also affects the sensor gain, sensitive axis and phase (Boto et al., 2018; Tierney et al., 2019; Iivanainen et al., 2019; Borna et al., 2022), meaning that if the head moves considerably, the signal will be degraded.

To mitigate this problem, in wearable OP-MEG experiments, the background field may be minimised using active shielding, on top of the passive shielding provided by the mu-metal in the MSR walls (Holmes et al., 2019). This minimises the change in magnetic field which occurs when the participant changes position (Boto et al., 2018). Additionally, the position of the participant can be optically tracked and then regressed out of the MEG signals in post-processing to minimise the remaining movement-related changes in the OP-MEG signal (Tierney et al., 2018). These methods have facilitated some novel experiments which previously had been largely restricted to EEG, for example with virtual reality (Roberts et al., 2019) and with children (Hill et al., 2019).

These methods are, nevertheless, imperfect. These external electromagnetic coils can only produce a magnetic field over a limited volume (Holmes et al., 2018). Work has been done to update the coil currents in response to movement during an experiment, but the high currents needed for complex spatial patterns and the speed of update limit its usefulness (Holmes et al., 2021). The regression of position with signal is also flawed, as it does not deal well with rotation (Iivanainen et al., 2019) and cannot correct for the gain errors observed as a result of the changing background field. In this thesis, we suggest an alternative active shielding method, using the on-board OPM coils to null the magnetic field at each sensor in real-time, as the participant moves.
1.4 Epilepsy and MEG

As well as use within neuroscience, MEG is a clinical tool, primarily for pre-surgical planning in epilepsy (De Tiège et al., 2017). In epilepsy surgery, the region of the brain believed to be causing seizures - the epileptogenic focus - is removed. This surgery may be curative, an enticing prospect since anti-epileptic drugs are ineffective for around 30% to 40% of patients (Laxer et al., 2014) and have a number of side effects which can have an impact on quality of life (Taylor et al., 2011).

MEG can be used to identify this epileptogenic focus while simultaneously identifying necessary functional areas that the surgeon should avoid, known as the eloquent cortex (Stufflebeam et al., 2009). Other neuroimaging techniques - commonly fMRI, EEG and SPECT - can be and are being used for this purpose, but MEG has advantages in certain cases. In general, the spatial resolution of scalp EEG is insufficient to confidently localise the epileptogenic focus, so on its own it is likely to be insufficient for surgical planning. Intracranial EEG (iEEG) will therefore likely be performed. Here, electrodes are inserted directly into the brain. This avoids blurring from the scalp and skull so the spatial resolution is greatly improved but it is naturally highly invasive. Additionally, since the number of inserted electrodes is minimised to minimise damage to healthy cortex, coverage of the full brain is practically impossible. Conversely, fMRI performs well at identifying the eloquent cortex but lacks the temporal resolution to identify the epileptogenic focus without simultaneously recording EEG.

Therefore, the combined high temporal and spatial resolution of MEG makes it a valuable tool providing unique information towards the localisation of the epileptogenic focus. A number of studies have demonstrated its utility, both for identification of the epileptogenic focus and for identification of surgical candidates (Knowlton, 2006; Sutherling et al., 2008). However, its clinical use is limited; in a survey of epilepsy centres in Europe, only 28% performed MEG (Mouthaan et al., 2016). This is largely for the reasons outlined in Section 1.2.1: cryogenic MEG is uncomfortable and expensive. Nevertheless, the limited use of MEG is arguably surprising, since it is in spite of results, such as those shown by (Englot et al., 2015), which indicate that MEG can be a strong predictor of epilepsy surgery outcome. They showed that patients were more likely to be seizure free after surgery if the surgical resection zone included the epileptogenic source found with MEG. This was recently confirmed by Rampp et al. (2019) in the largest retrospective cohort study of MEG and surgical outcome to date. They looked at 1000 patients whose presurgical workup included MEG, 405 of whom went on to have epilepsy surgery. They again found that complete resection of the zone identified with MEG was associated with higher probability of seizure freedom post-surgery, as well as concluding that patients with epilepsy which localised to a small area in MEG were better candidates for surgery.

Within MEG, the epileptogenic focus is typically mapped from activity between seizures, known as interictal activity. These are spontaneous electrical discharges, generally believed to be from the epileptogenic focus, of less than 250 ms duration (Staley et al., 2011) released between seizures, which can be recorded with MEG or EEG. These interictal discharges are generally chosen over ictal activity in MEG as the movement of a patient during a seizure will often prohibit accurate SQUID-MEG. Additionally, seizures are not necessarily frequent and while there are activities which can increase the likelihood of a seizure, in EEG-telemetry, patients may have week long recordings to wait for a seizure. This would not be tolerated in SQUID-MEG due to the relative discomfort. However, in some studies using ictal MEG during motionless or near-motionless seizures, or where significant motion correction is applied, there are results suggesting that ictal MEG could localise the epileptogenic focus more accurately than interictal MEG (Fujiwara et al., 2012; Ramanujam et al., 2017; Alkawadri et al., 2018; Katagiri et al., 2022). This is by no means con-
firmed, due generally to the small sample of patients with successful ictal MEG source localisation and subsequent surgery. For example, in the retrospective study carried out by Alkawadri et al. (2018), there were only 16 patients who went on to have surgery out of 44 who had had ictal MEG. This study indicates the impracticality of ictal cryogenic MEG but also how valuable a tool it could be.

There has, therefore, been some interest in measuring epileptogenic activity with OP-MEG. This would not only alleviate the discomfort to the patient and expense of an MEG recording, but it also opens the possibility of ictal OP-MEG since the participant is unconstrained during the recording. Due to the novelty of OP-MEG, there are currently very few studies in this area. Alem et al. (2014) successfully recorded epileptiform discharges from a rat using a single OPM. We have performed the first recording of interictal discharges with an OP-MEG system from a human patient (Vivekananda et al., 2019). To demonstrate the advantages of OP-MEG over SQUID-MEG, Feys et al. (2022) compared the two modalities in 5 children with epilepsy. Looking at the interictal recordings, they showed that the SNR of the interictal events was higher in OP-MEG for 4 out of 5 children and that the localisation was similar between the two modalities in all 5 children.

1.5 MEG analysis methods

The principle of MEG is that underlying neural activity can be estimated from an externally measured neuromagnetic field. However, there are two key challenges. Firstly, the magnitude of that field is approximately 1 billion times smaller than the strength of the Earth’s magnetic field, and approximately 100 million times smaller than the strength of the field from urban noise (Vrba, 2002). The analysis of the data is therefore critical to ensuring that the neuromagnetic field can be picked out from the background. In Section 1.5.1 we will discuss data processing steps commonly used to reduce external interference in MEG data. Secondly, the inverse problem in MEG, whereby neural activity is inferred from the external signal, is ill-posed. In Section 1.5.2 we discuss common methods used to make this inference. Many of these methods also improve the noise reduction of the data.

1.5.1 Data pre-processing

The first step in any MEG analysis is to pre-process the data. This generally involves some form of noise reduction and spatial or temporal filtering.

Data Regression

If a model of the background magnetic interference can be produced, this interference can be suppressed in the OP-MEG recordings by regressing it from the data. In Chapter 2 we will suggest an alternative method for building this model but here we discuss two commonly used methods: reference and position regression.

In reference regression or synthetic gradiometry, recordings from additional reference sensors are regressed out of the primary, neural sensor recordings. These reference sensors can be fixed relative to the neural sensors or can be independent from them. The key qualification is that the reference sensors must be distal from the primary magnetometers in order for the background interference to be similar but for the neural signal to be different. That said, ideally, the reference and primary sensors would be fixed relative to one another, so that the relationship between the two remains constant (Robinson et al., 2022), as is the case with cryogenic MEG (Fife et al., 1999). However, for OP-MEG where head movement is allowed, this
requires either additional holders for the sensors above the primary OPMs, which is an unwieldy solution, or for other sensors on the scalp to be used. This has been shown to be highly effective in reducing interference (Roberts et al., 2019), but effectively reduces sensor coverage on the scalp since two sensors must be used to create one channel. It has similarly been shown that stationary reference sensors placed around the participant can reduce the background interference (Boto et al., 2017) but as the participant moves, the relationship between the reference and primary sensors changes (Iivanainen et al., 2019). This means that the coefficients weighting the sum of the reference sensors for each primary sensor change and should be recalculated. However, to recalculate the values accurately, a certain amount of data is required for the regression. As such, there is a debate to be had about how often to update this value and how best to do so for moving OP-MEG. Practically, the biggest disadvantage of reference regression is that it requires sensors which would otherwise be used for neuromagnetic recordings. This has the effect of reducing sensor coverage, which with the current number of sensors available given that OPMs are still relatively new to the market, may be enough of a reason to not use reference regression.

The position and orientation of the OPMs is a strong factor in determining the background interference at the sensor. As such, regressing the position and rotation of the participant’s head from the neuromagnetic recordings is an effective way to reduce background interference (Seymour et al., 2021; Holmes et al., 2018). Theoretically however, the relationship between position and particularly rotation and OPM recording is not linear, meaning that a linear regression cannot capture the full complexity of this relationship. This is discussed further in Chapter 2.

Filtering

Filtering of some kind is used in practically all MEG analysis. The most commonly used filters are temporal filters. Here the signal of interest is separated from background noise by frequency. Temporal filters and their use have been greatly discussed in the previous literature (Gross et al., 2013; Widmann et al., 2015; de Cheveigné and Nelken, 2019; Seymour et al., 2022). Of greater relevance for this thesis are spatial filters.

In the case of spatial filters, the distinct spatial profiles of the noise and signal components of an MEG recording are used to separate the two. This is possible because MEG is usually recorded with an array of sensors at different positions. A number of methods rely on this concept, but here we shall focus on signal space projection (SSP) (Uusitalo and Ilmoniemi, 1997), signal space separation (SSS) (Taulu et al., 2004), homogeneous field correction (HFC) (Tierney et al., 2021a) and independent component analysis (ICA) (Makeig et al., 1996). Beamforming is also highly effective for reducing interference from background noise based on its spatial profile and, although mentioned briefly here, is covered in more detail in Section 1.5.2.

In Signal Space Projection (SSP), the MEG data is projected into a space orthogonal to the interference. The principal components of this interference are usually determined from an empty room MEG recording (for the background magnetic field) or from participant MEG recordings for physiological interference, epoched around the interference of interest, such as heart beats or eye-blinks. Principle component analysis of this data is used to determine the column space of the interference $U'$, and the orthogonal projector $I - UU^T$ is constructed. This has been shown to be highly powerful in SQUID-MEG, reducing interference by 50 dB to 60 dB (Taulu et al., 2019; Helle et al., 2021) based on an empty room recording. The simplicity of the method is that the model of the interference is based purely on the statistics of the recording; no prior knowledge of the anatomy of the participant or physics of the interference is required. However, the use of SSP is more challenging for moving, wearable OP-MEG. Tierney et al. (2021a) demonstrated that SSP
can still be beneficial for moving OP-MEG, but it is nevertheless a challenge that as the participant moves around the room, the statistical properties of the background magnetic field will change. Consequently, the SSP projection matrix will not be optimal over the full space. One possibility would be to update the projection matrix over the course of the experiment, but this is yet to be demonstrated.

Signal Space Separation (SSS) relies on Maxwell’s equations to separate the MEG recordings into components from inside and outside of the head. This effectively removes external noise components while maintaining the internal, neuromagnetic signal. The assumption is made that the system is quasi-static and source-free, and as such,

$$\nabla \times B = 0$$  \hspace{1cm} (1.3)

where $B$ is the magnetic field. Consequently, a magnetic scalar potential, $\psi$, can be defined such that

$$-\nabla \psi = B$$  \hspace{1cm} (1.4)

Then, also from Maxwell’s equations, $\nabla \cdot B = 0$, and so

$$-\nabla^2 \psi = 0$$  \hspace{1cm} (1.5)

In other words, solutions for $\psi$ must satisfy the Laplace equation. When expanded in spherical polar coordinates $(r, \theta, \phi)$, equation 1.5 is equivalent to

$$\frac{\nabla^2 \psi}{r} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \psi}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial \psi}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial^2 \psi}{\partial \phi^2} = 0$$  \hspace{1cm} (1.6)

To solve this equation, we consider solutions of the form $\psi(r, \theta, \phi) = R(r)Y(\theta, \phi)$. Following from equation 1.6, it can then be seen that

$$\frac{\nabla^2 \psi}{\psi} = \frac{1}{R} \frac{\partial}{\partial r} \left( r^2 \frac{\partial R}{\partial r} \right) + \frac{1}{Y} \left( \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial Y}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial^2 Y}{\partial \phi^2} \right) = 0$$  \hspace{1cm} (1.7)

and therefore,

$$\frac{1}{R} \frac{\partial}{\partial r} \left( r^2 \frac{\partial R}{\partial r} \right) = -\left( \frac{1}{Y} \left( \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial Y}{\partial \theta} \right) + \frac{1}{\sin^2 \theta} \frac{\partial^2 Y}{\partial \phi^2} \right) \right) = \lambda$$  \hspace{1cm} (1.8)

where $\lambda$ is an arbitrary constant. Conventionally, $\lambda$ is set to $\ell(\ell + 1)$ where $\ell$ is also a constant. It can then be shown that $R(r)$ has solutions of the form $R(r) = Ar^\ell + Br^{-(\ell+1)}$ where $A$ and $B$ are constants.

Applying the separation of variables again to the right-hand section of equation 1.8, with $Y(\theta, \phi) = \Theta(\theta)\Phi(\phi)$, gives

$$\ell(\ell + 1) \sin^2 \theta + \frac{\sin \theta}{\Theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial \Theta}{\partial \theta} \right) = -\frac{1}{\Phi} \frac{\partial^2 \Phi}{\partial \phi^2} = m^2$$  \hspace{1cm} (1.9)

where $m$ is a constant. $\Phi(\phi)$ therefore takes solutions of the form $e^{\pm im\phi}$. Enforcing the condition that $\Phi(\phi)$ is periodic with a period of $2\pi$, means that $m$ must be an integer of positive and negative values. Now solving for $\Theta(\theta)$, by making the substitution $z = \cos \theta$, equation 1.9 can be expressed as the associated Legendre equation:

$$\frac{\partial}{\partial z} \left( (1 - z^2) \frac{\partial \Theta}{\partial z} \right) + \left( \ell(\ell + 1) - \frac{m^2}{1 - z^2} \right) \Theta = 0$$  \hspace{1cm} (1.10)

The solution to the associated Legendre equation is a multiple of the associated Legendre polynomials,
\( P_m^\ell(z) \). As such, \( \Theta(\theta) = CP_m^\ell(\cos \theta) \), where \( C \) is a constant.

Therefore, \( \psi = R(r)\Theta(\theta)\Phi(\phi) \) can be described by

\[
\psi = (Ar^\ell + Br^{-(\ell+1)})CP_m^\ell(\cos \theta)e^{im\phi}
\]  \hspace{1cm} (1.11)

SSS models the recorded magnetic field using this expression of the magnetic scalar potential. Linear regression with variables for terms of \( \psi \) which go as \( r^\ell \) and \( r^{-(\ell+1)} \) is used to separate interference from the neural signal of interest. The assumption is made that terms which go as \( r^\ell \) originate from outside of the brain and so are discarded, while terms which follow \( r^{-(\ell+1)} \) are physiological and kept for further analysis.

The main decision which has to be made in this model is which values of \( \ell \) (and consequently \( m \)) to include. Generally, in cryogenic MEG, the internal subspace is modelled with values of \( \ell \) up to 8, while the external subspace is modelled with values of \( \ell \) up to 3. This choice does, however, rely on the large number of SQUID sensors available (\( \approx 300 \)) in an array for high spatial sampling. This is not the case in an OP-MEG array, where the size of the sensor and presence of cross-talk means that the sensors are separated from one another by at least 1.5 cm. This and the fact that sensor arrays are still early in development means that the number of sensors is considerably lower than in cryogenic MEG, with typically 20-60 OPMs, leading to 40-180 channels depending on whether each OPM records 2 or 3 magnetic field components. As a result, this spatial oversampling condition is no longer so easily met. Therefore, it is inappropriate to use the same number of model coefficients as there will be a high degree of shared variance between the internal and external field states. One solution to this is Homogeneous Field Correction (HFC) (Tierney et al., 2021a). Here, rather than modelling the internal and external subspaces separately, the external subspace is regressed out of the OP-MEG signal and only values of \( \ell = 1 \) are used to described the background space (although as sensor numbers increase this could be extended to higher order terms). This avoids these issues of under-sampling and still significantly reduces the background interference.

Independent component analysis (ICA) is another method frequently used to decompose the recorded MEG signal into noise and signal components. Unlike SSS or HFC, ICA does not inherently make any prediction about which signal components are noise and which are signal of interest, but simply aims to separate the recording into independent source components. It is assumed that source signals are independent from one another and are non-Gaussian. There are many different ICA algorithms, but generally to maximise the independence of the inferred source components, it is usual to either minimise the mutual information of the selected components, or maximise their non-Gaussianity.

ICA outputs a mixing matrix, \( W \), with \( M \) (the number of channels) rows and \( C \) (the number of independent components) columns. This matrix projects from the underlying, independent noise sources to the data \( X \in \mathbb{R}^{M \times N} \) (where \( N \) is the number of samples) through \( WS = X \) where \( S \in \mathbb{R}^{C \times N} \) is a matrix of the independent components. To remove a component from the signal \( X \), the the column of \( W \) corresponding to that component would only have to be set to zeros and then this projection performed. ICA is typically used in MEG analysis to remove cardiac and eye-blink artefacts and occasionally for 50 Hz line noise. Typically in cryogenic MEG, two independent cardiac components will be observed. Without adaptation, ICA may not be ideal for cardiac artefacts in OP-MEG since if the sensors move relative to the participant’s heart, the observed cardiac artefact will be different over time.

Lastly, beamforming is a source reconstruction method which can be used to reduce the level of background interference in an MEG recording (Hillebrand and Barnes, 2005). The mathematical details of the method are discussed in Section 1.5.2. At its core, the beamformer is a spatial filter, retaining signals from
an area or volume of interest, while external signals are attenuated. The main assumption is that neural signals are uncorrelated over time. Through this assumption and the forward model (which determines how a region of the brain affects the OP-MEG recording), the signal and noise can be effectively separated.

1.5.2 Source localisation

A key goal of MEG is to estimate which area of the brain is active and when, based on external magnetic recordings. Before solving this inverse problem, it is first necessary to model the impact of a particular area being active on the observed recordings - the forward problem.

Forward Model

Typically, the assumption is made that each region of the brain can be modelled as a current dipole. The model of the brain is often discretised into $M$ current dipoles. The MEG sensor recordings, $b(t)$, can then be mathematically described by

$$b(t) = \sum_{m=1}^{M} l_m q_m(t)$$

(1.12)

Here, $q_m(t)$ is the strength of dipole $m$ at time $t$. $l_m$ is the lead field of dipole $m$. $l_m$ describes the recordings of each MEG sensor for a unit dipole $m$. The values of this lead field are determined by the forward model of the brain.

Considering dipoles at all $M$ locations, equation 1.12 can be expressed in matrix notation. The lead field or gain matrix, $L$, and dipole strengths, $q(t)$ are created by concatenating the individual dipole lead fields and strengths:

$$L = \begin{bmatrix} l_1 & l_2 & l_3 & \ldots & l_m \end{bmatrix}$$

(1.13)

$$q(t) = \begin{bmatrix} q_1(t) \\ q_2(t) \\ q_3(t) \\ \vdots \\ q_m(t) \end{bmatrix}$$

(1.14)

The generative model in equation 1.12 can then be rewritten

$$b(t) = Lq(t).$$

(1.15)

The aim of the forward model then is to estimate this lead-field matrix $L$. To determine these lead fields, a generative model of the brain, skull and scalp must first be specified. This model is informed by the participant’s anatomy, generally using a T1-weighted MRI. From this, these three surfaces (cortex, skull and scalp) can be extracted and used to determine the propagation of the neuromagnetic fields through the head to the sensors.

There are several different forward models which can be used; here we will give a basic overview of the single shell model (Nolte, 2003), since this will be used throughout the remainder of the thesis. In the single shell model, the lead fields are calculated by applying a usually small correction to the lead fields found when the head is modelled as a single sphere with a single conductivity - the single sphere model (Sarvas, 1987). Typically in MEG, the single shell model is sufficient, as the signal is largely determined by primary
currents, which are not dependent on the conductivity of the head. In EEG source modelling however, a more complex and computationally demanding model, such as a boundary element model (BEM), would be required.

In the single shell model, it is assumed that the neuronal currents are quasistatic and that the head can be modelled as a volume with a single conductivity value. Under this quasistatic assumption, the Biot-Savart law describes the magnetic field produced by a given current.

\[ B(r) = \frac{\mu_0}{4\pi} \iiint_S d^3r' \mathbf{J}(r') \times \frac{r - r'}{|r - r'|^3} \]  

(1.16)

\( r' \) is the location within the brain volume \( S \), and \( r \) is the location of the MEG sensor. For simplicity, we define

\[ G(r', r) = \frac{\mu_0}{4\pi} \frac{r - r'}{|r - r'|^3} \]  

(1.17)

For a single MEG sensor at position \( r \), replacing \( B \) in equation 1.16 with the definition of the lead fields, equation 1.16 then becomes:

\[ \mathbf{L}_q = \iiint_S d^3r' (\mathbf{J}(r') \times G(r', r)) \cdot \hat{n} \]  

(1.18)

where \( \hat{n} \) is the unit vector along the sensitive axis of the MEG sensor.

In the quasi-static approximation, the total current \( \mathbf{J} \) can be expressed as a sum of the primary (\( \mathbf{J}^P \)) and volume (\( \mathbf{J}^V \)) currents.

\[ \mathbf{J} = \mathbf{J}^P + \mathbf{J}^V = \mathbf{J}^P - \sigma \nabla V \]  

(1.19)

where \( V \) is the electric potential and \( \sigma \) is the electrical conductivity. The primary currents are defined with respect to the lead fields and dipole strengths such that

\[ \mathbf{L}_q = \iiint_S d^3r' l(r, r', \hat{n}) \cdot \mathbf{J}^P(r') \]  

(1.20)

It is assumed that the currents vanish at infinity and, due to the conservation of current, the total current \( \mathbf{J} \) is divergence free (\( \nabla \cdot \mathbf{J} = 0 \)). Substituting equation 1.19 and equation 1.20 into equation 1.18 gives

\[ \iiint_S d^3r' l \cdot \mathbf{J}^P = \iiint_S d^3r' ((\mathbf{J}^P - \sigma \nabla V) \times \mathbf{G}) \cdot \hat{n} \]  

(1.21)

For simplicity, we have dropped the dependencies in equation 1.21. Considering the vector identity, \( \mathbf{A} \cdot (\mathbf{B} \times \mathbf{C}) = \mathbf{B} \cdot (\mathbf{C} \times \mathbf{A}) \), and separating the lead fields into a divergence free part, \( \mathbf{A} \), and a curl free part \(-\nabla U\), equation 1.21 can be rearranged to give:

\[ \iiint_S d^3r' \mathbf{J}^P(r') \cdot (\mathbf{A}(r, r', \hat{n}) - \mathbf{G}(r', r) \times \hat{n}) = \iiint_S d^3r' ((\mathbf{J}^P - \sigma \nabla V) \times \mathbf{G}) \cdot \hat{n} \]  

(1.22)

From here we will omit the function dependencies for simplicity. Using the vector identity \( \nabla \cdot f \mathbf{A} = f \nabla \cdot \mathbf{A} + \mathbf{A} \cdot \nabla f \), the assumption that there is no net current flow along the integration surface normal and the conservation of current, through partial integration, equation 1.22 can be rewritten as:

\[ \iiint_S d^3r' \mathbf{J}^P \cdot (\mathbf{A} - \mathbf{G} \times \hat{n}) = \iiint_S d^3r' V \nabla \cdot \sigma^T (\mathbf{G} \times \hat{n} - \nabla U) \]  

(1.23)
This equation is satisfied for any value of $J^P$ if

$$A = G \times \hat{n}$$
$$\nabla \cdot \sigma^T (G \times \hat{n} - \nabla U) = 0$$

(1.24)

We can then choose to make $A$ the leadfields of a spherical volume conductor, $L_X$, which have been previously defined by Sarvas (1987). Importantly, these leadfields are divergence free.

Usually in MEG, the assumption is made that the head can be modelled as a set of compartments with constant conductivity. Therefore, from equation 1.24, it can be shown that $U$ obeys Laplace’s equation.

$$\nabla^2 U = 0$$

(1.25)

As such, $U$ can be expressed by an infinite sum of spherical harmonic functions. Naturally, in reality, only the sum of a subset of $M$ spherical harmonic functions is possible. Nolte recommends including 20 orders of spherical harmonics, although there is a balance to be made. The model accuracy increases as the number of spherical harmonics increases, but this comes at a cost to computational efficiency. Where source modelling is concerned for the remainder of this thesis, we use the single shell forward models in the SPM or FieldTrip software packages.

The MEG Inverse Problem

After defining the forward model, the inverse problem asks how to use that model to infer the underlying neural activity. This problem is not trivial for a number of reasons. Most importantly, the number of potential source locations greatly outnumbers the number of MEG sensors. Additionally, neural dipoles orientated radially to the scalp surface cannot be recorded with MEG, and the magnetic fields from nearby current sources may cancel one another out, so there are an infinite number of possible solutions to the MEG inverse problem which would produce the same MEG data. In this section, we focus on the methods used to overcome these difficulties.

There are two dominant frameworks to tackle the MEG inverse problem. Firstly, a distributed source solution assumes that a large number of dipoles are simultaneously active across the cortex and fits the amplitude of that activation. In the second, and arguably simpler framework, it is assumed that a small number of dipoles are active and the location of the dipoles are determined by fitting to the data using a non-linear search through the brain. Both have limitations. The second (dipole fitting) approach requires that the number of active sources is known a priori and suffers from local minima depending on the implementation. The first (distributed source) method avoids this problem of local minima as the model is linear with respect to the neuronal currents, but the large number of unknowns (due to the large number of sources) mean that the problem is ill-posed and can only be solved using prior information. Fundamentally, a single dipole and a patch of dipoles can produce the same MEG recordings. Which neural source is found will depend on the inverse method used, rather than the underlying biology.

Distributed source solutions

Returning to equation 1.15, assuming that $L$ has been determined from the participant’s anatomy and $b(t)$ is recorded, the question becomes how best to estimate $q(t)$. In a distributed source solution, the number of dipoles ($M$) is much larger than the number of channels ($N$), and so $L \in \mathbb{R}^{N \times M}$ is non-invertible.

The simplest solution to this problem is to minimise the summed square of the difference between the
recorded and modelled data. This is known as the minimum norm inverse solution and was first proposed by Hämäläinen and Ilmoniemi (1984). Expressed mathematically, this equates to

$$\hat{q} = \arg \min_q \| b(t) - Lq \|^2 \quad (1.26)$$

where $\hat{A}$ indicates the estimated inverse of $A$ and $\|A\|$ indicates the L2 norm of $A$. The solution to equation 1.26 is to invert $L$ using the Moore-Penrose inverse, $L^\dagger = L^T (LL^T)^{-1}$. This gives the following estimate for $\hat{q}$

$$\hat{q}(t) = L^T (LL^T)^{-1} b(t) \quad (1.27)$$

$$= L^T G^{-1} b(t) \quad (1.28)$$

Here $G = LL^T$ is the so-called Gram matrix. While $G$ is a square matrix, it is in practice often close to singular, meaning that its determinant is close to zero, and so multiplying $b$ by its inverse is close to effectively dividing by zero, which leads to mathematically unstable solutions for $\hat{q}$. Tikhonov regularisation can be used to overcome this problem. The regularised Gram matrix is defined as $G_r = G + \mu I$, where $\mu$ is the regularisation parameter.

This description of source localisation can be reframed in a Bayesian context. In this context, the estimated source activity is that which maximises the posterior probability distribution of $\hat{q}$ given the data $b$ (Baillet and Garnero, 1997). Expressed mathematically,

$$\hat{q} = \arg \max_q p(q|b) \quad (1.29)$$

This posterior probability can be computed using Bayes’ theorem:

$$p(q|b) = \frac{p(b|q)p(q)}{p(b)} \quad (1.30)$$

For a given dataset, $p(b)$ is constant and so to maximise $p(q|b)$, we seek only to maximise $p(b|q)p(q)$. We make the assumption a priori that $q$ is a zero mean Gaussian process with covariance $Q$. As previously, the probability of the data given the underlying neural currents ($p(b|q)$), is determined by the forward model and consequent leadfields. Expanding equation 1.15 to account for sensor noise ($\epsilon(t)$), $b(t) = Lq(t) + \epsilon(t)$. It is therefore reasonable to treat the probability of the data $b$ given underlying dipole magnitudes $q$ as a normal distribution with mean $Lq$ and covariance $Q_i = \text{Cov}(\epsilon)$. Under these assumptions,

$$p(b|q)p(q) \propto \exp\left( -\frac{(Lq - b)^T Q^{-1}_i (Lq - b)}{2} - \frac{q^T Q^{-1} q}{2} \right) \quad (1.31)$$

As such, solving equation 1.29 and seeking the most likely current distribution given the data, is equivalent to minimising $\Phi = (Lq - b)^T Q_i^{-1} (Lq - b) + q^T Q^{-1} q$. To find the value of $\hat{q}$ which minimises $\Phi$, we take the derivative of $\Phi$ with respect to $q$ and seek the value at which it equals zero.

$$\frac{d\Phi}{dq}_{q=\hat{q}} = 0 = L^T Q_i (L\hat{q} - b) + Q^{-1}\hat{q} \quad (1.32)$$
Solving equation 1.32 gives the following expression for $\hat{q}$ (López et al., 2014; Dale and Sereno, 1993)

$$\hat{q} = QL^T(Q_e + LQL^T)^{-1}b.$$  \hspace{1cm} (1.33)

All distributed source reconstruction algorithms based on Gaussian assumptions can be derived from this equation by changing the values of the two covariance matrices, $Q$ and $Q_e$. Without prior information about the sensor noise, it is generally assumed that $Q_e = h_0 I_N$ where $h_0$ is a the sensor noise variance, $I_N \in \mathbb{R}^{N \times N}$ is the identity matrix and $N$ is the number of channels. The inversion method used determines the value of $Q$. For the minimum norm estimation method described previously, $Q = I_M$ (where $M$ is the number of dipoles), implying that all dipoles have the same prior variance and no covariance. In other words, minimum norm estimation assumes that all dipole sources are independent and equiprobable (O’Neill et al., 2021). Alternative values for $Q$ can be chosen instead with the intention of incorporating prior knowledge about the underlying source activity into the source reconstruction. For example, the LORETA model assumes that sources vary smoothly over space (Pascual-Marqui et al., 1994).

Of particular interest are a set of inversion methods known as beamformers. Originally developed for use in radar (Van Veen and Buckley, 1988), beamformers spatially filter the MEG reconstruction by weighting the data before summing to estimate the source activity. Considering each voxel (or dipole location), $n$, separately, this can be expressed mathematically as

$$\hat{q}_n = w_n^T b$$ \hspace{1cm} (1.34)

where $w_n$ are the beamformer weights for dipole $n$ and $w_n^T$ is the transpose of $w_n$. To determine these weights, the (usual) key assumption of a beamformer is that no two cortical areas are coherently active (Hillebrand and Barnes, 2005)\(^1\). Beamformers are of particular importance for (particularly magnetometer) OP-MEG recordings as this spatial filtering suppresses interference, which is more of a concern for magnetometer OP-MEG recordings than gradiometer SQUID-MEG.

There are many different beamformer implementations; we will focus on the linearly constrained minimum variance (LCMV) beamformer, as described by van Drongelen et al. (1996), as it will be used extensively in Chapter 5. For simplicity, here we will consider that the orientation of each dipole is known. However, one of the advantages of beamformers is that it is possible to optimise the orientation of each dipole based on which gives the highest power (Hillebrand and Barnes, 2005).

In an ideal spatial filter, aiming to maintain any signal from dipole $n'$ but suppress signal from elsewhere,

$$\hat{q}_n = \begin{cases} q_{n'} & \text{if } n = n' \\ 0 & \text{otherwise} \end{cases}$$ \hspace{1cm} (1.35)

Combining equations 1.15, 1.34 and 1.35,

$$w_n^T Lq = \begin{cases} q_{n'} & \text{if } n = n' \\ 0 & \text{otherwise} \end{cases}$$ \hspace{1cm} (1.36)

\(^1\)There are beamformer implementations which assume that areas are coherently active, but these areas are generally pre-specified, typically assuming that if one area of cortex is active, the same region in the opposite hemisphere also is (Brookes et al., 2007; Quraan and Cheyne, 2010; Dalal et al., 2006; Diwakar et al., 2011; Popescu et al., 2008; Moiseev et al., 2011; Kimura et al., 2007; Kuznetsova et al., 2021; O’Neill et al., 2021).
Consequently, we seek a form of $w_n^T L$ which is akin to a Dirac delta function; it should be 1 when $n = n'$, but otherwise be zero. As with temporal filtering, it is generally impossible to create a filter which perfectly achieves this, so a compromise is made. The LCMV approach chooses the beamformer weights to minimise the variance of the beamformer output, in order to minimise signal contributions originating outside of the region of interest, subject to the linear constraint that $w_n^T l_n = 1$. This can be summarised as

$$\arg\min_w C_q \text{ subject to } w_n^T l_n = 1 \tag{1.37}$$

where $C_q$ is the variance of the reconstructed activity, such that $C_q = |\hat{q}_n|^2 = w_n^T b (w_n^T b)^T = w_n^T C_b w_n$, where $C_b = bb^T$ is the data covariance calculated over the time window of interest. The solution to equation 1.37 can be found analytically through the method of Lagrange multipliers (see Van Veen et al. (1997)). This gives the following solution for $w_n$:

$$w_n = (l_n^T C_b^{-1} l_n)^{-1} l_n^T C_b^{-1} \tag{1.38}$$

Unfortunately, this solution tends to bias the reconstructed activity towards the centre of the head, as the leadfields decrease with depth (as magnetic field decreases with distance and so a deep source creates a smaller MEG recording than a superficial source) and so the beamformer weights increase with depth. To correct for this intrinsic bias, the LCMV output is often normalised by the projected sensor noise (Hillebrand and Barnes, 2005). Alternatively, the beamformer weights may be normalised by their own magnitude, in which case, the resulting predictions for $\hat{q}$ may be referred to as a pseudo-z-statistic or neural activity index, rather than reconstructed power.

Beamformers are extremely powerful for noise rejection. They have been shown to considerably improve the SNR of MEG recordings, both with OPMs and SQUID sensors (Seymour et al., 2021; Van Klink et al., 2016; Cao et al., 2022). There are some limitations. As mentioned, as with all MEG reconstruction methods, some assumptions must be made and in this case it is assumed that no two brain areas are simultaneously, coherently active. This may lead to areas of the brain being missed in the reconstruction, or being merged into a single active region between two true locations (Van Veen et al., 1997). Additionally, the output may depend on how the data covariance is estimated (Barratt et al., 2018). This is rarely an issue for a traditional SQUID-MEG neuroscience experiment, where the data covariance changes (comparatively) minimally, but for moving OP-MEG, where background interference is larger and changes whenever the participant moves their head, high precision imaging may be limited by the ability to accurately represent the data covariance. For applications in epilepsy in particular, this may be especially true since there are fewer trials than in a traditional neuroscience experiment, making it harder to estimate the data covariance as would be representative for that limited number of events.

**Dipole fitting**

The alternative approach to MEG source imaging involves assuming that a small number of sources (typically 1 or 2) are active, and then fitting the location and orientation of these sources to the data. This is known as dipole fitting or equivalent current dipole (ECD) fitting, and is a popular technique for source imaging in epilepsy with SQUID-MEG (Tenney et al., 2020; Rampp et al., 2019; Pataaraia et al., 2005). However, the user is required to select, a priori, the number of dipoles which are active, the success of the solution may be limited by local minima and it does not benefit from the noise suppression of beamformer methods. Here we summarise the functionality of the dipole fit implemented in FieldTrip (Oostenveld et al.,
We will consider the case where only a single dipole is assumed to be active and use language to that effect, although everything could be extended to fit a small number of dipoles.

The dipole fit seeks to minimise the difference between the modelled and recorded data. By default (although there are many other options), FieldTrip uses the relative residual variance to quantify this difference. As such, the cost function for the optimisation is

\[
\arg\min_{r, \omega} \frac{\left(b - l(r, \omega)l^\dagger(r, \omega)b\right)^T}{b^Tb} \left(b - l(r, \omega)l^\dagger(r, \omega)b\right)
\]

(1.39)

where \(l(r, \omega)\) is the leadfield equal to the recording observed on each MEG channel, for a dipole at position \(r\) and orientation \(\omega\). In the FieldTrip implementation, (again by default) the Matlab function \(fminunc\) is used to optimise the dipole position and orientation simultaneously. The dipole location is initialised either by the user or by defining an evenly spaced grid across the cortex and finding the gridpoint which minimises the cost function.

The advantage of this method is that it requires relatively little user input and does not considerably constrain the output by prior information (such as requiring the activity to lie on the provided cortical surface). However, this arguably makes the method more susceptible to noise and local minima, since there is less information on which to base the reconstruction.

Overview

The aim of this PhD project is to minimise movement artefacts in OP-MEG so that a participant can move by more than 1 m during an OP-MEG scan, and demonstrate OP-MEG with a clinical cohort. As described above, movement artefacts appear in OP-MEG because the magnetic field around the head is not homogeneous, so the background field at the OPMs changes as the participant moves.

Chapter 2 focusses on modelling these non-homogeneous background fields. We measured the magnetic field at different positions in a magnetically shielded room. We found that the magnetometer position was strongly predictive of the field value, and that the field in the room was well modelled by a spherical harmonic model. We demonstrate that the magnetic field distribution changes over time, making it difficult to create one constant description of the background noise in the room. We show that by creating a field model from OP-MEG recordings, we can reduce the movement related noise in the dataset.

In Chapter 3, we introduce real-time movement correction in simulation. Rather than record the data and subtract the field model later, we propose using electromagnetic coils on-board each OPM to subtract this field model in real-time, during an experiment. This has the advantage of avoiding any gain errors in the OPM recordings which come from a non-zero background field. In simulation, we show that a control system based on the magnetometer’s position could reduce the movement related noise dramatically but that its performance is determined by the errors on the inputs and outputs of the control. Noise in the measurements of the OPM position and systematic errors in the calibration of the magnetic field output of the control appear to be the most significant factors in the control’s success.

In Chapter 4, we demonstrate real-time field correction empirically. We updated our methodology to remove any reliance on recording the OPM position and orientation, and instead treated each time point independently. This simplified the implementation of the control proposed in Chapter 3. We show improvements in the low-frequency noise in a stationary OPM recording and demonstrate improvements in SNR of an auditory evoked response when a participant walks around the room, moving a maximum of
2 m in any direction, when this real-time correction is included.

Chapter 5 shows an OP-MEG recording from a patient with epilepsy. We see interictal epileptogenic activity, which source localised to a location plausibly consistent with their previous clinical work up. However, the impact of movement in the data is clear. Roughly 60% of events identified as potential epileptiform activity were rejected as likely being movement artefacts. After improving the way in which the OPM cables were secured and with greater experience identifying epileptiform events in OP-MEG, in Chapter 6, we present a more recent case, where only 1 out of 9 identified epileptiform events was rejected. This shows clear and well localised interictal activity, while the patient sat comfortably with their head unconstrained.
2 Experiment 1: Magnetic Field Mapping and Correction for Moving OP-MEG

2.1 Introduction

In this chapter, we aim to map the spatial variation across a magnetically shielded room (MSR). As discussed, the main motivation for this is to measure and ideally reduce movement related field changes as a participant moves through the MSR during an OP-MEG recording. Although many varieties of OPM sensor now exist, we focus on OPMs that operate in the Spin Exchange Relaxation Free (SERF) regime. These OPMs typically operate in very low magnetic fields, below \( \sim 2 \text{ nT} \). One practical problem that impacts OPMs is how to maintain a fixed operating point as the participant moves. The field gradient within the OPM-dedicated Magnetically Shielded Room (MSR) at UCL is around 1000 pT/m (Altarev et al., 2015); we wish to measure fields in the femto-Tesla range (typically 0.01-1 pT). This means that any small movements of any magnetic field sensor present a considerable source of interference: 1 mm of head movement could produce a field change equivalent to a large (1 pT) brain signal. Rotations within the field cause additional artefacts.

These field changes lead to direct and indirect artefacts from movement in OP-MEG: a direct increase or decrease in the recorded value, as described above, and a consequential change in the gain and sensitive axis of the OPMs, which is dependent on the ambient field of the sensor (Iivanainen et al., 2019; Borna et al., 2022). The relationship between the ambient field and OPM gain means that these sensors operate optimally at magnetic fields close to zero (\( \sim \pm 1 \text{nT} \)) (Tierney et al., 2019). Movement is one common reason why the field at an OPM would step outside of this range during an OP-MEG recording. These effects usually occur at low frequency (below 4 Hz), as the movements themselves are typically low frequency (see Figure 2.6). It is partially for this reason that alpha (8 Hz–15 Hz), beta (15 Hz–30 Hz) and gamma (>30 Hz) activity has successfully been recorded with OP-MEG during movement (Boto et al., 2018; Hill et al., 2019; Roberts et al., 2019; Rea et al., 2021), theta (4 Hz–8 Hz) has been recorded while the participant was unconstrained (Barry et al., 2019), but delta and infra-slow waves (<4 Hz) remain a topic of future research.

A number of methods have been suggested for minimizing changes in the background magnetic field during an OP-MEG experiment, with the most successful involving the placement of electromagnetic coils in the MSR around the participant (Iivanainen et al., 2019; Holmes et al., 2018, 2019; Jodko-Władzińska et al., 2020). The currents in these coils can be adjusted to minimize the magnetic field within the volume around the head, meaning that when the participant moves, the change in field is minimal (Boto et al., 2018; Holmes et al., 2018). The currents in the coils can be continually updated to keep the background field close to zero, minimizing temporal changes in the background field which are introduced by external sources of interference (Iivanainen et al., 2019; Holmes et al., 2019). The electromagnetic coils presented by Holmes et al. (2019) have been shown to be capable of keeping the magnetic field to below 2 nT within a 40 cm \( \times \) 40 cm \( \times \) 40 cm box around the participant’s head, allowing the participant to move within this region. This has opened up a number of new areas of research within MEG (Hill et al., 2019; Roberts et al., 2019).
et al., 2019).

However, even when these field nulling coils are used, the magnetic field around the head is not zero. This makes rotations during OP-MEG challenging (Iivanainen et al., 2019). If it were possible to record OP-MEG outside of this region, it would allow experiments that could not previously be considered; for example, recording as people walk about an MSR. This could be achieved by locally nulling the magnetic field at each sensor (using the internal coils that each sensor incorporates), as is done in some novel OPM designs that include closed-loop operating modes (Sheng et al., 2017; Yang et al., 2019; Oelsner et al., 2020; Fourcault et al., 2021; Pratt et al., 2021). Here we work towards selectively controlling for movement-related field changes by creating a model of the background field. Previous simulation studies have shown how a generative model, comprised of current dipole sources located on a shell around the room, could be used to null this interference (Lopez et al., 2019). It has also been shown that modelling the background field as a spatially homogeneous mean field can offer significant improvement (Tierney et al., 2021a). We explore an alternative model in which we express the low-frequency background field in the room as the sum of a real-valued spherical harmonic series (Dietrich, 2015). Due to the wearability of OP-MEG, here we build a model of the spatial distribution of the noise from the participant’s movements. The advantage of the spherical harmonic approach over a dipolar generative model is that we expect the field models to be computationally simpler to estimate and update in real-time. In this work, we establish proof-of-principle and use this information to minimize the movement-related changes in an OP-MEG recording post-hoc.

2.2 Methods

2.2.1 Theory

Vectors and matrices have been emboldened. Vectors are additionally italicized to differentiate the two.

For a singular OPM on the scalp, at position \( r \in \mathbb{R}^{3\times1} \) and time \( t \), we assume that the recording \( (B_{OPM}(r,t)) \) is the sum of the magnetic field \( (B(r,t) \in \mathbb{R}^{3\times1}) \) along the recording axis of the sensor \( (\rho_{OPM} \in \mathbb{R}^{3\times1}) \), multiplied by the sensor gain \( (G) \), plus any sensor error terms \( (e_{OPM}) \)

\[
B_{OPM}(r,t) = G(B(r,t) \cdot \rho_{OPM} + e_{offset} + e_{Gaussian})
\]  

(2.40)

The dot indicates the dot product between the magnetic field at the sensor’s location and the orientation of its sensitive axis. \( B(r,t) \) has contributions from both the environment (background noise) and the brain (the signal of interest). Here we seek to model the background noise component of \( B(r,t) \).

We make the assumption that \( G = 1 \). We also assume that the sensitive axis of the sensor remains aligned with its exterior shell and that the error term, \( e_{OPM} \), consists of a random, Gaussian error and a static offset term. There are multiple causes of this offset, the largest being an intentionally applied field to null the initial magnetic field at the start of any experiment, described in Chapter 1, Section 1.2.2. Additional sources of this offset include slight magnetization of the internal OPM components, effective DC fields from the cell heater, internal magnetic field gradients, and light shift (a fictitious magnetic field created from the interaction of Rubidium atoms and the laser) (Shah and Romalis, 2009).

Equation 2.40 simplifies to

\[
B_{OPM}(r,t) = B(r,t) \cdot \rho_{OPM} + e_{offset} + e_{Gaussian}
\]  

(2.41)

We also assume that the MSR can be approximated as a static, source-free space. The magnetic field can
then be described by
\[ B(r) = -\mu_0 \sum_{l=1}^{\infty} \sum_{m=-l}^{l} \beta_{lm} \nabla (r^l Y_{lm}(\theta, \phi)) \]  
\( (2.42) \)
as shown by (Whaler and Gubbins, 1981; Taulu et al., 2005; Wyszyński et al., 2017). This is derived from equation 1.11, except that only the components external to the head (which go as \( r^l \) have been included. \( l = 0 \) has not been included in equation 2.42 since the derivative of \( Y_{00} \) is 0 and so this term has no impact on the observed magnetic field. In equation 2.42, \((r, \theta, \phi)\) are spherical coordinates, such that
\[ x = r \sin \theta \cos \phi, \quad y = r \sin \theta \sin \phi, \quad z = r \cos \theta, \]
where \(x\), \(y\) and \(z\) are the Cartesian coordinates. \( \beta_{lm} \) are coefficients to be modelled. \( Y_{lm}(\theta, \phi) \) are the spherical harmonic functions, as defined in equation 2.43. As the magnetic field being modelled is real, we used the real-valued spherical harmonics \( (S_{lm}) \), as defined by Chisholm (1976) and given here in equation 2.44, in place of \( Y_{lm} \) to ensure this condition. The first 4 orders are listed in table 2.1.

\[ Y_{lm}(\theta, \phi) = (-1)^m \sqrt{\frac{(2l+1)(l-m)!}{4\pi (l+m)!}} P^m_l(\cos \theta) e^{im\phi} \]
\( (2.43) \)
\[ S_{lm}(\theta, \phi) = \begin{cases} \frac{i}{\sqrt{2}} (Y_{l(-|m|)} - (-1)^m Y_{l|m|}), & m < 0 \\ Y_{l0}, & m = 0 \\ \frac{i}{\sqrt{2}} (Y_{l(-|m|)} - (-1)^m Y_{l|m|}), & m > 0 \end{cases} \]
\( (2.44) \)
\[ P^m_l \] represents the associated Legendre polynomials. In equation 2.44, the function dependencies on \( \theta \) and \( \phi \) have been removed to keep the equation concise. Due to the nature of the associated Legendre polynomials, equation 2.44 can be equivalently expressed as:

\[ S_{lm}(\theta, \phi) = \begin{cases} T_{lm}(\theta) \sin(|m|\phi), & m < 0 \\ \sqrt{\frac{2l+1}{4\pi}} P^0_l(\cos \theta), & m = 0 \\ T_{lm}(\theta) \cos(|m|\phi), & m > 0 \end{cases} \]
\( (2.45) \)

Whenever we refer to model order, we are referring to the maximum value of \( l \) used \( (l_{\text{max}}) \). We used linear regression to create the model from all recorded channels and timepoints.

\[ Y = X\beta + e_{\text{Gaussian}} \]  
\( (2.46) \)
Where \( Y \) is the measured field data and \( X \), the design matrix, contains the spherical harmonic model of magnetic field change over space. As such,

\[ \beta = X^\dagger Y \]
\[ Y_{\text{pred}} = X\beta \]
\( (2.47) \)
\( X^\dagger \) is the pseudoinverse of \( X \). The movement can therefore be modelled out of the recording to create a
\[
\ell \quad m \quad r^\ell S_{lm} \quad \frac{\partial r^\ell S_{lm}}{\partial x} \quad \frac{\partial r^\ell S_{lm}}{\partial y} \quad \frac{\partial r^\ell S_{lm}}{\partial z}
\]

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<td>4x(x^2 - 3y^2)</td>
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Table 2.1: Real-valued spherical harmonic functions for the first 4 orders, multiplied by \( r^\ell \), and their partial derivatives with respect to \( x, y \) and \( z \). \( x, y \) and \( z \) are the three components of displacement \( (r) \) and \( r = |r| = \sqrt{x^2 + y^2 + z^2} \). All multiplying constants have been ignored for convenience.

The corrected data vector \( \vec{Y}_{\text{corrected}} \) as follows

\[
\vec{Y}_{\text{corrected}} = \vec{Y} - \vec{Y}_{\text{pred}} = (I - XX^T)\vec{Y}
\]

(2.48)

The first \( M \) (where \( M \) is the number of channels) columns of the design matrix \( (X) \) are used to account for constant (channel specific) offsets. The remaining columns describe the change in the magnetic field over space, such that the expression agrees with equation 2.41 and equation 2.42. The number of columns of \( X \) is therefore determined by the number of channels and the model complexity and is equal to \( (M + l_{\text{max}}(l_{\text{max}} + 2)) \). The rows of \( X \) correspond to the timepoint and sensor. We chose to list all timepoints of sensor 1, then all times of sensor 2 etc. Consequently, the data for the regression \( (\vec{Y}) \) is given as follows:

\[
\vec{Y} = [B_1(r_{11}, t_1), B_1(r_{12}, t_2), \ldots, B_1(r_{1N}, t_N), B_2(r_{21}, t_1), \ldots, B_M(r_{MN}, t_N)]^T
\]

(2.49)

\( \vec{Y} \) has length \( (NM) \), where \( N \) is the number of datapoints modelled over. \( B_m(r_{mn}, t_n) \) refers to the recording of OPM \( m \) at timepoint \( n \) and position \( r_{mn}(t_n) \).

As an example, in the simplest case considered here, \( l_{\text{max}} = 1 \), and so the background magnetic field is modelled by \( \vec{B} = \beta_1 \hat{x} + \beta_1 \hat{y} + \beta_0 \hat{z} \), where \( \hat{x}, \hat{y}, \hat{z} \) are the standard unit vectors in the direction of
the $x$, $y$ and $z$ axes. In this scenario, the design matrix is as follows,

$$X = [\Gamma, \rho_x \circ [0, 0, 1] + \rho_y \circ [1, 0, 0] + \rho_z \circ [0, 1, 0]]$$  \hspace{1cm} (2.50)

where $\Gamma \in \mathbb{R}^{(NM) \times M}$ represents the matrix for the channel offsets. Each column of $\Gamma$ corresponds to a sensor channel and is zero, unless, for column $m$, row $k$, the data in row $k$ of $Y$ was recorded by OPM channel number $m$. Apart from $\Gamma$, all terms in equation 2.50 are column vectors with values corresponding to the position and orientation of the channel in the corresponding row of $Y$, e.g. the first element of $\rho_x$ is the component of the orientation of OPM channel 1 in the $x$ direction at timepoint 0, the second is its orientation in $x$ at timepoint 1 and so on, until the last element is the component of the orientation of OPM channel $M$ in the $x$ direction at timepoint $N$. $\mathbf{1}$ is a column of ones and, similarly, $\mathbf{0}$ is a column of zeros. $\circ$ indicates elementwise multiplication. In this case where $l_{\text{max}} = 1$, the estimated parameters would be

$$\beta = [e_{\text{offset}, 1}, e_{\text{offset}, 2}, \ldots, e_{\text{offset}, M}, \beta_{1-1}, \beta_{10}, \beta_{11}]^T$$  \hspace{1cm} (2.51)

For simplicity, we have only written this out for the simplest model. To expand this to include higher order models, the real spherical harmonics, as listed in table 2.1, need only be concatenated to the inner arrays. For example, considering only the magnetic field in the $x$ direction, in going from a first order model to second,

$$[0, 0, 1] \rightarrow [0, 0, 1, y, 0, x, x]$$  \hspace{1cm} (2.52)

### 2.2.2 Recording Setup

Two experiments for two different sensor configurations – triaxial and whole-head, as described in Section 2.2.3 – were undertaken. Figure 2.1 shows the setup of the triaxial field mapping experiment. In both cases, we used QuSpin QZFM 2nd generation OPMs (https://quspin.com/products-qzfm/). The OPMs were moved manually, pseudo-randomly, either on the end of stick or on the participant’s head, around the central $1 \text{ m}^3$ to $2 \text{ m}^3$ of a 4-layer MSR (Magnetic Shields, Ltd.; internal dimensions $3 \text{ m} \times 4 \text{ m} \times 2.2 \text{ m}$) for 5 minutes. Before the start of the experiments, the inner layer of mu-metal lining the room was degaussed by passing a low-frequency decaying sinusoidal current through cables within the walls.

The position of a rigid array of 4 retroreflective markers, which was fixed relative to the OPMs, was recorded using an OptiTrack v120:duo motion tracking camera in the triaxial experiment or, in the case of the OP-MEG experiment, 6 OptiTrack Flex 13 cameras spaced around the room.

The magnetometer outputs, which are limited to $\pm 5 \text{ V}$, were recorded at 6 kHz using LabView with a National Instruments (NI) DAQ (NI-9205, 16-bit, $\pm 10 \text{ V}$ input range), using QuSpin’s adapter (https://quspin.com/products-qzfm/ni-9205-data-acquisition-unit/). The position information was recorded on a separate computer using OptiTrack’s Motive software at 120 Hz. A 5 V voltage pulse was sent to both systems for synchronization.

Occasional occlusion of one or multiple markers led to gaps in the position data. In the triaxial recording, these gaps were filled in using cubic spline interpolation in Motive. In the OP-MEG experiment, an initial “pattern-based” interpolation was performed prior to spline fitting. In this case, when only one marker was missing (i.e. the position of the other three markers was known), the trajectory data from the other markers was used to determine the position of the occluded marker by the constraints of the rigid body. Any remaining gaps were then filled with cubic spline interpolation. The magnetometer outputs were
Figure 2.1: Field Mapping system set up. In the triaxial experiment, the position and orientation of two magnetometers were tracked optically, while the field along two of their axes were recorded. These two data streams (magnetic field and position/orientation) were synchronously recorded. The OPMs used here operate optimally in ambient magnetic fields close to zero ($\sim \pm 1.5 \text{ nT}$), so at the start of each experiment, electromagnetic coils on board each sensor were optimized to produce a magnetic field equal and opposite to the ambient field at the time of the calibration. This bias field (typically 0.1 nT to 2 nT for our OPM-dedicated MSR) was recorded and left on throughout each recording. The gain of the OPMs was set to allow recordings of up to $\pm 5.56 \text{ nT}$. This was necessary to ensure that all of the data was within range, although, as discussed previously, larger magnitude OPM recordings have higher gain errors, meaning that there is more uncertainty in the larger field values.

The OptiTrack coordinate system was set using an initial Ground Plane recording, where a right-angled triangle frame with retro-reflective markers at the corners was placed at the origin of and aligned along the axes of the desired coordinate system. This coordinate system was chosen to be related to the geometry of the MSR. The origin was set approximately in the center of the room, with the x-axis pointing towards the door, y-axis pointing down and z-axis defined so that the coordinate system is right-handed. To find the position and orientation of the OPMs from the position of the markers, we used the Kabsch method (Kabsch, 1976) to find the optimal transformation between the known coordinates of the markers relative to the OPMs and the OptiTrack recordings. We then applied the same transformation to the known OPM coordinates and orientations at each data point.

2.2.3 Experiments

Triaxial Field Mapping

We created a triaxial magnetometer from two, orthogonally oriented OPMs, shown in Figure 2.2. Each OPM recorded two orthogonal directions of field change, although only three axes were selected for modelling (i.e. only one of the two parallel axes was used). We recorded for 5 minutes while moving the sensor around the room, waited 20 minutes and then repeated the recording.

Three filters were applied to the OPM recordings: a 4th-order 60 Hz low-pass Butterworth filter and two 5th-order band-stop Butterworth filters at 50 Hz (line noise) and 120 Hz (infra-red interference from the OptiTrack cameras).
To determine the number of spherical harmonic functions required to reasonably describe the magnetic field in our MSR, we tested the first six model orders. We performed a 10-fold cross-validation test to compare the different models for both recordings and evaluated their performance by the variance in the data explained by each model, quantified by the Coefficient of Determination ($R^2$) across the full dataset.

$$R^2 = 1 - \frac{\sum_{i=1}^{NM}(Y_{\text{measured},i} - Y_{\text{modelled},i})^2}{\sum_{i=1}^{NM}(Y_{\text{measured},i} - \langle Y_{\text{measured}} \rangle)^2}$$

(2.53)

Here the brackets around $Y_{\text{measured}}$ indicate the mean over all channels and times. Additionally, we wished to avoid overfitting and also establish whether the magnetic field changed with time. Therefore, we trained a model on the first 80% of the data and tested it on the last 20%. For this purpose, we also trained the model on the alternative run, recorded 20 minutes apart.

**OP-MEG Recording**

We sought to recreate this modelling with OP-MEG data based on recordings from multiple scalp-based sensors. To create a test dataset, 43 (dual-axis) OPMs were placed evenly around a participant’s head in a 3D printed, bespoke, rigid scanner-cast. The sensor and OptiTrack marker positions relative to the scalp are shown in Figure 2.3.

The participant was standing and was asked to move such that their head made large translational and rotational movements (shown in Figure 2.7). The experimental protocol was approved by the UCL Research Ethics Committee and informed consent was obtained prior to participation.

Aiming to compensate for the temporal changes in the magnetic field, we performed this modelling on sliding windows of the data. Six different window lengths — 5s, 10s, 30s, 60s, 120s and 240s — were tested. We did not update the model at every data point for efficiency. Instead, unless otherwise stated, we set the modelling step size, i.e. how often we update the model, to half of the length of the modelling
window.

To evaluate the model’s performance, we looked at the shielding factor of the resulting correction, calculated with SPM (https://github.com/tierneytim/OPM).

\[
\text{shielding factor (dB)} = 20 \log_{10} \left( \frac{Y_{\text{measured}}}{Y_{\text{measured}} - Y_{\text{modelled}}} \right) \tag{2.54}
\]

For three windows (5 s, 30 s and 120 s), we also looked at the percentage decrease in the root-mean-square (RMS) value of the OP-MEG recording and how that varied between the channels.

In order to evaluate the impact of the step size/time we waited before recalculating the model, we repeated this analysis, keeping the window length fixed at 10 s and changing the step size. For this evaluation, we only used the first 20 s of data and used a 1st order model rather than 2nd to minimize the time to run the experiment. We looked at the median (across channels) shielding factor, root mean (over all data) square error or the residuals and total computation time.

The position data was low-pass filtered at 2 Hz with a 6th–order Butterworth filter before modelling. The model predictions were low pass filtered at 2 Hz with a 5th–order Butterworth filter. This filter was necessary because we found that above this frequency, the noise from the motion tracking camera was larger than the noise from the movement. This is consistent with Figure 2.6, which shows that most of the movement here is described by frequency components below 2 Hz.

2.3 Results

2.3.1 Triaxial Recording

The modelled magnetic field in the OPM–dedicated MSR at UCL from the two triaxial recordings using a 3rd order model is shown in Figure 2.4. The figure shows the trajectory of the movement, which for the first recording begins in the bottom left of the grid shown (as the researcher picks the sensor up from a table). The range of movement in the first recording was 1.2 m, 1.4 m and 0.8 m in x, y, and z respectively. For both recordings, the model is spatially smooth, as you would expect given the basis functions, with a gradient in the x direction (towards the door).

Figure 2.5 shows the variance in both triaxial recordings for spherical harmonic models of different complexity. As one would expect, the model error decreases as the complexity of the model increases. When a 10-fold cross-validation test was performed, the difference between the within-sample variance explained and out-of-sample variance explained was within the error bars for all the models. This suggests that all the models generalize well. However, for both recordings, the same cannot be said when training on the first 80% of the data and testing on the last 20%. The model explains over 96% of the variance in the hold out set and, indeed, the variance explained in the hold out set exceeds that in the training set. The fact that they are different implies that the magnetic field is changing in time.

It is highly surprising that the variance explained in the hold out set is higher than in the training set. One possible explanation may be that the way that we have calculated the variance explained (concatenating all the channels into one dataset) means that the mean offset of the channel is effectively included in the estimation of variance. As such, if there is comparatively little variation in the hold out set but the offset is constant, the offset accounts for a higher degree of the variance and so the model appears to out-perform in the hold out set than in the training data. Alternatively, it could be that there is a higher degree of movement in the hold out set, or that the temporal field changes (from, for example, a car passing outside)
Figure 2.4: Background magnetic field in the Magnetic Shields Limited (MSL) MSR at UCL at the mean OPM position for the three recordings, according to a 3rd order real spherical harmonic model. The three columns are the three magnetic field components. The graphs are oriented to be representative of the room such that down the page is nearer to the ground in the room. In 2.4a, the two trails coming out of the main space bottom left and top right are respectively caused by the magnetometer being picked up off the table at the start of the experiment and moving it nearer the camera (to see how this affected the field).
Figure 2.5: Variance explained ($R^2$) by different order spherical harmonic models in three different analyses: 10 fold cross validation (blue circles), training on the first 80% of the data (orange triangles) and training on the opposite run (yellow squares). The within sample (testing and training data are the same) variance explained is given by complete lines, the out of sample (testing and training data are different) variance explained is given a dashed line. The two recordings are shown on separate graphs. Run 1 (left) was recorded first, then run 2 (right) recorded 20 minutes later. Note the different scales on the two graphs.

were fewer in the 1 min of the hold out set than in the 4 min training set.

In line with this, there is a notable drop in the variance explained when training on the alternative recording, i.e. training on data recorded in the same room, without opening or closing the door but recorded 20 minutes later or earlier. Unlike testing on the same dataset, the variance explained does not increase as the model order increases. In this case, the lower order models appear to be more stable. Additionally, the number of model parameters is $l_{\text{max}}(l_{\text{max}} + 2)$. As the number of parameters increases, so does the size of the design matrix $X$ and the time required to invert it. Therefore, for computational efficiency and robustness, a spherical harmonic model of order 2 is a pragmatic compromise for the space sampled. For the rest of the paper, if a model order is not explicitly given, a 2nd order real spherical harmonic model was used.

2.3.2 OP-MEG Recording

Having established that it is possible to describe the field in the center of the room using a low-order spherical harmonic model, we set out to examine how effective these models and estimates might be during a real participant recording. As we expect the optimal field model to change depending on the room space moved within (i.e. high orders for large spaces or spaces close to the walls), we were aiming to use the participant’s own movements to define the optimal field model, rather than reusing the models from the previous triaxial experiments.

The power spectral density (PSD) of the motion tracking recording of the participant’s movements is shown in Figure 2.6. For comparison, a recording where the participant was asked to remain as still as possible and one where the scanner-cast was placed on the table are also shown. The width of the line is given by the standard error of the mean over $x$, $y$ and $z$ directions. It suggests that the movement is predominantly low frequency, with the majority of power below 4 Hz.

A 100 s segment of the OPM recordings from three randomly selected example channels, as well as the movement and rotation of the scanner-cast in the OP-MEG experiment, is shown in Figure 2.7. The movements (approximately 60 cm) here are notably larger than the typical movement range for SQUID-MEG.
Figure 2.6: Power spectral density (PSD) of the participant movement, as recorded with OptiTrack Flex 13 cameras (yellow). For comparison, a separate recording where the participant stood as still as possible (orange) and a recording with the scanner-cast sitting stationary on the table (blue) are also shown. Each recording was 5 minutes long. The position data was demeaned before the PSD was estimated using Welch’s method, with 100s segments. The figure shows the average over the three dimensions. The width of the line is given by the standard error of the mean.

(1 cm) (Gross et al., 2013).

Figure 2.7 also shows the predictions from a 2nd order spherical harmonic model fit to these data. The predicted field is shown for three different sliding window lengths – 5 s, 30 s and 120 s. For the three channels shown, it appears from visual inspection that the 5 s window fits to the original data most closely. The average maximum absolute value in the original data across all channels is $(1.35 \pm 0.03) \text{nT}$. After subtracting the model from the data, this was reduced to $(0.60 \pm 0.02) \text{nT}$, $(0.86 \pm 0.03) \text{nT}$ and $(1.02 \pm 0.03) \text{nT}$ for the 5 s, 30 s and 120 s windows respectively.

The per-sample noise reduction (as defined by the percentage decrease in the root mean square of the OPM recording) for these three window lengths and all 86 channels is shown as a histogram in Figure 2.8. There is variation between the 86 channels, with noise reduction value ranging from $(51.8 \pm 0.3)\%$ to $(81.4 \pm 0.1)\%$ for the 5 s window, with an average of $(65.2 \pm 0.9)\%$. This corresponds to an average (over channels) reduction in the RMS OPM recording of $(215.6 \pm 5.4)\text{pT}$.

The level of noise reduction was found to be dependent on the length of the window used. As the window length increases, the average noise reduction decreases while the variation between channels increases. Consequently, for a 120 s window, we saw a reduction between $(13.1 \pm 0.5)\%$ and $(57.9 \pm 0.3)\%$ with an average of $(36.7 \pm 1.1)\%$.

To look at the dependence of performance on frequency, the shielding factor for different window lengths is examined in Figure 2.9. When the model is tested on the same data as it was created on (within-sample, Figure 2.9a), the impact of the correction is largest at 0 Hz for all window lengths, with maxima at $(7.7 \pm 0.5)\text{dB}$, $(13.9 \pm 0.5)\text{dB}$ and $(27.8 \pm 0.6)\text{dB}$ for 120 s, 30 s and 5 s windows respectively. However, above 1 Hz, particularly for the 5 s and 10 s windows, the algorithm can have a detrimental effect, with shielding factors below 0 dB suggesting that the additional noise from the OptiTrack introduced by applying the correction is higher than the original movement noise in this region.
Figure 2.7: Example OPM recordings (first three rows) and corresponding movement information (last two rows) for the participant experiment. In the OPM recordings, the measured data is shown in blue. The model predictions for a second order model with three window lengths is shown: 5 s (orange), 30 s (yellow) and 120 s (purple). The position information is shown as the movement (position minus starting position, 4th row) and rotation (bottom) of the scanner cast during the field mapping recording. In the movement panel, the x (blue), y (orange) and z (yellow) components of the position of the scanner-cast in the same room based coordinate system as the triaxial recording are shown. The bottom panel shows the pitch (blue), roll (orange) and yaw (yellow) of the scanner-cast, as recorded by the OptiTrack camera.

Figure 2.8: The RMS noise reduction for 120 s, 30 s and 5 s sliding modelling windows as a histogram of the values for different channels.
Figure 2.9: Shielding factor for a 2nd order spherical harmonic model on the OP-MEG recording for different window lengths. The values shown are the mean over all channels, with the width of the line given by the standard error of the mean.

When longer (60 s, 120 s and 240 s) windows are used, the algorithm is less detrimental; the noise in the position recordings has less of an impact by simply having more datapoints from which to create the model. This is also the case for the out-of-sample shielding factor, shown in Figure 2.9b. However, in this scenario, the field modelling also has limited benefit, with a maximum within-sample shielding factor of (7.7 ± 0.5) dB for the 120 s window. Along with model complexity, modelling window length will be an important factor to be considered when using this method to reduce movement noise in OP-MEG.

Figure 2.10 shows that the model performance was not greatly impacted by increasing or reducing the time between recalculating the model (step size). If anything, increasing the step size improved the performance, with the RMSE (over all time and channels) at a minimum at half the window length, as we have used throughout the remainder of the chapter. The computation time is greater when a smaller step size is used, since the model needs to be recalculated more often. This suggests that recalculating at half of the window length is a reasonable choice.

We do observe that the computation time per model calculation increases with the step size. This is understandable, since while the size of the window we are modelling on remains the same, the number of datapoints we calculate at the end is smaller when the step size is smaller.

To compare these OP-MEG recordings with the previous triaxial recording, we also analysed the OP-MEG data without a moving window, and repeated the 10-fold cross-validation analysis. The results are shown in Figure 2.11. When compared with Figure 2.5 (the equivalent figure for the triaxial recording), it is clear that considerably less variance in the data is explained in the OP-MEG recording.

2.4 Discussion

We tested a method to compensate for sensor movement within the central portion of a magnetically shielded room using a spherical harmonic field model. We created models from recordings made while moving a triaxial sensor and a whole-head sensor array. We showed that low-order spherical harmonics could explain (and predict) over 80% of the variance in the data.

We used the same spherical harmonic models with an on-scalp array but we note the performance gains were much less striking. Although large noise reduction was achieved for short time windows ((65.2 ± 0.9) dB...
Figure 2.10: Impact of changing the modeling step size. A) shows the shielding factor for the different modeling step sizes tested. There does not appear to be a difference between the performance, apart from at near DC frequencies where higher step sizes seem to give an advantage. This is reflected in B), which shows the RMSE across the data. C) shows the total computation time while D) shows C) divided by the number of times the model is recalculated, i.e. the computation time per model calculation. D) has been linearly fitted using Matlab’s fitting toolbox. The equation for the line is shown in the top left corner of the graph.

Figure 2.11: Variance explained ($R^2$) by different order spherical harmonic models in the participant data, from a 10-fold cross-validation analysis. The blue circles are the within-sample variance explained, the orange dots are the out-of-sample variance explained.
at 5 s) with the on-scalp array, the performance for longer windows was relatively modest. This is likely to be due to a number of factors. First, the magnetic field in the room was changing temporally as well as spatially, due, for example, to passing traffic. Second, there was additional noise due to movement of the sensor cabling. These cables pull on and consequently move the magnetically sensitive cell within the OPM housing, creating field changes due to internal device movement. The cables also interact as they move across one another, creating movement-related but unpredictable artefacts. These issues have since been ameliorated with improved cable fastening and layout. These factors may help to explain the poorer performance at long window lengths and why, when we repeated the 10-fold cross-validation used in the triaxial experiment on the OP-MEG data, the variance explained was notably lower (Figure 2.11). One future improvement to the method could be to add regularisation, in particular on the OPM offsets which should change far more slowly than the background magnetic field. A Bayesian update method for example would allow some parameters to be updated more slowly than others.

This method draws inspiration from the signal space separation method (SSS) (Taulu et al., 2005, 2004; Taulu and Kajola, 2005), and homogeneous field correction (HFC) of the background magnetic field in an MSR (Tierney et al., 2021a). SSS makes use of the spherical harmonic description of the magnetic field to separate fields arising from within and outside of the head. Here we make use of the fact that the head is moving and assume that brain activity is negligible compared to the movement induced artefacts. The assumption in HFC is that the background magnetic field across the head is spatially constant and can therefore be removed. This takes place time-point by time-point without any knowledge of head-position. It is therefore well-suited to temporally non-stationary interference. In contrast, here we assume that the background magnetic field varies spatially and only changes slowly in time. This makes the model slower to compute but means that the magnetic field at a new position, orientation, and time can be predicted.

In this chapter we considered the change in the OPM recordings from movement while the OPMs are operating within the range of ±5.56 nT (Jodko-Wladzińska et al., 2020). We are fortunate that the central part of our room meets these specifications after degaussing the inner mu-metal layer, but for other rooms or different ranges of movement, we envisage that real-time field correction may be required to keep the OPMs within their operating range. If the sensors can continuously be kept close to their optimal (0 T) operating point this also mitigates the gain errors (∼1% per nT (Boto et al., 2018; Iivanainen et al., 2019; Tierney et al., 2019; Meyer, 2016)) which are incurred as a result of operating at an offset field during movement. The space the participant moves through will likely be important in the choice of model parameters, in particular the window length and model order. Here we looked at continuous, large movements; arguably the worst case scenario for OP-MEG recordings. However, typical neuroimaging experiments are likely to contain less frequent and smaller movements. A longer modelling window and a lower order model may be preferable in these situations.

The timing of the applied field is also likely to be important. In the way we have used field modelling here, time is not a significant limitation, since the modelling is done offline after an experiment. However, in this real-time scenario, computation time will be critical and should not be more than the time between recalculating the model. This recalculation time will depend to some extent on the stationarity of the environment. It is encouraging, therefore, that in Figure 2.5, over 80% of the field variation in the room can be predicted from measurements taken 20 minutes apart. The computation time is dependent on the size of the design matrix, itself determined by the number of OPM channels, number of datapoints in a modelling window, and model complexity. The time between recalculating the model, equivalent to the step size for the sliding window, should be chosen to be small enough to account for the changes in magnetic
field with time, but larger than the computation time. Unless otherwise stated, we have consistently used a step size of half the sliding window length. The relationship between this step size and the model accuracy, computation time, and noise reduction is considered in Figure 2.10. One of the advantages of a spherical harmonic model as we have used here, is the relative simplicity by comparison with a more complicated source model (Lopez et al., 2019).

2.5 Conclusion

In summary, we have explored a method to model the spatial variation of background magnetic fields within a magnetically shielded room and the interference they cause during an OP-MEG recording. We used a spherical harmonic field model and found that for the central portion of our shielded room, effective field cancellation could be achieved for low model orders. This is consistent with prior work and encouraging for future use of external field nulling coils typically used in OP-MEG, which are generally capable of producing 1st order magnetic field gradients (Iivanainen et al., 2019; Holmes et al., 2018, 2019).

This demonstrates the potential for real-time correction based on these models in the future. These preliminary steps hold promise for OP-MEG systems with greater movement tolerance requiring less passive shielding.
3 Experiment 2: Optimising OPM feedback based on field models: A simulation study

3.1 Introduction

In the previous chapter, we showed that the field inside of the MSR is spatially dependent. We demonstrated that this leads to motion related artefacts as the participant moves through the room and the background field at the OPMs changes. Neither subtraction of the field model nor regression of the marker positions from the recordings, as was done in Chapter 2, fully solve the problem. The OPM response to magnetic fields is only linear at zero magnetic field. As such, the gain of the sensors decreases as the magnetic field strength increases. Magnetic fields of just 1.5 nT have been shown to decrease the gain of the sensors by 4% (Boto et al., 2018). Additionally, so-called cross axis projection errors (CAPE) occur when there is a non-zero magnetic field along the laser axis of an OPM (Borna et al., 2022). CAPE affect the orientation of the OPM sensitive axes, their gain and phase. These gain and CAPE errors reduce the accuracy of source localisation in MEG and limit the performance of any movement correction performed in post-processing, as the field cannot be correctly modelled when it is not correctly measured.

Here we suggest dynamically updating the magnetic field at each OPM during an experiment using the electromagnetic coils built in to each sensor. This will only work if the background magnetic field is well modelled. From Figure 2.5, we know that the magnetic field in the room is not stationary, and so we seek to update both the field at the magnetometers and the model determining that field. In simulation, we use the participant’s position and a field model to determine what field to send to the on-board coils. The aim would be to hold the background magnetic field constant as the position and orientation of the OPMs changes. By nulling based on the person’s position and based on a whole array of OPMs, the brain signal of interest should be relatively unaffected. One risk is however, that that the feedback process itself adds considerable noise to the measurement.

Naturally, the background field at each OPM is never perfectly known. Errors can be introduced from the model, the position measurement and in the field applied with the electromagnetic coils. These errors may be random noise or may be due to a systematic calibration error. Since this control is working in real-time, time delays will also impact its performance. Here we present a simulation of this control system where we have introduced errors in the position measurement, magnetometer measurement, magnetic field produced by the coils and introduced time delays. With this simulation, we aim to answer which parameters will be the limiting factors in the control’s performance, in order to know which error source is most important to minimise when implementing such a system empirically.

3.2 Methods

As a basis for this simulation, we used the recordings from the triaxial experiment in Chapter 2. In Matlab, we simulated the triaxial recordings for run 1, using the empirical sensor positions and estimated $3^{rd}$ order vector spherical harmonic parameters. For computational efficiency, we sampled the data at 120 Hz and
Figure 3.1: Diagram showing feedback mechanism. Position and the previous best prediction for the spherical harmonic model of the field in the room are input to the algorithm. The predicted field at this position is then calculated and fed back to the OPM. The OPM recording is then input to the algorithm and the field in room space calculated and used with the position information to update the spherical harmonic model parameters.

only simulated the first 150 s of the recording (approximately half of the total recording). During this time, the stick holding the OPMs was moved a total of 1.12 m along the x-axis (forward-back), 1.33 m vertically and 0.69 m along the z-axis (left-right).

The control system we propose functions as follows. At each time step, the position of three retro-reflective markers were input to the algorithm. The current field model parameter estimates were then used to calculate the expected field at the current magnetometer positions and this value was fed back to the OPMs using the on-board coils. The OPM output was recorded and added to the field which was fed back, in order to estimate the background field in the room at this position. The model was then updated: the window was moved along a step, with the earliest data position and magnetic field measurement replaced with the current measurements, and following the mathematics in Chapter 2, a 3rd order vector spherical harmonic model created from this window of data. We chose to use a 30 s window (3600 samples), based on Figure 2.9. This is shown diagrammatically in Figure 3.1. To initialise the system, the first 30 s of the second triaxial run (Figure 2.5) was used.

The aim of this simulation was to answer which noise factors will most impede the performance of this control. Therefore, we added a collection of different, realistic noise sources, listed in table 3.1, to the simulation. For the random errors, the values listed in table 3.1 are the standard deviation of the Gaussian distribution. The systematic errors were kept constant for each run of the simulation but were selected from a Gaussian distribution with a mean of zero and standard deviation given in table 3.1 at the start of each simulation run.

It was suspected that these error sources would not simply add, but would rather interact non-linearly as they all impact the quality of the field model. Therefore, the effect of each noise source was estimated first by running the experiment with only one source of noise, and second with all the sources of noise apart
Table 3.1: Sources of error or noise input to feedback simulation.

<table>
<thead>
<tr>
<th>Noise Source</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaussian white noise on the magnetometer output</td>
<td>25 fT</td>
</tr>
<tr>
<td>Gaussian white noise on the marker position</td>
<td>1 mm</td>
</tr>
<tr>
<td>Constant magnetometer gain error</td>
<td>2%</td>
</tr>
<tr>
<td>Constant magnetometer offset error</td>
<td>0.1 nT</td>
</tr>
<tr>
<td>Gaussian white noise on the output magnetic field</td>
<td>3 pT</td>
</tr>
<tr>
<td>Systematic error in the nulling coil calibration</td>
<td>5%</td>
</tr>
<tr>
<td>Delay between the OPMs being in a position and the field being applied</td>
<td>10 ms</td>
</tr>
</tbody>
</table>

The mean and standard deviation of the simulated OPM measurements were used to evaluate the performance of the control. To mitigate coupling the results with the added noise, we used the mean and standard deviation of the simulated, noiseless signal without any correction minus the correction applied by the control, rather than the output signals. Otherwise, naturally the standard deviation of the output signal would increase when more noise was added to the nulling coil output, but it would only be indicative of the noise added, not the model and control performance.

Two key assumptions were made during the simulation. Firstly, we assumed that the background magnetic field is perfectly described by a third order spherical harmonic model and does not change during the experiment. Secondly, that the magnetometer output is independent of the field it is in. The validity of these is discussed in detail in Section 3.4.

### 3.3 Results

Figures 3.2a and 3.2c show two time series, one without and one with the feedback control applied, where there is no noise in the data. Each of the three lines is a different simulated magnetometer axis. In Figure 3.2a, any variance in the recordings comes from movement, no other signal source is simulated, other than the background magnetic field. It is clear that when the control is applied in this noiseless environment, after an initial period where the model parameters are optimised, the control removes the movement related field variation. However, Figure 3.2d shows that this is more complicated when the expected noise is added. This shows the simulated time series when the control is used and the noise listed in table 3.1 is included in the data. Each of the three magnetometer recordings gain white noise, even when compared with the noisy recordings without the control in Figure 3.2b (suggesting that the control is adding white noise), although the movement related drifts are dramatically reduced and the mean signal values appear close to zero.

We break down Figure 3.2d into separate error sources in Figure 3.3. From visual inspection, in this one run, uncertainty in the position measurement appears to lead to the largest increase in noise in the OPM recordings. However, in all cases, the magnetic field on each channel remains below 100 pT, well below the original maximum variation on any channel of approximately 1.5 nT over the course of the recording.

Figure 3.4 shows the average errors introduced by the different noise sources after 50 repeats. The top row looks at the absolute value of the mean magnetometer output; in other words, is the signal centred around zero. The bottom row looks at its standard deviation to give a measure of how wildly the signal is varying around its mean. The first column shows the results of only adding one noise source. If an error is
Figure 3.2: Simulated time series during triaxial experiment in Chapter 2. Each line is a different axis of the magnetometer. A) and B): the raw simulated recordings without any control/feedback system applied. In A), no noise is present in the data; the signal variation is purely from background field changes. In B), Gaussian white noise, an offset and a gain error has been added to each OPM channel. C) and D): the simulated recordings with feedback applied. In C), no noise has been added. In D), all noise sources (as listed in table 3.1 have been included. particularly detrimental to the feedback performance, it will have a high value in this column. The second column shows the results from having every error source apart from one, so if an error source is unusually detrimental, it will have a low bar here, because removing it dropped the overall baseline or variance of the OPM output. The value of the bar is given by the mean over all 50 repeats and 3 channels (i.e. effectively 150 samples total) and the error bars are the standard error of the mean. Only the simulated recording after one window length was used for analysis (i.e. after 30 s) so that the control was only using simulated data, and not relying on data simply used to pad the initial dataset.

A one-way ANOVA showed significant differences in the average absolute signal mean for different error sources at the $p<0.05$ level. The largest effect is from adding an offset to the magnetometer recordings and was significantly different from all other error sources both when added and when removed. Magnetometer gain and coil calibration were also significantly different from other error sources when added but not when removed. Position noise, magnetometer offset and coil calibration error had the largest effect on the standard deviation of the signal. Pairwise comparison showed that there was no significant difference between the variance introduced by position noise and coil calibration errors, but that they were significantly larger than that introduced by any other noise source when only one noise source was present. When every error but one was present, the reduction in variance from removing errors in magnetometer offset was not significantly different from that from removing position and coil calibration errors, but otherwise the reduction from these error sources was significantly larger than that from any other error source. Consequently, minimising position error, coil calibration errors and magnetometer offsets will be a key area
Figure 3.3: Simulated time series with feedback applied when each error source is independently present (i.e. only one error source is present in each figure). As in Figure 3.2, each line is a separate OPM data channel. A) Gaussian white noise (zero mean, standard deviation ($\sigma$) 25 fT) was added to the magnetometer output. B) Gaussian white noise (zero mean, $\sigma = 1$ mm) was added to the motion tracking marker position. C) The OPM recordings from channel $i$ were multiplied by $1 + x_i$, where $x_i$ was selected from a Gaussian distribution with zero mean and $\sigma = 2\%$ of the maximum simulated recording on channel $i$. D) An offset selected from a Gaussian distribution with zero mean and $\sigma = 0.1$ nT was added to the OPM recordings. E) Gaussian white noise (zero mean, $\sigma = 3$ pT) added to the output, feedback correction magnetic field. F) Uncertainty added to the coil parameters (to go from voltage to magnetic field) of $x\%$, where $x$ is selected from a Gaussian distribution with zero mean and $\sigma = 5$. G) Delay of $x$ms added between OPM being in a position and feedback being applied, where $x$ is selected from a Gaussian distribution with zero mean and $\sigma = 10$ ms.

of research as we work towards implementing this control system in OP-MEG.

3.4 Discussion and Conclusions

We simulated a feedback control which could be implemented in OP-MEG to remove or minimise movement related noise in real-time. We used a model of the background field and the magnetometer position to cancel the background magnetic field at a triaxial OPM. These simulations show that such a system could be highly effective but that noise in the control inputs and outputs will impede its performance.

We looked at the impact of realistic noise from different sources and found that it is important to know the position of the sensors you are trying to null to sub-millimetre accuracy. The calibration of the output magnetic field was also important: ensuring that we get the desired field out of the on-board OPM coils will be pertinent for the use of such a control system.

Offsets on the magnetometer outputs were also found to have a significant impact on both the mean and standard deviation of the OPM recordings. As outlined in Chapter 2, these can come from a number of sources, with the largest erroneous source being magnetisation of the internal OPM components. It is likely that little can be done to remove such error sources since they are part of the manufacture of the OPM, but for optimal control performance, it may be beneficial to measure and correct for them.

Two assumptions were made in this simulation: that the background field is static and perfectly described by a 3rd order spherical harmonic model, and that the magnetometer gain is independent of the background field. The former is not the case in our MSR at UCL, as shown in Figure 2.5. As a result, it would be
Figure 3.4: Four bar charts looking at the impact of different noise sources on feedback control performance. The first row looks at the mean of the magnetometer output. The second row shows the standard deviation of the magnetometer output. The first column is where only one noise source has been added, in the second column, all sources of noise but the one on the x-axis was added. If a noise source was particularly detrimental to the feedback, it would have a large bar on the left and a small bar on the right. The x-axis labels refer to the noise sources in table 3.1 and are written in the same order as in the table.
unrealistic to expect the level of noise reduction displayed in this simulation in a real system. The latter assumption is not true for many magnetometers, including OPMs. However, the change in their gain with magnetic field would be less than 10% for the recordings with the control on, and by not including it we are underestimating the control performance. If we made the gain dependent on field, there would be more noise in the control free recording and approximately similar noise in the simulated recording with the control, meaning a higher overall noise reduction.

When implementing this control in reality, one limitation is that it is relatively slow. The OptiTrack records at 120 Hz and the OPMs at over 1200 Hz, but implemented in this way, the control is limited to 10 Hz by the speed of the matrix inversion in the field modelling. One possible solution is to use the Sherman-Morrison formula to calculate the design matrix inverse. This updates the existing value of a matrix inverse, rather than re-calculating it from scratch and so is more computationally efficient. This is, in our experience, roughly three times faster. However, the inversion is less stable and as a result, it did reduce the noise reduction offered by the control in the noiseless simulation. An alternative solution would be to predict the next position of the participant before they reach it using a predictive filter such as a Kalman filter. This would give the time between the position prediction and the participant reaching it to adjust the magnetic field at the OPMs and so could merit further investigation.

There is a possibility that this control could remove the MEG signal of interest as well as the movement related noise, if this is not considered during the implementation. There are two factors which will determine this: the length of the moving horizon window (chosen as 3000 samples in this simulation) and the relationship between the movement and the desired neural activation. Addressing the former first, if the window of the control is of a similar length to the neural activation, the neural activation may correlate with position and so the control will remove this too. Addressing the latter, if the MEG task of interest and movement are correlated (for example, if the task involves repeatedly turning your head by the same degree), the model embedded in the control would not know which part of the change in magnetic field was from the rotational change and which part was the brain’s field. This would be a problem with any such task, even if you did not have the control on, as you could not determine how much of the observed change in magnetic field was from the room and what was from the brain. One solution is to decouple the two within the experimental design. Continuing this example, that would mean changing the task so that the participant moved more randomly and turned their body at various points throughout the experiment. Some comfort may also be taken from the knowledge that the spatial distribution of the background magnetic field and neuromagnetic signals are different, as shown by Tierney et al. (2021a). The impact of such a control system on the neural signal is therefore likely to be dependent on the coverage of the OPMs over the participant’s head.

The main purpose of this control system is to allow OP-MEG experiments in which a participant can move further than the current 40 cm allowed by bi-planar nulling coils (Holmes et al., 2019). This has the potential to allow measurements from participants while they move freely and are not necessarily seated.
4 Experiment 3: Local, real-time magnetic field update for OP-MEG

4.1 Introduction

To summarise a problem we have now talked extensively about: the range of movement allowed in wearable OP-MEG is limited by the background magnetic field. The OPMs we use are so-called zero-resonance sensors, meaning that they have a limited operating range around zero-field. Fundamentally, their absolute maximum range is limited to within $\pm 10 \text{nT}$ but their gain is non-linear and reduces with magnetic field strength, as discussed in the introduction and shown in Figure 1.2. As such, an increasing magnetic field means increasing gain errors. Additionally, magnetic fields on the OPM laser axis lead to so-called cross-axis projection errors or CAPE (Borna et al., 2022), whereby the sensitive axis of the OPM is altered. Therefore, it is generally advisable that the magnetic field is kept below $1.5 \text{nT}$ over the course of an OP-MEG recording. No brain signal of interest will ever be this large, but the background magnetic field from the environment is several orders of magnitude larger than this value.

Therefore, to allow OP-MEG recordings, these gain and saturation issues are minimised through use of magnetic shielding. Magnetically shielded rooms (MSRs), made of passive magnetic shielding such as mu-metal or aluminium, can bring the background magnetic field to below $10 \text{nT}$. Additional, active electromagnetic shielding may also be used (Holmes et al., 2018, 2019, 2021; Zhang et al., 2020b; Iivanainen et al., 2019; Zetter et al., 2020; Tayler et al., 2022; Nardelli et al., 2019). Here, electromagnetic coils aim to generate a magnetic field which is equal and opposite to the background magnetic field, thus cancelling it out. Most if not all OPMs contain electromagnetic coils to cancel the magnetic field locally at the sensor. These fields are generally set at the beginning of a recording and not changed until it is finished, although dynamic, closed-loop systems are becoming more common (Nardelli et al., 2019; Robinson et al., 2022).

Here we implement a dynamic feedback system, whereby the background magnetic field is predicted from the recordings from a whole-head OP-MEG array, and then nulled at each sensor using the electromagnetic coils on-board each OPM. Rather than continue with the models used in Chapters 2 and 3, we model the background magnetic field in the coordinate frame of the OPM array, at a given time-point, as a homogeneous field. We update this model continually, meaning that the nulling can compensate for changes in the background magnetic field over time. In essence, we have implemented homogeneous field correction (HFC) (Tierney et al., 2021a) in real-time. We made this choice to simplify the implementation of the control, and thus minimise calculation time, and to remove the reliance on the position measurements, a factor which was found to be likely to significantly contribute to higher signal variance in Chapter 3.

The chapter proceeds as follows. Firstly, we provide a brief introduction to the HFC model and into how we have implemented it for our OP-MEG system. We then demonstrate this system with a stationary, empty helmet and look at its effectiveness in minimising temporal changes in magnetic field when different low-pass filters are applied. To examine the frequency dependence of performance, we applied an external, oscillating magnetic field across the OPM array. Lastly, we look at the system's effectiveness in minimising movement related magnetic field changes in an auditory OP-MEG experiment with large ($> 1.5 \text{m}$) partic-
ipant movements and examine the auditory evoked responses with and without this feedback in place. We show that introducing this feedback increases the number of usable trials in this case of large movement by 125%.

4.2 Theory: Homogeneous Field Correction

The main assumption within Homogeneous Field Correction (HFC) is that the background magnetic field across the OPM array is described by a sum of the gradients of regular solid harmonics at a given time point, in the coordinate frame of the OPM array. In its simplest form (which we use here), this is equivalent to saying that at a given time point, the background magnetic field is spatially homogeneous across the OPM array, and can be described by a three-vector, $B_{\text{background}} = [B_x, B_y, B_z]$. Consequently, the interference from the background field recorded by any given sensor is

$$y_i = B_{\text{background}} \cdot \rho_i = B_x \rho_{ix} + B_y \rho_{iy} + B_z \rho_{iz}$$

(4.55)

where $\rho_i$ is the orientation of sensor channel $i$. Considering the entire array, the background interference can then be described as

$$Y = N B_{\text{background}} \hat{Y}$$

(4.56)

where

$$N = \begin{pmatrix} \rho_1 & \rho_2 & \rho_3 & \ldots \end{pmatrix}^T$$

$$Y = \begin{pmatrix} y_1 & y_2 & y_3 & \ldots \end{pmatrix}^T$$

(4.57)

Then the background magnetic field can be estimated by the multiplication of $Y$ with the Moore-Penrose pseudo-inverse of the sensor orientation matrix $N$. The background interference at any orientation is then estimated by the dot product between that orientation vector and the estimated magnetic field. Going from a single channel to the whole array, we construct an orientation matrix $M$ for orientations to feedback to. $M$ is the same matrix as $N$, except that it is the orientations of the coils to feedback to rather than the channels from which the model was created, which are not necessarily the same. Then the desired feedback can be simply calculated as:

$$\text{Desired Feedback} = MN^\dagger Y.$$

(4.58)

Comparing this with the models described in Chapter 2, HFC is a first-order spherical harmonic model, but in the coordinate frame of the OPM sensor array. The coordinate frame is the key difference between HFC and the models described in Chapter 2. Additionally, rather than modelling based on data over a certain time period, the model is recreated at every time point. This recreation of the model means that it is no longer necessary to know the helmet position within the room and so makes the model much simpler and quicker to calculate.
Figure 4.1: Control system employed to minimise background field at the OPMs. We seek to minimise the error (e) between the background field (B_{\text{background}}) and the feedback, modelled field (B_{\text{model}}). The sensor recording, y, which is determined by the OPM gain (G), the difference between the background field and the feedback field (e), the signal of interest (B_{\text{neural}}), the sensitive axis orientation of the OPM (\rho_{\text{OPM}}) and the noise profile of the OPM (\epsilon_{\text{OPM}}), is added to the previously feedback magnetic field (along the sensitive axis of the OPM), in order to calculate the total field at the OPM. HFC is then applied to this sum (u), through the matrix multiplication MN^\dagger u. The matrix N is the orientation of all sensors ordered to correspond to the input from the OPMs, while M is also the orientation of the sensors but ordered to correspond to the digital output of the computer.

4.3 Methods

4.3.1 Control Algorithm

The basic control algorithm is shown in Figure 4.1. The modelled background magnetic field (B_{\text{model}}) was fed-back via the on-board OPM coils along the two recording axes. The difference between the true and modelled background field is denoted here by e. This was recorded by the OPM channel, along with any signal magnetic field (here denoted with B_{\text{neural}}). The OPM channel recorded the field along its sensitive axis (\rho_{\text{OPM}}) with a multiplicative gain of G. The error on the OPM recording is included as \epsilon_{\text{OPM}}. The OPM output, y, was then added to the feedback which was most recently applied to estimate what would have been recorded had there been no feedback. This was then used to model the background magnetic field for the next loop.

The required feedback was calculated by multiplying the OPM output which would have been recorded had no feedback previously been applied (u) by the Moore-Penrose inverse of the orientation of the OPMs ordered by their analogue output (N^\dagger) and the orientation of the OPM channels we sought to feedback to (M). This gave a new value of B_{\text{model}} to be applied in the next loop.

4.3.2 Implementation

This algorithm was implemented in LabView 2017, into the acquisition program we typically use to record from the OPMs. The output from an array of dual-axis, zero-field magnetometers (Gen-2.0 QZFM, QuSpin; Louisville, CO) was recorded via a 16-bit analogue to digital converter (NI-9205, National Instruments; Austin, TX). The data was read into LabView in 60 sample chunks and was sampled at 6 kHz. As such, each chunk spanned 10 ms. To model the feedback, rather than create a new model for every datapoint, each chunk of data was averaged and a model created from the averaged data. This was done for two reasons. Firstly, it operated as a moving average filter, minimising aliasing from higher frequency signals than we could feedback at. Secondly, creating a model at each time-point was computationally infeasible.

\footnote{No feedback was provided along the X axis of the OPM to avoid impacting the cross-talk correction, for which the X axis coils of the second generation QuSpin OPMs are generally employed.}
given the high sampling rate, and unnecessary since the rate at which we could apply the feedback was far lower.

In a separate thread from the recording loop, the modelled background field was applied to the sensitive axes of the sensors - named the Y and Z axes. The X axis was left in its initialised state as the magnetic field across it is optimised, for this generation of QuSpin OPMs, to minimise cross-talk between the OPMs, rather than to minimise the background field. The field was applied using the on-board OPM coils, which were each controlled via 16-bit digital to analogue to digital converters, commands to which were sent digitally via USB. Commands were sent to each sensitive axis every 10 ms. The field was first updated on every Y axis, then after a 5 ms wait, the field on the Z axis was updated. When this 5 ms wait time was not included, the OPMs did not behave as intended, with a new command being delivered before the first was fully processed, leading to the OPMs changing, for example, their operating mode unexpectedly. For this reason, the model was only created once for every 60 samples.

Filtering

We tested filtering both the model input and output in order to improve the feedback performance. As the base version of LabView does not provide an inbuilt point-by-point (i.e. real-time) multi-channel filter, one was written for this project. The type of filter was a fourth order linear filter, comprised of two digital biquads, which are second order filters, so named because their transfer function in the z-domain (a complex frequency domain, akin to the s-domain but for a discrete time signal rather than a continuous signal) is the ratio of two quadratic functions:

\[
H(z) = \frac{b_0 + b_1 z^{-1} + b_2 z^{-2}}{a_0 + a_1 z^{-1} + a_2 z^{-2}} \tag{4.59}
\]

where \(b_i\) and \(a_i\) are coefficients which determine the performance of the filter. In this case, they were chosen to produce a low-pass filter with a 1 Hz cut-off frequency (at which the transfer function was equal to \(-3\) dB). The biquads were implemented in the transposed direct form II (Chowdhury, 2020; Smith, 2007).

4.3.3 Validation Experiments

To test this system, we performed three different validation experiments. All three were performed within the OPM MSR at UCL (Magnetic Shields Limited, 4-layer MSR, internal dimensions 3 m × 4 m × 2.2 m).

Firstly, we set the array of OPMs onto the table and recorded the environmental noise. We looked at the decrease in this noise when feedback was turned on to a subset of the OPMs, although the model was created from all recording channels. Secondly, still with the sensor array on the table, we applied a sinusoidal magnetic field across the array at a range of frequencies with and without feedback on all of the sensors. Lastly, we recorded MEG from a healthy participant during an auditory evoked paradigm while walking around the room, both with and without feedback to all of the sensors. In all experiments, the OPMs were placed within a 3D printed scanner-cast of known geometry, in order to determine the sensor orientations relative to one another. The sensor arrays for each experiment are shown in Figure 4.2. The sensors were operated in dual axis mode, meaning that they recorded the magnetic field radial to the scalp and along one axis tangential to it, but the field component along the OPM laser axis was unmeasured.

Prior to OPM recordings, the field at each OPM was minimised by degaussing the MSR (Altarev et al., 2015) and, to null the remnant background magnetic field locally, the currents through the on-sensor coils.
Environmental Drift

External Coil Recordings

Auditory Evoked Paradigm

Figure 4.2: Positions of the OPMs used in each validation experiment. The participant’s head is represented by the grey mesh (https://www.turbosquid.com/3d-models/male-head-obj/346686). In (a), the pink OPMs had feedback applied, while the blue OPMs were used for reference measurement.

(the same coils which were used to feedback) were optimised according to the manufacturers’ procedures. During the OPM recordings, the intended feedback ($B_{\text{model}}$ in Figure 4.1) was added to these initial field zeroing magnetic fields. The OPMs were then calibrated according to the manufacturer’s procedure. This involves a magnetic field of known amplitude being applied to the sensor, again using the on-sensor coils. The output of the sensor is then measured and calibrated against the known field. This full procedure (degaussing, sensor field zeroing and calibration) was performed once for each set of experiments, i.e. the environmental noise recordings were taken one after another, first without any filter and then with one included, and the calibration was performed only before the first recording. The door to the MSR was not opened between runs of the same experiment.

Environmental Noise Recordings

In testing the performance of this feedback to compensate for environmental drifts, we first left the sensor array stationary in the centre of the room and recorded for 40 minutes. We turned the feedback on to a subset of the channels for the central 30 minutes of the recording. The channel positions are shown in Figure 4.2a. There were 21 recording OPMs (equating to 42 channels) and feedback was applied to 11 of them (22 channels). We performed this recording twice, once without any filtering and once with a 1 Hz low-pass filter to the intended feedback.

We evaluated the performance of the system by the median shielding factor, defined as follows:

$$mSF(f) = 10 \log \left( \frac{\text{median}(P SD_{\text{feedback on}})}{\text{median}(P SD_{\text{feedback off}})} \right)$$

(4.60)

where $f$ is frequency and the power spectral density (PSD) was calculated according to Welch’s method with 10 s chunks of the data, using data only during the period where the feedback was turned on. The median is taken over channels.

External Coil Recordings

To further examine the dependence of feedback performance on the frequency of the external interference, we placed a set of external coils around the sensor array in the centre of the room. These coils were simple loops of wire on opposite walls on one side of the room, held up by hooks at each of the corners. The shape of the walls and their spacing meant that these were not Helmholtz coils, and so there will be some inhomogeneity in the magnetic field they produced across the OPM array. Nevertheless, they were successful in creating a varying external magnetic field in a controlled manner.

We recorded from the OPM array for 8 different coil frequencies: 0.1 Hz, 0.5 Hz, 1 Hz, 2 Hz, 4 Hz, 6 Hz,
8 Hz and 10 Hz. We repeated the recordings with the feedback off and on and did not include any additional filtering, beyond the implicit 100 Hz moving average filter introduced by the implementation of the model. The length of the recordings was set to 10 wavelengths of the external signal. There were 26 OPMs, each recording from 2 axes and with feedback (when present) on all sensors. We also recorded what we had intended to output from LabView at each time point for each OPM channel.

To evaluate the performance of the feedback, we compared the recordings with feedback on and off, both looking at the time series and the shielding factor. This time the shielding factor was recorded in the same way as in Chapter 2; each sensor channel was compared with itself between recordings. Additionally, we looked at the difference between what we would expect to have recorded if we had feedback what we were intending to and what was actually recorded.

We found that there was likely to be a time delay between what we were intending to feedback and what was in fact feedback to the sensor on-board coils. We inferred this as the amplitude of the feedback on recordings increased above the original feedback off amplitude when the frequency of the external interference was increased. To explain this further, it is known that the sum of two sinusoids is also a sinusoid

\[
A_1 \sin(\omega t + \phi_1) + A_2 \sin(\omega t + \phi_2) = A_3 \sin(\omega t + \phi_3)
\]  

(4.61)

Comparing this to the OPM recordings with feedback on during sinusoidal external interference, sine wave 1 is the external interference, wave 2 is what we feedback and wave 3 is the consequent recording. Consider subtracting a sine wave from another sine wave, where they are perfectly out of phase but otherwise identical. The resulting amplitude (\(A_3\)) will be double that of the original sine wave (\(A_1\)) as the trough of one wave is subtracted from the peak of the other. We therefore sought to find the time delay between our intended feedback and the true feedback by determining the relationship between \(A_3/A_1\) and the external interference frequency. Explicitly, when \(A_3/A_1 = 2\), the phase difference \(\phi_2 - \phi_1\) equals \(\pi\), and the time that corresponds to can be determined by \(\pi/\omega\), so it is only necessary to determine the frequency \(\omega\) at which \(A_3/A_1 = 2\) to determine an expected time delay. This was a key motivation behind recording with multiple different interference frequencies.

**Auditory Evoked Response Paradigm**

As a final validation experiment, we recorded OP-MEG from a healthy adult participant (male, right-handed, 55-years-old) during an auditory evoked response paradigm. The participant walked around the MSR, while their position was recorded using an array of 5 OptiTrack Flex 13 cameras, which sampled the participant’s position at 120 Hz. The auditory stimulus was delivered via an MEG compatible ear tube to the participant’s right ear. The participant provided written informed consent and the study was approved by the University College London Research Ethics Committee.

The auditory evoked paradigm was the same as used by Seymour et al. (2021). It is a roving mismatch negativity task based on Garrido et al. (2008). 70 ms long tones were presented to the participant (with 5 ms rise and fall times) with frequencies at 50 Hz steps between 500 Hz and 800 Hz inclusive. The inter-stimulus interval between tones was 0.5 s and no stimulus jitter was included. The same frequency was repeated 2 to 8 times, after which a deviant tone of a different frequency was presented. This led to approximately 570 tones in each run of 80 deviant tones. Each run was approximately 275 s to 300 s long. We collapsed our analysis across all of the tones, rather than focussing on the difference between deviants and repeated tones. The volume of the stimuli were adjusted to be comfortable for the participant. The
stimuli were presented via PsychoPy (Peirce, 2009).

For the recording, 23 dual-axis OPMs were used, with feedback applied to all of them. They were held on the participant’s head with a bespoke, 3D printed scanner-cast, based on the participant’s MRI (Meyer et al., 2017), simplifying co-registration between the MRI and sensor positions. Five retro-reflective markers were also placed on the scanner-cast in order to track the participant’s position through the MSR. The participant was asked to walk around the room in a repeating pattern, moving outside of the central 1 m³ where experiments usually occur. The gain of the OPMs was set such that the OPMs saturated at ±1.5 nT. Four runs of the approximately 5 min task were undertaken. During two runs, no feedback was applied. Feedback was applied during the other two. A 1 Hz low-pass filter was applied to the intended coil output. The order of the runs was feedback on, off, off then on and the participant was informed of the order of the first two runs but was unaware of whether feedback was on or off for the second two.

Analysis of the data was performed in Matlab 2021b, using SPM (Litvak et al., 2011) for the analysis and the FieldTrip Toolbox (Oostenveld et al., 2011) for the topographical representation of the data, as well as custom scripts to identify saturated periods in the OPM data and to synchronise it with the motion tracking recordings. The OPM data were pre-processed by first downsampling to 1 kHz for computational efficiency. The OPM data were then cropped to match the period when the motion tracking was recording, and the motion tracking data was up-sampled to match this 1 kHz sampling rate.

We then determined the datapoints at which each channel was saturated. This is not a trivial quantity to determine automatically as the saturation point, although approximately 1.5 nT, varies between sensors. We therefore wrote a dedicated function, which, for each channel of the OPM data, created a histogram of the recorded data. The data were discretized into bins of 1 pT width. If there are more than double the number of datapoints in the maximum (or minimum) 3 bins than the previous 3 bins, any datapoints in the maximum (or minimum) 3 bins were marked as saturated. An additional check was included so that no recordings with a magnitude lower than 1 nT could be marked as saturated.

OPM data were denoised using homogeneous field correction, regardless of whether feedback had been applied (and hence real-time HFC had been applied). We applied three band-stop filters at 50 Hz, 120 Hz and 83 Hz corresponding to line noise, the optitrack camera sampling frequency and the mixing frequency of the 840 Hz harmonic of the optitrack sampling and the 923 Hz OPM modulation frequency. We then applied a high-pass filter at 2 Hz and a low-pass filter at 40 Hz. All of these filters were 5th order Butterworth filters applied bidirectionally to achieve zero-phase shift. The data were then epoched into 700 ms trials around the tones (-200 ms pre-stimulus, 500 ms post-stimulus) and the runs combined based on whether feedback was on or off (i.e. as though there were two approximately 10 min recordings with feedback on in one and off in the other). This left two datasets with 1197 trials with feedback off and 1137 trials with feedback on.

To allow fair comparison between the feedback off and on conditions, when analysing the auditory evoked response, we only considered 1130 randomly selected trials from each dataset. However, when any trials containing saturated sensors were removed from these 1130 trials, there were considerably fewer trials in the feedback off case. This is the major advantage of the feedback - that data can be recorded when previously the background field was too high - and so we performed the analysis with 453 trials in the feedback off case and 1097 trials when feedback was used.

OP-MEG data were averaged and a one sample t-test performed across trials. Sensor level fieldmaps were produced for the evoked response between 80 ms and 120 ms. We then projected this data into the source space.
Figure 4.3: The time series, power spectral density (PSD) and corresponding relative PSD for a 40-minute recording in which feedback was turned on between times 5 min and 35 min for 22 channels, with no feedback on 20 channels. The pink lines are sensors for which feedback was used, the blue lines are sensors where feedback was not used. In the PSD, the median (over channels) value for each case is shown as a black line. The relative median PSD shows the difference between these median curves in decibels. A value above 0 would imply that the feedback was beneficial, while below zero it is detrimental. The range (the shaded grey area) is calculated from the standard deviation (over channels) of each set of feedback or without feedback channels.

The forward model for the participant was created from their MRI. A single shell model was used based on the inner skull surface (Nolte, 2003). Minimum norm inversion was used (Hämäläinen and Ilmoniemi, 1994) to reconstruct the source level time courses, as implemented in SPM12 (López et al., 2014). The source space was the cortical surface, constructed by warping the SPM template mesh based on the participant’s MRI. For each vertex on this mesh, we performed one-sample t-tests over trials (similarly to at the sensor level).

4.4 Results

4.4.1 Environmental Noise Recordings

Figure 4.3 shows recordings from 42 OPM channels, where feedback was turned on for 22 channels (shown in pink/red). The channels were recorded simultaneously. The median PSD (over channels) for the feedback off and on groups is shown as the two thick, black lines in Figure 4.3. The median shielding factor is also shown, with the range given by the standard deviation of the feedback on and off groups, propagated through to the relative difference. Note that this is not calculated in the same way as the shielding factors in Chapter 2, as the feedback on and off cases were recorded simultaneously, and so it is not possible to compare a channel with itself. As a result, there may be inaccuracies due to the differing noise profiles and locations of the different channels, but this is expected to average out when considering all of the on or off channels as a group. This relative PSD implies that the feedback is beneficial at low frequencies, with the maximum at 0.1 Hz (the lowest frequency possible to interpret as the PSD was calculated from 10's chunks of data) of (27.07 ± 10.03) dB. However, above 1.33 Hz, the feedback is detrimental and raises the noise floor of the sensors.

To minimise this issue above 1.33 Hz, we introduced a 1 Hz low-pass filter on the output of the model.
The relative median PSDs with and without a 1 Hz low-pass filter on the intended feedback to each OPM channel. In each case, feedback was applied to the same 22 OPM channels, while 20 OPM channels recorded background noise for 30 minutes. In the no filter case, this is a repeat of Figure 4.3. The resulting relative PSD is shown in Figure 4.4, alongside the unfiltered case for comparison. It appears that the filter reduces the performance of the feedback at low frequencies and perhaps reduces the frequency at which the feedback becomes detrimental, but it does improve the feedback performance at frequencies above 5 Hz. It is also clear that the impact of the filter is negligible after 200 Hz, since the model for feedback is created on averaged 10 ms section of data - effectively introducing a 100 Hz moving average filter.

### 4.4.2 External Coil Recordings

In order to create a more controlled background field for the feedback to remove, we applied sinusoids of different frequencies to external coils on the MSR walls. Figure 4.5 shows the time series for eight different frequencies of interest. The time series is shown with and without feedback. As could be anticipated from Figure 4.3 and Figure 4.4, the feedback appears to work well for frequencies up to 2 Hz. However, above 4 Hz, the feedback distorts the external interference without noticeably reducing it. This is reflected in Figure 4.6, which shows the shielding factor (or relative power spectral density) for the recordings in Figure 4.5. The PSD was calculated using Welch’s method with 4 s spectrograms. This implies that up to the 4 Hz sinusoid, the feedback is reducing the interference. Above this, the feedback is increasing the noise at each of the applied frequencies.

To test how well the feedback could perform if there were no time delays or added noise from applying the feedback, i.e. if what we intended to feedback was indeed what was feedback, Figure 4.7 shows the recording without feedback for a single channel, randomly selected, for a subset of the recorded frequencies (0.5 Hz, 4 Hz and 10 Hz), alongside the values which were intended to be fed back. Figure 4.7 also shows the model subtracted out of the data and the recording with feedback. The theoretical performance is clearly higher than that in reality, showing that what we intended to feedback is not what is being feedback. Looking at the 10 Hz interference in particular, introducing the feedback leads to both an increase in amplitude and an increase in apparent "spikiness" of the recording.

We suggest, based on these results and those shown in Chapter 3, that the discrepancies between the ideal scenario and what was recorded could be at least partially explained by inaccuracies in the timing
Figure 4.5: Feedback off vs on for sinusoidal external interference of eight different frequencies.
Figure 4.6: Shielding factor for feedback off vs on for sinusoidal external interference of eight different frequencies. Values above zero indicate that the feedback is beneficial, while values below zero imply that the feedback is adding noise.
Figure 4.7: The potential performance of the feedback for a single, randomly chosen channel. Each row is a different frequency (0.5 Hz, 4 Hz or 10 Hz). The first column shows the recording without any feedback and what is intended to be fed back. The middle column shows the difference between the recording and what was intended to be fed back, i.e. the best possible feedback performance. The right column is the true recording when, at a different time, the feedback was turned on for this channel with a sine wave of the given frequency produced by the external coils.
Figure 4.8: Impact of updating feedback at discreet intervals. Repeat of the 10 Hz case in Figure 4.7, except that the intended feedback is held constant for 1 sample, 5 ms, 10 ms and 50 ms.

of the feedback system. We speculate that the spikiness is related to the time between updates to the feedback values. Figure 4.8 tests this theory using the 10 Hz recording, by downsampling the intended feedback by increasing degrees, then interpolating the to the nearest neighbour, to effectively simulate the case where the feedback is on at a single value for, for example, 50 ms, then steps to the next modelled value. The 10 ms and 50 ms cases in particular appears to recreate some of the spikiness of the recording with feedback on. Given the limitations of the serial control of the feedback currents, we know that there is a wait of at least 10 ms between one feedback update and the next, so this may explain some of the unusual behaviour observed.

Considering the increase in amplitude between the ideal case and what we recorded, we speculated that this was due to a phase lag between the feedback and the input signal from the external coils. Figure 4.9 shows the ratio of the amplitude of the interference with feedback on to the amplitude with feedback off for each of the different interference frequencies tested. Extrapolating these data via a linear fit, we expect that applying the feedback would double the amplitude of an 11.97 Hz interfering sinusoid. Consequently, as outlined in Section 4.3.3, we found an expected time delay of 41.8 ms between the intended feedback and what was truly fedback. The results of applying this to the intended feedback are shown in Figure 4.10.
Figure 4.9: Ratio of amplitude of signals with ($A_3$) and without feedback ($A_1$). Median value is shown by the point and errorbars given by the standard error of the mean across channels. Linear line of best fit also shown, extrapolated out to the point where the amplitude is double, at 11.97 Hz.

Figure 4.10: Impact of introducing a lag to the intended feedback. Repeat of Figure 4.7, except with a column added where the intended feedback has been lagged behind the recording by 41.8 ms.
The trajectory of the participant through the room in each of the runs. The dark blue points are the position as recorded with the optitrack Flex 13 motion tracking cameras. The red markers were added into the data manually and are based on a simultaneously recorded video of the participant. The light blue points were interpolated from this data.

**Figure 4.11:**

<table>
<thead>
<tr>
<th>Run</th>
<th>With Interpolated Points</th>
<th>Without Interpolated Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range of Position (m)</td>
<td>Range of Position (m)</td>
</tr>
<tr>
<td></td>
<td>Forward-Back</td>
<td>Left-Right</td>
</tr>
<tr>
<td>1</td>
<td>NaN</td>
<td>1.56</td>
</tr>
<tr>
<td>2</td>
<td>1.71</td>
<td>1.72</td>
</tr>
<tr>
<td>3</td>
<td>1.73</td>
<td>1.57</td>
</tr>
<tr>
<td>4</td>
<td>1.79</td>
<td>1.63</td>
</tr>
</tbody>
</table>

**Table 4.1:** Range of rigid body values across each recording. Only the forward-back movement is included when the interpolated points are included since it is only in this direction that they make a difference greater than 4 mm.

### 4.4.3 Auditory Evoked Response Paradigm

The trajectory of the participant for each of the four recordings is shown in Figure 4.11. Note that the smaller, lighter coloured points were interpolated from the motion tracking recordings. For gaps of less than 0.2s, this was done via linear interpolation. For larger gaps, this was done by shape-preserving piecewise cubic interpolation, using matlab’s fit function with the ‘pchip’ model option. The front of the room was particularly badly sampled by the motion tracking system, as it is normally not used for OP-MEG recordings due to the relatively high background magnetic field ($\approx 4.5$ nT). Therefore, a few (4 for run 3, 5 for runs 2 and 4) positions at the front of the room were estimated from a simultaneously recorded video and manually added to the recording. These are shown by the red crosses. This was not possible for run 1 as the video was lost. The range of movement (assuming these estimated points) is given in table 4.1. These suggest that the degree of movement is comparable between runs.

The recordings for each run are shown in Figure 4.12. There is clear evidence of the impact of feedback on the time series. Most apparent, when the feedback is off, the sensors frequently saturate. Over the two feedback off recordings, counting any datapoint where any sensor is saturated, 57% of the data were saturated. By comparison, when feedback was turned on, only 1.4% of the data were saturated. We rejected any auditory trial where at least 1 OPM channel was saturated. This meant rejecting 60% of feedback off trials and 3% of feedback on trials, leaving 453 feedback off trials and 1097 feedback on trials.

Looking at only these good trials, the sensor level results are shown in Figure 4.13. In both cases, there is some evidence for the M100 auditory evoked response with bilateral sources. However, the data is, in
The auditory evoked power between 0 ms and 250 ms, as estimated in SPM and using minimum norm estimation, is shown in Figure 4.14. There appears to be lower power in the left hemisphere, but this may be due to the very low sensor coverage on the left side of the head, as shown in Figure 4.2c. For both feedback on and off conditions, power is raised in the right auditory cortex.

We then estimated the time-series at each vertex of the cortical mesh, using the weights from the minimum norm reconstruction. We observed an earlier M100 response at $\sim 92$ ms in the left hemisphere and a later M100 response at $\sim 110$ ms originating from the right hemisphere. Previous literature on auditory evoked potentials from monaural stimulation is somewhat inconclusive as to latency differences between hemispheres, but an earlier, larger amplitude response in the contralateral hemisphere (in this case...
Figure 4.15: T-statistic maps at 92 ms and 110 ms when feedback is off (left) and on (right). The earlier 92 ms map shows a response in or near the left auditory cortex. The later 110 ms map shows a response in the right auditory cortex for the feedback on case but there were no significant values when feedback was off.

left) has been frequently observed (Rothenberger et al., 1982; Majkowski et al., 1971; Butler et al., 2009). The statistical maps of these two responses are shown on the cortical mesh in Figure 4.15. The 92 ms response has much larger t-values than the later 110 ms response, perhaps consistent with this previous literature, but it is difficult to confidently conclude such given the limited sensor coverage over the left hemisphere, as shown in Figure 4.2c. Nevertheless, for both the feedback on and off conditions, the 92 ms response appears to originate from or near to the left auditory cortex and the feedback on case has higher statistical power (in line with the larger number of trials) and more supra-threshold vertices (although some appear erroneous). By comparison, no vertices are statistically significant after Bonferroni correction for the 110 ms response when feedback was not used. When feedback was used, the t-values are smaller than the earlier 92 ms response but are consistent with a response from the right auditory cortex.

The source-level time series at the vertex with the average maximum evoked power over the feedback on and off conditions from Figure 4.14 is shown in Figure 4.16. The evoked waveforms appear similar in morphology whether feedback was used or not. This suggests that the feedback has not considerably distorted the auditory signal of interest. However, the statistical significance of the feedback on case is higher. This is consistent with Figure 4.15 and likely due to the larger number of trials in the feedback on case. There were 2.42 times as many trials in the feedback on case as feedback off. Since the t-statistic scales as the square-root of the number of trials, we would expect that the feedback on condition led to t-values 1.56 times higher than the feedback off condition. This is approximately what is observed in Figure 4.16 at the times of high signal (∼100 ms and ∼200 ms).

4.5 Discussion and Conclusions

We have demonstrated a model-based method for feeding back to an array of magnetometers, which reduced the very slow drifts in the background magnetic field by a factor of approximately 25 dB. We demonstrated that introducing this feedback allowed OP-MEG measurements during movements of over 1.5 m reduced the changes in background field due to movement and so increased the number of usable
Figure 4.16: Evoked response waveforms from the vertex of the cortical mesh with the highest power according to Figure 4.14 (averaged over the feedback off/on results), for the feedback off and on recordings. The significance threshold after Bonferroni correction for multiple comparisons is indicated with a dashed black line.

trials by 142%. Feedback did not appear to considerably distort the recorded auditory evoked responses.

This is the first demonstration of a field nulling system using the on-sensor coils during an OP-MEG experiment and large movements. Existing closed-loop OPMs generally use a proportional, integral, derivative (PID) control system (Nardelli et al., 2020) or rely on reference sensors fixed to the main sensor array (Robinson et al., 2022). Unlike a PID controller, there is no need to optimise our system to the temporal properties of the background interference, only the spatial properties. While the limitations of the implementation mean that the feedback performance is dependent on the frequency of the interference, theoretically, the model can handle the relatively slow environmental noise as well as the relatively quickly changing movement noise. Additionally, modelling the field in this way allows an estimation of the field on an unmeasured OPM axis. This is pertinent for OPMs where the fields on only two axes are recorded, but where interference along the third axis leads to cross-axis projection errors (CAPE) (Borna et al., 2022), altering the orientation of the recording axes. This would not be possible with a PID based system but is the motivation behind dynamic field compensation (DFC) (Robinson et al., 2022). DFC is a very sensible solution to CAPE for seated OP-MEG, but requires an additional reference array of sensors to be fixed to the MEG array. This adds extra weight and bulk to the OP-MEG headset, which makes it less ideal for wearing during large, naturalistic movements. By implementing real-time HFC, we can achieve this same goal of estimating the field on the third OPM axis but dispense with the need for this extra hardware. However, this was not demonstrated here; further work is needed to determine the improvements in CAPE that could be achieved were we to implement feedback to the non-sensing axis.

Another consideration is cross-talk between sensors. When a field is applied to a single sensor using the on-board coils, it will in some regard impact neighbouring sensors. We have not considered this in this methodology. It could, however, be a great advantage of using a model based method rather than individual PID controllers to decide what to feedback, since there are fewer parameters in the model and the field to nearby sensors is likely to be similar. Alternatively, there are OPMs with internal coils specifically designed to minimise cross-talk Nardelli et al. (2019).

However, the method was detrimental at frequencies above 2 Hz, raising the noise floor by a factor of approximately 10 dB below 50 Hz. We were able to reduce but not remove the issue by applying a filter to the HFC model output. Further recordings with a controlled, sinusoidal background field from a set of external coils were used to interrogate the sources of this increased noise floor. It appears that some
of the issues may be driven by the timing of the feedback. While the fundamental limit on the speed of the feedback is in the OPM hardware, discussed in the following paragraph, improvements to the coding could also improve the speed of the feedback; for example by limiting other background processes, such as plotting, when the feedback is running. The introduction of a real-time filter, as used for the auditory experiment here, also introduces a time delay/phase lag.

In two key regards, our system is limited by the hardware currently provided with the QuSpin OPMs. Firstly, the digital-to-analogue converters (DACs) used to produce the requested magnetic fields are 16-bit. This least significant bit (LSB - smallest possible field change) of each coil is approximately 3.1 pT or 1.8 pT for the Z and Y axes respectively (although this does depend on the OPM). This leads to quantisation noise of $0.895 \text{pT}_{\text{rms}}$ and $0.520 \text{pT}_{\text{rms}}$ on each axis respectively. Additionally, the command to produce a particular field is sent via serial connection from the computer to the OPMs. This is a slow connection inevitably leading to a delay between intending to send a value and it being applied to the OPMs. This could be alleviated by future changes to the OPM electronics, which promise to send commands in 5 ms.

Considering the auditory experiment undertaken, the results show a considerable improvement in the range of background fields for which the sensitive axes of the OPMs remain within $\pm 1.5 \text{nT}$. However, there was very low sensor coverage over the left side of the brain, meaning that the left hemisphere response to the auditory stimulus is difficult to confidently conclude much from, and most likely leading to the noisy results for the 92 ms response in Figure 4.15.

Additionally, we have not considered any forward modelling errors introduced by applying HFC to the recordings in real-time. As is shown by Tierney et al. (2021b), by multiplying the data by a projection matrix $\mathbf{MN}^\dagger$, it is necessary to multiply the leadfields of the forward model by the same matrix. This was not explicitly done here, although some correction was implicitly applied when HFC was used in pre-processing the data, as this automatically applies a correction to the leadfields. However, due to the feedback being applied every 10 ms to each axis (and the correction to the Y-axis preceding the Z-axis by 5 ms), the real-time homogeneous field correction made cannot be so easily summarised as a projection matrix. The lack of this leadfield correction also makes the results in Figure 4.15 difficult to interpret, although some confidence can be gained from the frequencies of the signal and the correction: the real-time correction was low-pass filtered at 1 Hz while the signal was high-pass filtered at 2 Hz. Further work is required to more completely solve this leadfield correction.

Increasingly, the research field is moving towards unshielded OP-MEG (Limes et al., 2020; Zhang et al., 2020a). In such an environment, background field drifts are likely to be of the order of 100s of nano Tesla, rather than 100s of pico Tesla, assuming that the worst of the static field (of the order of micro Tesla) can be handled by some form of light passive or active magnetic shielding. To allow OP-MEG recordings in an urban environment without an MSR, on-board feedback such as this is likely to be necessary to minimise these drifts, regardless of the design of the OPM. Therefore, while this system no doubt has limitations and is, in its current state, not ideal for OP-MEG experiments which can be performed with little movement in the centre of an MSR, it has considerable promise to allow us to ask questions in a naturalistic environment which were previously impossible.
5 Experiment 4: OP-MEG and Epilepsy Pilot

5.1 Introduction

Magnetoencephalography (MEG) can be a useful imaging modality for pre-surgical planning in epilepsy (Knowlton, 2006; Sutherling et al., 2008; Englot et al., 2015; Murakami et al., 2016; Ramanujam et al., 2017). MEG can guide the implantation of intracranial electrodes (Sutherling et al., 2008), map the eloquent cortex (Stufflebeam et al., 2009; Collinge et al., 2017) and predict seizure freedom after surgery (Englot et al., 2015). In a recent retrospective study of 1000 patients (Rampp et al., 2019), it was shown that complete resection of MEG localisations was associated with significantly higher probability of Engel 1 outcome (free from disabling seizures) over the 10 years following surgery.

However, MEG is often not clinically available. A survey of epilepsy surgery centres found only 1/3 of the centres had access to MEG (Mouthaan et al., 2016). OP-MEG has many advantages which could make it more accessible in a clinical setting than the currently more standard SQUID based MEG. The scope for the patient to move is particularly important for less compliant patient groups such as children (Wehner et al., 2008; Larson and Taulu, 2017) or patients requiring long-term monitoring for the purpose of capturing ictal events. Motion tracking in OP-MEG could allow for recordings of semiology, far more akin to EEG telemetry than traditional SQUID-MEG. Additionally, the fact that the sensors can be placed directly on the scalp, rather than the one-size-fits-all array which is typical for SQUID-MEG, means that it is possible to capture maximal signal for any head-size, which can increase the signal-to-noise ratio (SNR) of observed interictal epileptogenic discharges (IEDs) (Feys et al., 2022). It has been shown with on-scalp SQUID-MEG (known as high critical temperate or high-$T_C$ MEG, so called because the SQUIDs need to be cooled to 77 K rather than 3 K), that higher proximity of the sensors to the scalp can also increase the number of interictal discharges that are observed (Westin et al., 2020). This improvement would be particularly important for children due to their smaller head size (Boto et al., 2016; Hill et al., 2019), and is pertinent for epilepsy since there is an incidence peak in childhood (Kotsopoulos et al., 2002; Fiest et al., 2017).

OP-MEG studies have demonstrated epileptogenic discharges in mice (Alem et al., 2014), in a single subject (Vivekananda et al., 2020) and in 5 pediatric patients (Feys et al., 2022). One of the main applications for OP-MEG in epilepsy is identification of the epileptogenic focus for pre-surgical planning. In this study, we report the results of OP-MEG from a single patient with focal cortical dysplasia (FCD) in the right superior frontal sulcus. We recorded and localised spontaneous interictal epileptiform discharges (IEDs) while the patient was resting. As the patient has a radiologically identifiable lesion, we have a prior expectation of the epileptogenic focus. This proof-of-concept experiment shows that further studies with more patients would be worthwhile and could provide a viable pathway to the clinical translation of OP-MEG.
Figure 5.1: Sensor and marker positions for the OP-MEG recordings. The black cubes represent the OPMs. The blue dots are the retro-reflective markers for the motion tracking. Although the scanner-cast was subject specific, the OPM positions are shown in MNI coordinates and the head mesh displayed is a generic head object file (https://www.turbosquid.com/3d-models/male-head-obj/346686). Only the 31 OPMs used for analysis are shown.

5.2 Methods

A right-handed, 39-year-old male with FCD in the right superior frontal sulcus participated in this study. He was aged 9 at seizure onset and is currently on four antiepileptic agents. He experiences up to six motor seizures a night. Previous interictal scalp EEG and video-EEG telemetry, which were recorded in 2013, 7 years prior to the OP-MEG, had not recorded any interictal epileptiform activity. Seizures had been recorded and semiology – dystonic posturing of the left arm and leg – was consistent with seizures originating from the area of dysplasia, but the ictal EEG was obscured by artefact. No further functional imaging (e.g. PET, SPECT or EEG-fMRI) was previously performed.

Ethical approval for the study was granted by the Medicines and Healthcare products Regulatory Agency, and informed consent was obtained from the patient prior to participation. Throughout the experiment, the participant was monitored by a clinician from outside of the recording room via video and audio.

5.2.1 Recordings

Thirty minutes of OP-MEG data were recorded from 37 QuSpin Gen-2 QZFM OPMs. The sensors were placed into a scanner-cast bespoke to the participant (Boto et al., 2017). This scanner-cast was 3D-printed to match their scalp surface, as measured from a previous structural 3T MRI (Meyer et al., 2017). The sensors were positioned approximately evenly around the head, with greater coverage over the right, frontal cortex, as shown in Figure 5.1. The magnetic field perturbations along two axes of the OPMs – one radial to the scalp and one tangential – were recorded, meaning that there were 74 recording channels in total. 4 OPMs were later removed from the analysis due to abnormally high noise floors and 2 were removed due to faults in the OPM heating hardware creating erroneous signals. This left 62 recording channels.

The recording was performed in a 4-layer Magnetically Shielded Room (MSR) (Magnetic Shields, Ltd.; internal dimensions 3 m × 4 m × 2.2 m). The participant was seated on a beanbag for the experiment and, consequently, remained within the central cubic meter of the room. The static field at the centre of the UCL room is approximately 2 nT and the field gradient is approximately 1 nT m⁻¹ (Mellor et al., 2021). No additional active shielding was used. The recording was split into three runs of 10 minutes each. In the first and second runs, the patient was reading a book. In the second run, for the first and last minute of the 10-minute recording, we asked the participant to move their head. In the third and final run, the
participant sat still and at rest with their eyes open. No overt task was performed during the recording.

The OPM data was were recorded using a custom acquisition software, built in Labview. Each OPM channel was measured as a voltage ($\pm 5$ V, 500 Hz antialiasing hardware filter) and sampled at 6 kHz by a National Instruments (NI) analogue-to-digital converter (NI-9205, 16-bit, $\pm 10$ V input range) using QuSpin’s adapter (https://quspin.com/products-qzfm/ni-9205-data-acquisition-unit/). This voltage was then multiplied by a calibration factor to calculate the recorded magnetic field. In addition to the OPM data, the patient’s movements were recorded with an array of 6 OptiTrack Flex 13 cameras. The cameras were positioned in three corners of the room, with one low and one close to the ceiling in each corner. All cameras were positioned so that the participant’s head was within their field of view. The cameras were calibrated according to the manufacturer’s instructions, using the OptiTrack CW-500 calibration wand. To track the participant’s head, four retroreflective markers were placed onto the OPM scanner-cast. These are shown in blue in Figure 5.1. A rigid body was created from the four markers in Motive, the acquisition programme associated with the OptiTrack cameras. The rigid body position and orientation was recorded by the Flex 13 motion tracking cameras and then the corresponding positions and orientations of the OPM channels were calculated at each time point.

The marker positions were recorded at 120 Hz. A 5 V pulse was used to synchronize the motion tracking with the MEG recordings. Where markers were occluded, usually due to the wires from the OPMs, the missing data were interpolated using Motive. Firstly, for any gap where only one marker was missing, a pattern-based method was used to interpolate the missing marker data. In this case, the other three markers are used to estimate the position of the missing one. Then for the remaining gaps where multiple markers were occluded, cubic spline interpolation was used to fill in the missing data.

5.2.2 Analysis

Before interictal epileptiform discharge (IED) detection, we performed the following pre-processing steps. Firstly, the OPM data was downsampled to 240 Hz using SPM12. The start and end were then trimmed to match the motion tracking recording and the motion data was upsampled to 240 Hz using linear interpolation in order to match the OPM data. A 10 Hz, 6th order Butterworth low-pass filter was applied to the rigid body position and orientation using FieldTrip to remove high frequency noise caused by marker vibrations.

A 5th order Butterworth low-pass filter with a cut-off frequency of 118 Hz was applied to the OP-MEG data in FieldTrip. Three 5th order Butterworth notch filters were also applied. One was at 50 Hz to remove the mains noise; the other two were at 37 Hz and 83 Hz to remove noise caused by the motion tracking cameras. Environmental noise was then reduced by modelling the background magnetic field as a homogeneous field at each timepoint (Tierney et al., 2021a). A 5th order Butterworth high-pass filter was then applied to the MEG data at 1 Hz.

IEDs were identified by visual inspection of the pre-processed data and manually marked on the OP-MEG traces for each session by consensus between the author and an experienced clinician (Umesh Vivekananda). The reviewers were blinded to the magnetometer positions. Initially, 27 potential IEDs were identified across the 30-minute recording. These selections were then used to create 2 s trials. The centre of the epileptiform trials was determined by maximising the cross-correlation with the fourth identified IED trial. Trial 4 was selected because it was the clearest spike in the time domain. For each IED trial, the central timepoint was shifted by $\pm 0.5$ s in steps of 1/240 s and the mean (across channels) correlation between the shifted trial and fourth IED trial was calculated. The shift which corresponded to the maximum correlation was
chosen to be the centre of the IED trial. The remaining data were split into 2 s baseline trials.

To ensure that the identified epileptiform activity was not caused by movement artefact, we set a threshold for the amount of variance in the OPM data in the trial which could be explained by the patient’s position and orientation, above which a trial was rejected. The percentage of variance explained was given by the coefficient of determination when the orientation and position of the patient’s head, as calculated by the motion tracking software (NaturalPoint Motive), was linearly regressed from the OPM recordings. Prior to regression, the OPM data and position/orientation data were detrended. The coefficient of determination was calculated for each channel and each trial, then the mean taken over channels to give a single value per trial. We set the threshold on this coefficient of determination based on runs 1 and 3, since there was more movement in run 2 which made it unrepresentative of the other two recordings. The threshold was set so that 20 % of all trials (baseline and epileptiform) in runs 1 and 3 were rejected. This equated to 13.8 % of the variance in the trial and led to rejection of 43 % of the data once run 2 was included, leaving 11 accepted epileptiform trials and 500 baseline trials. Note that this means that 59 % of identified potential epileptiform trials were rejected, higher than the average of 43 % over all data, indicating that some movement artefacts were mistaken for epileptiform activity, and not simply that the movement is underlying the true epileptiform activity in these trials. The implications of this rejection criteria are considered further in section 5.4.

Source localisation was performed using an F contrast on the source power output of an LCMV beamformer from DAiSS (https://github.com/spm/DAiSS). The epileptiform activity was compared with other sections of the data where no abnormal or epileptiform activity was identified. Rather than use all baseline trials, 11 were randomly selected to match the number of IED trials. A confidence volume was estimated by iteratively leaving out one spike and noise trial pair, then recalculating the beamformer results. We then estimated the 95 % confidence volume from the standard error of the mean. We also performed a dipole fit of the average spike peak (between 0.975 s and 1.025 s in the averaged trial) in FieldTrip. We repeated the leave-one-out procedure to produce a confidence volume. In all cases, we used the Nolte single shell head model (Nolte, 2003).
5.3 Results

In total, the data was split into 893, 2 s trials, 382 of which were rejected due to the degree of the data which was explained by movement in the trial. The percentage of variance in the OPM data which is explained by the rotation and position of the patient’s head in each trial is shown in Figure 5.2. Encouragingly, for most trials, less than 20% of the data can be explained by movement. The distance travelled by the patient in each accepted 2 s trial is shown in Figure 5.2. This demonstrates that these trials were accepted because there is little movement in them.

Figure 5.3 shows the sensor level results of the accepted spike trials. In Figure 5.3A, a single spike trial (trial 1) is shown on all channels. The selected trial is shaded in blue. Each individual spike trial is shown in Figure 5.3B only on channel 1C-RAD. The average of all 11 trials is also shown. The topography of the average is shown in Figure 5.3C for the radially oriented OPM channels.

Figure 5.4 shows an example of a rejected potential IED trial. In Figure 5.4A and Figure 5.4B, the identified event is shaded in blue. From the time series in Figure 5.4A, when looked at in isolation, it is clear why this time period was selected. There is a reasonably sharp change in the OPM recordings, with reversal between channels and the magnitude of the change varying between channels. However, Figure 5.4B shows the position and rotation of the patient’s head over the same time period, and it is
clear that there is a movement in the middle of the identified trial. The topography of the event is shown in Figure 5.4C. This does not have a dipolar pattern, providing further evidence that this rejected trial is most likely movement artefact.

The source localisation from the accepted epileptiform activity is shown in Figure 5.5. The results in Figure 5.5A are from a beamformer F contrast between epileptiform and non-epileptiform trials. A 5 mm volumetric grid was used for the possible source locations. The peak F-value is shown by the crosshairs. The F-statistics shown have been thresholded at 50 % of the maximum. The global peak of the beamformer is at (25.74, 0.40, 33.94) in MNI coordinates, which equates to 2.99 cm from the centre of the identified MRI lesion location ((20.12, -16.87, 58.94) in MNI coordinates), and 2.26 cm from the lesion boundary.

Figure 5.5B shows the dipole fit of the average IED, shown at the scalp level in Figure 5.3C. The location ((6.19, 46.62, 3.02) in MNI coordinates) is more inferior than the beamformer global peak and is 5.96 cm from the centre of the dysplasia as identified in MRI, and 4.78 cm from the lesion boundary.

We then iteratively left one trial out of each localisation, in order to estimate a confidence volume for the localisation. For the beamformer, we removed one spike trial and one baseline trial pair. As there were 11 spike trials, this equated to 121 different pairs. We then looked at the global peak location for each localisation. The F values of the peaks ranged from 10.6 to 17.9 with a mean of 13.6 ± 0.2. The locations were also reasonably consistent across samples, with a mean (2.83 ± 0.10) cm from the centre of the MRI FCD, (2.13 ± 0.13) cm from the boundary. The 95 % confidence volume is shown in Figure 5.6.
Figure 5.5: Source localisation of epileptiform activity identified in OP-MEG. A) & B) Multivariate LCMV beamformer localisation of the epileptiform activity. The colour indicates the F-statistic for a comparison of epileptiform activity > baseline. The cross-hairs mark the mean location of the leave-one-out analysis. In B), a slice has been constructed at an angle in order to show the lesion and beamformer peak together. The bottom image shows the location and orientation of the slice. The orange region is the MRI lesion. C) & D) Dipole fit of the average spike activity on the peak. The red ring marks the found dipole location; the line is its orientation. Similar to B), a slice is constructed at an angle to show the dipole fit and lesion together in D). The bottom image shows the orientation of the slice and the orange region is the lesion as found in MRI.
Figure 5.6: Leave-one-out analysis. Grey mesh shows the MNI template cortex from SPM. The orange region is a mask of the FCD. The estimated confidence volume is shown as a blue ellipsoid for A) the beamformer location and B) the dipole fit. The confidence volume was estimated from the mean and standard error of the mean. For A), the mean was taken of the global peak from 121 beamformer runs, for each of which a different spike and baseline trial pair was removed from the beamformer analysis. In B), each of the 11 spike trials was removed from the dipole fit.
Figure 5.7: Virtual electrode time series along a 1 cm-spaced grid around the MRI FCD location. A) The time series of each virtual electrode for spike trial 1. The channel numbers correspond to the positions labelled in B).
Lastly, we constructed virtual electrodes across a grid to look at the time series of this beamformed activity. This is shown in Figure 5.7. The time series in Figure 5.7 corresponds to the time around the first identified IED, as shown at the OPM sensor level in Figure 5.3A. The spike, as identified in the OP-MEG sensor data, is clearly visible.

5.4 Discussion

We report whole-head OP-MEG recordings of epileptiform activity. This patient had an anatomically identifiable FCD and our source localisation is consistent with epileptiform activity arising from a region bordering the FCD. The patient was seated and head-movement was unconstrained. This is positive for future studies involving recordings over long time periods or with cohorts who are less able to remain still.

We have argued here that MRI-lesion positive is a sensible patient population to evaluate OP-MEG, since the lesion location is known. The lesion is a clear anatomical marker and it is highly likely that epileptiform activity arises from either within or around this highly epileptogenic lesion (Jackson et al., 2005). Findings from other imaging modalities have shown, however, that the seizure generating zone may extend beyond the structural lesion seen in MRI (Aubert et al., 2009). This provides a certain degree of confidence that our OP-MEG recordings could be useful for delineating the epileptogenic zone and supports the need for studies in larger numbers of patients with surgical outcome data.

In this case, the patient was EEG negative after 2 days of telemetry recording. Here we observed 11 potential IEDs in a 30-minute recording session. We cannot make a strong case for spike yield in OP-MEG over EEG in this instance as the EEG was recorded 7 years prior to the OP-MEG. However, it is promising and consistent with previous SQUID-MEG studies, which show that MEG is able to detect epileptiform activity not captured by EEG (and vice-versa) (Iwasaki et al., 2005; Knake et al., 2006; Ossenblok et al., 2007; Paulini et al., 2007; Heers et al., 2010). This is recognised as one of the clinical added values of MEG in the presurgical evaluation of epilepsy.

IED detection was made more difficult by movement artefacts and other background noise from, for example, cars on the road outside of the OP-MEG shielded room. This is arguably more of a problem for OP-MEG than for SQUID-MEG since SQUID-MEG typically uses gradiometers which provide inherent noise reduction (Hämäläinen et al., 1993). While there are gradiometer OP-MEG designs (Nardelli et al., 2020; Zhang et al., 2020a), our array was based on magnetometers. It has been shown that high SNR OP-MEG data can be achieved when there is large participant movement (Boto et al., 2018; Holmes et al., 2021; Seymour et al., 2021), but in these scenarios, the timing of the trials is set by an external stimulus. Here however, we required a researcher or clinician to manually select the interesting events in the sensor level data; sudden head-movements or movements of cables had a spike-like appearance which made this selection difficult (see Figure 5.4). As a result, there is some uncertainty over the detected IEDs. We therefore used a conservative criterion to reject all epochs showing movement related activity. Consequently, whilst we did not constrain head movement in this study, we have not analysed data during the movement itself. It should be noted that data recorded after head movements of the order of 20 cm was still usable after the movement, it is only during the movement that the interpretation of the data is more difficult.

There are hardware solutions to reduce these issues. In this study, the most pernicious noise was due to the OPM cables moving relative to one another. This produces artefacts which can appear as opposing deflections on nearby sensors (see Figure 5.4). This can be reduced by improving the shielding on the
cables and with better cable management on the scanner-cast. Additionally, whilst not ideal, cable and movement noise can of course be minimised with alternative OP-MEG set-ups which keep the sensors stationary (Johnson et al., 2013; Boto et al., 2017; livanainen et al., 2019; Limes et al., 2020; Vivekananda et al., 2020). Other background magnetic noise, from for example urban traffic or the underground train system, can also be reduced with additional, external, active magnetic shielding (Holmes et al., 2019; livanainen et al., 2019; Zhang et al., 2020a; Rea et al., 2021). We were fortunate here to have an excellent MSR and so chose not to use additional external coils, to maximize the space available to the patient. Alternatively, the challenges in IED detection could motivate a sparse, simultaneous EEG recording (Boto et al., 2019), since it is already well studied and could provide this necessary timing information.

There are also multiple software-based approaches to minimising OP-MEG noise. Here we have modelled the background field as a homogeneous field across the sensors and corrected for the model predictions (Tierney et al., 2021b). Alternative or additional approaches include signal space separation (SSS) (Taulu et al., 2005), synthetic gradiometry (Fife et al., 1999; Boto et al., 2016), signal-space projection (SSP) (Uusitalo and Ilmoniemi, 1997) and using the participant’s movements to model the static field within the room (Mellor et al., 2021). Unsupervised learning techniques such as independent component analysis (ICA), principal component analysis (PCA) or hidden Markov modelling (HMM) could also be used to reduce the dimensionality of the data and select signals with similar spatial topographies, indicative of interictal activity (Seedat et al., 2022; Chirkov et al., 2022). Beamformers have also been used to reduce components of MEG data which do not originate from the brain (Cheyne et al., 2007; Van Klink et al., 2016; Seymour et al., 2021). Virtual sensors constructed from the output of a beamformer, as we showed in Figure 5.7, could reduce interference and improve the probability of detecting more subtle epileptiform activity (Van Klink et al., 2016). This is already used in epilepsy in synthetic aperture magnetometry and excess kurtosis mapping (SAM(g2)), which avoids manual IED detection altogether. In kurtosis mapping, a beamformer is used to create virtual electrodes in a grid across the cortex. The excess kurtosis in each virtual electrode is calculated and mapped (Robinson et al., 2004; Hall et al., 2018). For paediatric epilepsy surgery in particular, this pipeline has been shown to be predictive of seizure outcome (Gofshteyn et al., 2019).

The morphology of the average IED seen here appears to be a polyspike. Polyspikes have previously been associated with extra-temporal lobe FCDs (Noachtar et al., 2008). However, this may be detrimental to the alignment of the spike trials; if there are a varying number of spikes in each IED emanating from different regions, the alignment of the trials may not align the same spikes and so the average may not be representative of the individual interictal discharges. This is a key motivation for showing the beamformer alongside the dipole fitting. The beamformer is calculated along the entire 2s epoch and is not as dependent on the alignment of the individual spikes; it may give a clearer picture of whether there are multiple underlying foci. We found that the LCMV beamformer localisation was 3 cm nearer to the MRI lesion than the dipole fit. The alignment of the spikes may be one explanation. Dipole fits are also usually more susceptible to background noise and local minima (Hillebrand and Barnes, 2003), which may have affected the results here.

Our sensor coverage for this patient was neither uniform across the scalp nor symmetric. We had a limited number of OPM channels and a strong prior hypothesis that the lesion site would produce epileptogenic activity. We therefore placed more sensors around this region. However, in doing so we run the risk of not only missing sources from the undersampled cortical regions, but also introducing noise from these regions, which could bias the localisation, due to aliasing (livanainen et al., 2021; Tierney et al., 2020). As OPM
systems continue to grow in size and complexity, we expect that these sampling issue will be somewhat mitigated.

The interpretation of the results presented here is left intentionally open. Without surgical follow-up or intracranial EEG, it is not possible to know how the dipole fit or beamformer localisation relates to the epileptogenic focus. While the cleanest outcome of this experiment would be a localisation to a single source, consistent between the dipole fitting and beamformer, which overlapped with the FCD location, the disagreement may nevertheless be influential and beneficial for pre-surgical planning, in particular as potential sites for intracranial electrodes. Additionally, it may be indicative of the wider epileptogenic network (Bartolomei et al., 2017). Further studies are needed with patients undergoing surgical evaluation, to determine the impact of OP-MEG on surgical decisions.

An alternative approach to validation would be to compare with SQUID-MEG. Feys et al. (2022) recently published a compelling study, in which they compared the localisation and spike SNR from OP-MEG with SQUID-MEG. In 4 out of 5 paediatric patients, they showed that the SNR of OP-MEG was significantly higher than SQUID-MEG and in all patients, they showed that the localisation was comparable between the two modalities, with a maximum of 15.6 mm between the two localisations. The only disadvantage here, is that the patient selection must then be people who could already undergo a successful SQUID-MEG recording. This may prove a strong argument once OP-MEG is a more established tool within clinical evaluation of epilepsy, but for such early results, further tests with SQUID-MEG, scalp and intracranial EEG may prove useful for the validation of OP-MEG.

We see the recording during subject movement as key to the clinical success of OP-MEG. We know that this is possible from OP-MEG studies involving significant movement with an external stimulus (Boto et al., 2018; Seymour et al., 2021), it is simply selecting the interesting events which is more complicated for epilepsy. In this particular case, we were hampered by non-environmental (wire-based) movement noise coupled with the need to subjectively identify events of interest from sensor level data. Therefore, we suggest that this key limitation can be overcome with greater familiarity with OP-MEG data in epilepsy, improved instrumentation, and analysis methods.

Here we have presented OP-MEG recordings from a patient with epilepsy. With an LCMV beamformer, the localisation of the observed interictal activity was within 2.3 cm of the boundary of the FCD lesion. The patient was seated and their head was unconstrained, which is encouraging for future studies with cohorts who are less able to remain still and for longer periods of recording, which would allow more interictal activity to be captured.
6 Experiment 5: OP-MEG of hippocampal and temporal lobe epilepsies, a case study

Here we present OP-MEG recordings from an adult with temporal lobe epilepsy. Temporal lobe epilepsy is the most common epilepsy amongst adult surgical candidates (Asadi-Pooya et al., 2017) as it has high surgical success rates (Wiebe et al., 2001; Engel et al., 2012). However, OP-MEG of temporal lobe epilepsy may be more challenging than SQUID-MEG, due to the approximately 3 times higher noise floor of OPMs than SQUIDs. Although OPMs are nearer to the epileptogenic source than SQUIDs, due to the anatomy of the temporal lobe and sensor placement, the increase in signal may be smaller than the increase in noise for certain regions. In simulation, Boto et al. (2016) expect an approximately 3 times increase in signal at the temporal poles and 2 times increase from the hippocampus. Nevertheless, in this chapter we present clear temporal lobe epileptiform activity with OP-MEG, recorded from an adult sitting with their head unconstrained.

An additional patient (named patient 3) with hippocampal sclerosis also participated in the study but was excluded as although 13 suspected interictal spikes were identified in a 10 minute recording, 11 were potentially movement related, leaving only 2 events for analysis. In this chapter, we report the recordings from patient 4, who has temporal lobe epilepsy. We observed both interictal and ictal epileptiform activity. Due to developments in the scanner-cast design (see Figure 6.1) and greater experience in identifying interictal epileptiform discharges (IEDs) in OP-MEG, as well as OP-MEG artefacts and analysis methods, these data provide a much clearer picture than those reported in Chapter 5 and demonstrate the progression of OP-MEG.

As identified in Chapter 5, freely moving OPM cables created additional noise in the data which could not be easily removed due to its unpredictable nature. For this reason, with later OP-MEG recordings, we have been careful to constrain the cables on the scanner-cast. This is shown in Figure 6.1 (patients 3 and 4). In this chapter, we present patient 4 in Figure 6.1 as a case study.

6.1 Methods

The participant (referred to as patient 4) is a left-handed, 27-year-old male. Previous clinical video-EEG telemetry indicated left temporal lobe epilepsy. MRI shows grey matter heterotopia within the left temporal lobe. Ethical approval for the study was granted by the Medicines and Healthcare products Regulatory Agency, and informed consent was obtained from the patient prior to participation.

The recording procedure was the same as in Chapter 5. In summary, QuSpin QZFM gen-2 OPMs were used, with data recorded at 6 kHz via a National Instruments 9205 analogue to digital converter. They were operated in dual-axis mode (meaning the field component radial to the scalp and one axis tangential to it was recorded) and with the gain set such that the dynamic range was $\pm 5.56 \text{nT}$. The position of 6 retroreflective markers on the head were simultaneously recorded at 120 Hz with 6 OptiTrack Flex13 cameras (NaturalPoint Inc.). The recordings were synchronised via a 5 V pulse at the start of the position recording and both resampled to 1 kHz. The recordings took place in a 4-layer magnetically shielded room.
Figure 6.1: Progression of scanner-casts for different patients. Patient 1 was recorded from twice, once with the QuSpin Gen-1 sensors held in a plinth below their head and once with the Gen-2.0 sensors placed within a 3D printed scanner-cast. Results are presented in (Vivekananda et al., 2020). Data from patient 2 is reported in Chapter 5. In this chapter, we report data from patient 4. Patient 3’s scanner-cast is included here, but the data is not shown due to only a small number of interictal spikes observed.

(MSR) (Magnetic Shields, Ltd.; internal dimensions $3 \text{ m} \times 4 \text{ m} \times 2.2 \text{ m}$). The participant was seated on a beanbag in the centre of the room throughout. A clinician was also in the MSR, seated at the corner of the room. Prior to recording, the MSR was degaussed (Altarev et al., 2015). The patient was asked to sit as still as possible for 30 s while the currents through the on-board OPM coils were optimised to minimise remnant background fields and the OPMs were calibrated, following the manufacturer’s procedure. No additional active shielding or real-time correction (as described in Chapter 4 was used).

We recorded 10 minutes of OP-MEG data while the participant sat in the room, unconstrained, talking to the clinician. We then recorded for approximately 14 minutes while the participant performed a verb generation task based on the task from Tierney et al. (2018). In this task, a noun was visually presented to the participant for 4 s, during which time they were asked to think of associated verbs. Such a task is fairly commonly used clinically to lateralise language function, although it would generally be performed in functional MRI due to the limited availability of MEG (Abou-Khalil, 2007). The language lateralisation results will not be presented here, but during the task, the clinician in the MSR with the patient identified that they were having an ictal event, which will be presented. For both recordings, 42 OPMs were used, spaced evenly across the scalp. 7 channels were however removed from analysis due to exceptionally high noise floors, leaving 77 recording OP-MEG channels.

To process the data, the OP-MEG data were first downsampled in SPM to 1 kHz and trimmed to only the period when the motion tracking was simultaneously recording. The motion tracking data were low-pass filtered at 10 Hz and then upsampled using linear interpolation to match the OP-MEG data at 1 kHz. Homogeneous Field Correction (HFC) (Tierney et al., 2021a) was then applied to the OP-MEG and the data filtered in SPM (50 Hz bandstop filter, followed by an 80 Hz low-pass filter and a 1 Hz high-pass filter. All filters were 5th order Butterworth filters applied bidirectionally). ICA was then used to remove heartbeat and eye-blink artefacts. The FastICA algorithm as implemented in FieldTrip was used. 4 components were removed for patient 4 (2 heartbeat, 2 eye-blink) in the first run (during which they were resting and talking to the clinician) and 2 were removed (1 heartbeat, 1 eye-blink) from the language task recording. The
data were then exported to AnyWave for visual inspection.

Interictal epileptogenic discharges (IEDs) were identified from the pre-processed data by an experienced clinician (Umesh Vivekananda). The data were epoched into 1 s trials, with the peak of the suspected IED at the centre of the trial (500 ms). The selected data were then inspected for artefacts. One possible IED was rejected as potentially being a movement related artefact, leaving 8 interictal events. Source inversion of this data was then performed with an LCMV beamformer in DAISS, a toolbox for SPM. The source space was a 5 mm grid within the patient’s inner skull surface. The covariance matrix was constructed from only the identified IEDs in the 2 Hz to 70 Hz band. The covariance matrix was truncated to 75 components, to account for the dimensionality reduction resulting from HFC and ICA.

For each trial, the source level power was estimated at the peak of the IED (peak defined as between 400 ms to 600 ms) and for a baseline period 0.5 s prior to it (0 ms to 200 ms). A paired t-test was performed over trials to compare the power during the spike with the baseline period.

Additionally, a dipole fit was performed in FieldTrip for comparison. The dipole was fit to the spike peak (between 0.49 s and 0.50 s). A search over a 5 mm grid within the participant’s inner skull surface was initially performed to avoid local minima, with the result then optimised via gradient decent.

By consensus between the clinician and the author, the ictal event was also identified in the processed data. The main effect appeared to be an increase in beta power, and so a Dynamical Imaging of Coherent Sources (DICS) beamformer in FieldTrip was used to localise the power change in the beta band.

In all source reconstruction, the single shell forward model was used. The inner skull and cortical surfaces were extracted in FreeSurfer.

6.2 Results

The participant’s position and rotation during the interictal recording is shown in Figure 6.2. The position and rotation are expressed relative to the participant’s original position. Their maximum distance from this original position was 11.4 cm. From Figure 6.2, it is clear that the participant is moving continually and that the identified interictal events do not always correspond to times of high movement or rotation.

Figure 6.3 shows the median (over channels) power spectral density (PSD) of the patient’s data with each pre-processing step. HFC in particular has a considerable impact on reducing the background interference observed by the OPMs. Encouragingly, filtering and ICA do not have a considerable impact in the region of the spectrum of most interest, between 5 Hz to 45 Hz.

6.2.1 Interictal

The interictal results for patient 4 are shown in Figure 6.4. The average IED is shown in Figure 6.4A), with the spatial topography shown in Figure 6.4B). It appears temporally sharp and to have a dipolar topography. A dipole fit is shown in Figure 6.4C). This is convincingly left lateralised, as would be expected given the patient’s clinical presentation. However, the patient had left temporal lobe epilepsy, and this dipole fit is approximately 2.4 cm more superior than the grey matter heterotopia observed in MRI. This may be due to many reasons, including the fundamental limit of a dipole fit in that it can only describe as many dipoles as the user sets, whereas the epileptogenic network may be far more complicated. It is also possibly due to noise in the data, or from misidentified IEDs blurring the true signal.

An LCMV beamformer was run on every IED, and the power at the peak compared with the baseline power to give a t-statistic. This is shown in Figure 6.5. Like the dipole localisation, the peak t-stat is along
Figure 6.2: Position and rotation of patient’s head during recording. Top: position, bottom: rotation. X points left-right, Y points up-down and Z is forward-back. Yaw is rotations around Y, Pitch rotations around X and Roll rotations around Z. The black lines indicate the times of the identified interictal events. The red lines are the suspected interictal event which was later rejected.

Figure 6.3: The median (over channels) power spectral density (PSD) at each preprocessing stage of the data recorded from patient 4. The original data is shown in blue, after HFC in orange, after filtering in yellow and after ICA in purple. The width of the line is the standard error of the mean over OPM channels. As indicated, between 5 Hz to 45 Hz, the HFC, filtering and ICA lines overlap.
Figure 6.4: Interictal activity recorded in patient 4, averaged over IEDs. A) Time series average. A spike can be seen at 0.5 s. The channels tangential to the scalp (labelled -RAD) are on the left. The channels radial to the scalp (labelled -TAN) are on the right. B) The topography of the average IED, only on the channels radial to the scalp (labelled -TAN), expressed as a t-statistic from a one-sample t-test across trials. C) Dipole fit to the average IED.
Figure 6.5: LCMV beamformer localisation of interictal activity in patient 4. Each trial was reconstructed separately and a paired t-test performed on the difference in power between 400 ms to 600 ms and 0 ms to 200 ms in each trial.

the left insular, approximately 2 cm from the grey matter heterotopia in the left temporal lobe in the MRI, although the LCMV beamformer reconstruction is closer to the boundary of the heterotopia (referred to as the lesion in the figure). Beamformers are generally more robust to noise than a dipole fit (Hillebrand and Barnes, 2003), which may partially explain this. It is also possible that the irritative zone of the patient (the region causing interictal spiking) is more superior than the grey matter heterotopia, and indeed what we observe is close to the true irritative zone. This is discussed further in Section 6.3.

6.2.2 Ictal

The ictal recording for patient 4 is shown in Figure 6.6A). Time-frequency analysis was performed in FieldTrip using a Morlet wavelet time frequency transformation, with 0.5 s time windows and at frequencies between 1 Hz to 71 Hz with 2 Hz resolution. Averaged over channels, the time-frequency plot is shown in Figure 6.6B). There is relatively high activity in the beta band (13 Hz to 30 Hz) during the first 4 s. After this there appears to be a very quiet period for 4 s. The ictal activity was preceded by relatively large movement and so this proceeding quiet period was used as a baseline. Figure 6.6C) shows the change in beta power between this ictal period (723 s to 726 s) and post-ictal period (727 s to 730 s) on the radial channels spatially. There is a clear increase in power over the left side of the head.

To estimate the source location, we used a DICS beamformer implemented in FieldTrip. We contrasted the power in the 14 Hz to 22 Hz band between 724 s to 726 s with 728 s to 730 s. The cross-spectral density matrix was estimated based on these two time periods concatenated. The results are shown in Figure 6.6D). The activity appears to localise to the left temporal lobe, as expected given the patient’s diagnosis of left temporal lobe epilepsy, although the maximum power is 26 mm more superficial than the grey matter heterotopia in MRI. Therefore, although in the correct lobe, this is further from the expected epileptogenic focus than the interictal results. That said, we used the entire time period of the seizure for localisation, while it is generally the seizure onset which is of the most interest. There is clearly more work which could be done with ictal OP-MEG, particularly with regards to isolating the seizure onset and further examining seizure progression.
Figure 6.6: Ictal activity observed from patient 4. A) Time series. There is a visible increase in oscillatory activity between 723s to 727s. There may also be a spike, as is often seen at the end of a seizure, at 731s. B) Time-frequency spectrum of this ictal period of interest. This oscillatory activity appears to be in the beta band (13 Hz to 30 Hz). C) Topography (only on the OPM channels radial to the scalp) of the change in average beta power between 723s to 726s and 727s to 730s. It is largest over the left hemisphere. D) DICS beamformer localisation of this beta power increase. The maximum power increase lies in the left temporal lobe.
6.3 Discussion and Outlook

These data appear more promising than those presented in Chapter 5. We believe that this is due to the improved scanner-cast design, higher sensor numbers and greater experience with identifying and analysing epileptoform activity in OP-MEG. While the localisation does not overlap with the focus in MRI, it is not inconsistent with previous clinical evaluation.

Nevertheless, the success of these recordings is still difficult to ascertain, for all the reasons given in Chapter 5. Without a ground truth epileptogenic focus, all we can compare to is the MRI lesion, which may not be the epileptogenic focus, or may not be the full extent of the epileptogenic network. In future epilepsy studies, selection of patients who will go on to have surgery or intracranial EEG may be one way to overcome these limitations.

We were fortunate to record ictal OP-MEG. Localising this activity, however, was not as straightforward as might initially be thought, since it was only one event. This means it is impossible to test across trials. As we wished to do a beamformer reconstruction (to minimise the impact of the noise in the OP-MEG data), we also had to estimate the cross-spectral density matrix. Ultimately, we only estimated this matrix for a short section of the data, within 722s to 731s. One major concern which may have to be addressed should OP-MEG to be used more frequently clinically, was that this data was recorded during a language task, and so the task may bias the cross-spectral density matrix, and so the localisation.

In general, there is a great deal more which could be done with this ictal data. It would be of particular interest to look at seizure progression. With a larger group of patients, it would be interesting to see whether the ictal or interictal data present a clearer picture of the true epileptogenic focus. We have shown that OPMs can observe both interictal and ictal MEG, with consistent results. These recordings were very short, at only approximately 30 minutes long total; a clinical SQUID-MEG scan would typically last up to 1 hour. We observed ictal and interictal OP-MEG despite this limited time. Importantly, the participant was seated comfortably and free to move, and so longer recordings are possible. In the future, longer OP-MEG recordings may allow for a deeper picture of the epileptogenic network and successful imaging for patients where the number of interictal events would previously have been a limitation.
7 Discussion

7.1 General Discussion

In this thesis, novel methods for reducing movement related noise in OP-MEG were presented. We began by characterising the background magnetic field in the room (Chapter 2). In Chapter 3, we examined the possibility of applying this correction in real-time in simulation, and in Chapter 4, we demonstrated a simplified version of the real-time correction empirically. We also showed some recordings from patients with epilepsy in Chapter 5 and in Chapter 6. These showed the development of OP-MEG as a technology throughout the PhD and motivate the need for the noise suppression techniques presented earlier in the thesis.

Chapter 2: Field Mapping

In Chapter 2 we introduced the concept of modelling the background magnetic field in an MSR with a set of spherical harmonic functions. We laid out the justification for using these functions and their relation to the recorded OPM data. To test this model, we collected data across the MSR by placing two OPMs orthogonally on a stick and moving it around the MSR, while tracking its position with an OptiTrack V120:DUO motion tracking camera. The coordinate frame was set relative to the door of the MSR. We found that a second order spherical harmonic model explained over 96% of the variance in the room and, if subtracted from the recordings post-hoc, reduced the residual magnetic field to below 2 nT within the central 1 m$^3$ of the room.

However, when we considered the shielding factor (i.e. power spectral density (PSD) reduction in decibels) provided by modelling the background interference in an OP-MEG recording in this way, the correction was only beneficial below 1 Hz and the performance was relatively poor, with a maximum shielding factor of $\approx 7$ dB. This value could be increased by applying the model over shorter time windows, but this led to a reduction in the generalisability of the model and to the correction being detrimental (i.e. adding noise) above 1 Hz. The other major limitation of the model was that it took a relatively long time to calculate, at approximately 2.3 s per recalculation.

One possible explanation for the increase in noise from the model is that it relies on the OptiTrack position recordings which are not noiseless. The most straightforward explanation is that the noise from movement is largest at frequencies below 1 Hz and so the model, which is optimised through linear regression, is biased towards minimising recordings in this frequency band. However, the motion tracking noise is at a higher frequency and so when the correction is applied, this noise gets added to the OPM recordings.

The motion tracking is essential to work in a room based coordinate frame. In the model created in this chapter, we built a map of the spatial pattern of the magnetic field by amalgamating data from multiple time points recorded from different positions. Motion tracking and working in a room based coordinate frame is also necessary to link the OPM recordings to anything in the environment. A recent study by Rea et al. (2021) links closely with this magnetic field mapping. Here, a second order spherical harmonic model of the background magnetic field was created from a set of specific head movements, and then...
large electromagnetic coils, fixed in position in the room, were used to produce a magnetic field opposite to this background model in order to cancel it out. The coils used in this experiment were designed such that they could only possibly cancel out 6 of the 8 independent components in a $2^{nd}$ order spherical harmonic model and could not correct for higher order spherical harmonics. The coils are effective in a $40 \text{ cm} \times 40 \text{ cm} \times 40 \text{ cm}$ volume around the participant’s head (Holmes et al., 2018). By better optimising these coils, in a seated OP-MEG experiment, Rea et al. (2021) were able to reduce the movement artefact between 0 Hz to 2 Hz by a factor of 5, by reducing the background magnetic field by a factor of $4.48 \pm 1.50$. This speaks to the potential of these magnetic field models to reduce movement noise in OP-MEG, and to the appropriateness of a second order spherical harmonic model.

A limitation of the method proposed by Rea et al. (2021), besides the requirement of external coil sets, is that an initial calibration step - where the participant performs a set of head movements twice - is required to create the model, after which the magnetic field is set throughout the experiment. This has two potential issues. Firstly, magnetic fields vary in time as well as space, and so setting the fields in this way means that these temporal changes cannot be corrected for. Secondly, less compliant participants (such as children) may not reliably perform the required head movements twice. For this reason, we opted to use the participant’s natural movement, rather than requesting particular head movements, but this may lead to worse spatial sampling of the field we wish to correct for. Rea et al. (2021) minimise temporal changes in the background field by updating the homogeneous components ($1^{st}$ order components) of their spherical harmonic model based on a reference array, which is stationary with respect to the external coils, but not with respect to the head. This minimises the issue very effectively, but requires extra reference sensors, does not track with the head position and does not allow for correction for changes in higher spatial order magnetic fields (e.g. spatial gradient magnetic fields). It is for this reason that we propose continually updating the magnetic field model using the on-scalp OPM recordings in this chapter. This does, however, lead to over-fitting depending on the time frame after which the model is updated, as we demonstrated with data from an OP-MEG experiment (shown in Figure 2.9).

One possible application of this field mapping work is in the evaluation and characterisation of magnetic shielding and electromagnetic coils. In particular, Iivanainen et al. (2022), recently demonstrated a method for determining OPM positions and orientations based on the OPM recordings of a magnetic field created from large, external electromagnetic coils. In order to do this, Iivanainen et al. (2022) had to precisely measure the magnetic field produced by each electromagnetic coil. Using the coil set, they produced a magnetic field corresponding to a component of the $2^{nd}$ order spherical harmonic model, e.g. the change in the $x$ component of the magnetic field ($B_x$) with translation in $z$ ($\partial B_x/\partial z$). With this magnetic field in place, they moved a triaxial Fluxgate magnetometer across a grid and recorded the magnetic field produced by the coils at each position. From these recordings, they fit a spherical harmonic model. This is a very precise and accurate but time consuming way to build a background magnetic field map. Should it be necessary to repeat this measurement regularly, a faster method using random movement, such as that presented in Chapter 2, may be preferable. However, it would be less precise and so the requirements of the application are certainly worth considering.

Overall, we showed that a $2^{nd}$ order spherical harmonic model is a reasonable choice to describe the background magnetic field in a magnetically shielded room. The methodology used is particularly pertinent when the external room needs to be related to the OPM recordings. Usually, this is in order to control currents through external electromagnetic coils to minimise the background magnetic field, but could also be valid for noise suppression of highly spatially local interference, such as a metal camera in the MSR. Rea
et al. (2021) demonstrated the potential of these spherical modelling methods for magnetic field suppression, although the challenge remains how best to update these models over the course of an experiment, and particularly how to optimise a system to allow participant movement outside of the effective region of a set of external electromagnetic coils.

Chapter 3: Real-time simulation

In this chapter, we looked at applying the spherical harmonic correction from Chapter 2 in real-time in simulation. We examined the impact of different errors in the system, such as noise on the motion tracking recordings and gain errors on the OPMs. We found that errors in the coil calibration and random position errors had the largest impact on the variance of the remnant background field at the simulated sensors. The mean value of the remnant field was predominantly influenced by systematic errors in the magnetometer offsets.

In this chapter we did not consider the degree of movement required for this model to be valid. The head movement with which we simulated the data was chosen based on an OPM being moved by hand around the room. This is not representative of seated experiments, where movements will likely be smaller and less frequent. It does not consider whether the degree of movement (and hence range of position) over which the model is calculated is sufficient. In Chapter 2, we only tested the model on an OP-MEG recording where the participant had been asked to move. One improvement which could be made to such a modelling technique would be to only update the model when the participant had moved a certain distance.

One improvement which could be made to this chapter would be to compare different methods for choosing the feedback. Techniques currently used include reference sensors placed on the OPM array, proportional-integral-derivative controllers, and in Chapter 4 we use homogeneous field correction (HFC) in real-time. A natural extension of the work in this chapter would be to look at these different methods under a range of uncertainties, head movements and background noise models.

This chapter examines creating a spherical harmonic model in the coordinate frame of the MSR, from data recorded over a number of time points and positions. However, we found that minimising noise in the position measurement should be a priority. It is for this reason that in Chapter 4, we implemented a system which creates the model at each time point and in the coordinate frame of the OPM array, dispensing with the need for motion tracking.

Chapter 4: Real-time correction

In Chapter 4, we implemented a real-time feedback system based HFC. This is a spherical harmonic model of the environmental interference, as considered in Chapter 2 and Chapter 3, but is expressed in the coordinate frame of the OPM array, rather than the room. Additionally, it is calculated at every time point, rather than over time, making it simpler and theoretically faster to calculate. The contrast in complexity between Figure 3.1 and Figure 4.1 is stark. We have not however, explicitly compared the performance of the two systems or looked at the calculation time. This would be an obvious extension of the work presented in Chapter 3.

We found that applying the feedback raised the noise floor of the recordings above 5 Hz. There is some evidence that this was due to the relatively slow timing of the correction, with a predicted delay of 41.8 ms between intending to send a signal to the OPMs and it having an observed impact, but may also be due to quantisation noise of the coils on-board the OPMs.
In Chapter 3, we found that errors in the calibration of the feedback coils and a constant offset on the OPM recordings could considerably decrease the performance of a real-time feedback system. In Chapter 4 however, we did not measure these factors. In order to improve the performance of the feedback system, a precise measurement of these factors may be necessary.

Nonetheless, at low frequencies (<5 Hz), including the feedback considerably reduced the background interference observed by the OPMs, leading to a reduction in environmental drift of approximately 25 dB. When tested on an experiment where a participant walked around the MSR, using the feedback system increased the number of usable trials by 125%. We believe this is a step towards a more mobile MEG system.

Following the earlier discussion of the work by Rea et al. (2021), this work should be placed in context with the work on external active magnetic shielding which is currently being undertaken. Holmes et al. (2021) have created electromagnetic coils which can be placed on the walls of an MSR. These coils are made of multiple overlapping square coils and so are known as matrix coils. The current through each coil can be individually changed to create total fields (considering all coils) with a variety of spatial patterns. The aim of these coils is to minimise the background field in the MSR and they can be adapted and updated in real-time. In short, they aim to answer many of the same demands as the research in this chapter. Two major disadvantages of on-board OPM shielding over external shielding are: there is cross-talk between the sensors caused by updating the on-board coils, and the magnetic field from the on-board coils is often limited by the manufacturer to approximately 50 nT to 200 nT. This is not too great of a concern in an MSR with a magnetic field below 30 nT, but limits the use of on-board nulling in a less well shielded environment, especially since higher fields will mean additional cross-talk. OP-MEG systems with comparatively little or no passive magnetic shielding using zero-field resonance SERF OPMs are likely to rely more heavily on external active electromagnetic shielding (Holmes et al., 2022; Zhang et al., 2020b). However, producing a spatially complex magnetic field pattern (described by spherical harmonics of 4th order and above) from such matrix coils requires high currents, above the present allowance. This could, by comparison, be easily achieved with on-board nulling, since (ignoring cross-talk) the field at each sensor is controlled independently. The only limitation would come from the validity of the model, given the number of sensors, spatial coverage and number of model parameters. Considering moving to a less well shielded environment in particular, it is clear that some combination of external and internal field nulling is likely to be necessary and complimentary.

One clear progression of this project could be to compare this method with other OPM closed-loop systems. However, to do so fairly would be challenging, given the comparatively high control that the manufacturers of the sensors have over the internal electronics and firmware. To highlight one such closed-loop system, Dynamic Field Compensation (DFC) (Robinson et al., 2022) was discussed in Chapter 4 as an alternative method for real-time correction of background magnetic fields. Unlike other closed-loop OPM systems, but very similarly to our proposed method, DFC was implemented by the end users of the OP-MEG system, in order to overcome a limitation of the sensors which was impacting their intended use. Researchers at NIH intend to build a highly precise OPM-MEG system, with limited spatial coverage but high sensor density. Cross-axis projection errors (CAPE) (Borna et al., 2022) limit the precision of OPMs, and so DFC was introduced to minimise these errors. Due to the low spatial coverage, our real-time implementation of HFC, which relies on approximately spherical sensor coverage (Tierney et al., 2021a), would likely be inappropriate. By comparison, DFC requires additional reference sensors to be held fixed on the head, above the existing sensor array. This additional weight and bulk makes DFC comparatively
inappropriate for a wearable, walking system, as we wish to achieve. The parallels between the two methods are apparent and show the different directions in which OP-MEG is developing.

In Chapter 4, we did not consider cross-talk between the sensors or correct for magnetic fields on the non-measurement axis of the OPMs. Moving to a less well shielded environment however, this is likely to become a larger issue as the fields which will need to be compensated for will be larger. As discussed in Chapter 4, with the benefit of hindsight, it would be useful to determine the level of cross-talk between sensors and to measure the improvement in sensor gain from controlling the field on the non-measurement axis as well as the other two. Both of these factors could be an advantage of basing the OPM feedback on a model of the background field, rather than directly feeding back the OPM recordings. Creating a model of the background field means that we can predict the field on an unmeasured axis, allowing us to control the field on all three axes, without needing to record all three. This is pertinent as many OPMs are dual axis. It also means that the field across the entire OPM array is quantified by relatively few parameters. It should therefore vary relatively smoothly across the array and the field applied to nearby OPMs should be similar, meaning cross-talk could be somewhat beneficial.

Regardless of the method for determining feedback, cross-talk could be considered as a final step in determining the field to apply to each set of OPM coils. As future work for this project, it would be interesting to look at this first in theory and then test with our feedback system. Theoretically, it should be straightforward to create a cross-talk matrix akin to a cross-correlation matrix to describe, based on the sensor positions and orientations, how a magnetic field applied along one sensor axis impacts the field at every other sensor. Then the feedback at a single OPM can be easily described as the sum of currents to each coil set, weighted by this cross-talk matrix. It is then only a choice of how to optimise the currents in order to minimise the difference between the delivered feedback and intended feedback. This simple idea could be used for any real-time feedback system to minimise the impact of cross-talk.

**Chapters 5 and 6: Epilepsy and OP-MEG**

In Chapter 5 and Chapter 6, we showed some OP-MEG recordings of epileptiform activity. Epilepsy is an interesting use case for OP-MEG, both because it is the main clinical application of MEG, and because unlike a classic neuroscience experiment, we have no knowledge of or control over when epileptic discharges will occur. This means that relatively small signals (∼2 pT to 15 pT) must be identified directly from the data. This is difficult even with very clean SQUID-MEG data such that, despite much research into data-driven automatic spike detection, the gold standard for the detection of epileptiform activity is visual inspection of the data by a trained neurophysiologist.

Despite previous statements about the motion robustness of OP-MEG, in the data in Chapter 5, we found it difficult to distinguish interictal epileptiform discharges (IEDs) from movement noise in the OP-MEG recordings presented in Chapter 5. Ultimately, we decided to reject trials where the motion tracking recordings explained over 13.8% of the variance in the MEG data. Further work into automatic spike detection alongside movement noise reduction methods, such as those presented earlier in the thesis, may help to better detect IEDs in moving OP-MEG data.

By comparison, this same rejection was not made in the data presented in Chapter 6. There are a few reasons for this. Firstly, from the recordings in Chapter 5, we learnt that an erroneous signal can be seen when the OPM cables move across one another. As shown in Figure 6.1, with later recordings, we therefore clamped down the OPM cables so that they could only move once off the scanner-cast. This appears to considerably reduce these artefacts. Secondly, the EEG of the participant in Chapter 5, though
admittedly recorded 7 years before the OP-MEG recording, had no observable interictal discharges. While speculative, it may be that we were looking for something that simply was not in the MEG recording, and so interpreted some of the movements as IEDs. Third and perhaps most importantly, when analysing the data presented in Chapter 6, both the OP-MEG and clinical researchers had more experience of the appearance of OP-MEG artefacts and of the appearance of IEDs in OP-MEG, and of how to best present the data to examine these, so were better able to distinguish the two. Rampp et al. (2019) make a similar statement about their earliest MEG recordings with epilepsy. They found that they identified more IEDs before 2000 than after, despite upgrading from a 37 channel MEG system that only covered a small area of the head to a 2x37 channel system in 1995. They argue that this is perhaps because they were not certain of what an IED should look like in MEG, and so were making more potential but ultimately false spikes.

The study from Rampp et al. (2019) is an excellent example of how to evaluate a neuroimaging modality’s performance at localising the epileptogenic focus (region causing seizures), but also demonstrates how difficult such evaluation can be. In our recordings, we only considered patients with an MRI-positive lesion. We assumed that there is one source of epileptogenic activity and that it is proximal to this lesion. This is a somewhat simplified view of epilepsy; prevailing thought is that there is, at least in many patients, an epileptogenic network which the lesion may or may not be part of (Aubert et al., 2009). As such, the best measure of whether the epileptogenic focus has been found is: if it is removed surgically, did the seizures stop? This is what makes the study by Rampp et al. (2019) so convincing; that they were able to look at surgical outcome in a large number of patients over approximately 5 years after surgery. However, this is exceptionally difficult to do as many patients will not go on to have surgery and if they do, outcome data may be difficult to obtain. For OP-MEG, if a bespoke scanner-cast is made for each participant, the time and expense required to design and make the scanner-cast, as well as to move OPMs between scanner-casts, means that it is difficult to record from patients in quick succession. To build up a cohort with surgical outcome data would take considerable time. Perhaps the next best evaluation metric was used by Feys et al. (2021). They compared their OP-MEG localisations with those from SQUID-MEG. With hindsight, it would have been beneficial to do the same for the patients presented in Chapter 5 and Chapter 6. However, in the long term, this limits the OP-MEG to patients and tasks which could already be recorded in SQUID-MEG. As such, it is an important stepping stone towards seeing OP-MEG used clinically, heading towards a longer term study of the importance of OP-MEG to surgical outcome.

A major potential advantage of OP-MEG over SQUID-MEG is that it could more easily be used to record ictal (during seizure) MEG. Seizures may include a wide variety of movements. This is naturally simpler to record in a wearable system than in the much more constricted SQUID-MEG. Nevertheless, studies of ictal MEG from SQUID-MEG (typically recorded either from low motion seizures or in the period before movement) provide some evidence that ictal MEG may be a better indicator of the epileptogenic focus than interictal MEG (Fujiwara et al., 2012; Yoshinaga et al., 2004; Koptelova et al., 2018). In Chapter 6, we presented what we believe to be ictal OP-MEG. While there is much more which can be done with this data, in particular looking more at the seizure progression, we were able to show that this activity localised comparatively to the interictal MEG, but was approximately 41 mm more posterior. This is plausible, given that ictal and interictal MEG do not necessarily overlap and since the grey matter heterotopia seen in the patient’s MRI was 45 mm in length, from the most anterior point to the most posterior. We were fortunate that this seizure was motionless. This allowed us to analyse the data without being overly concerned with movement artefacts. However, the challenge and opportunity for OP-MEG is to record seizures with greater movement. The movement noise discussed in Chapter 2 is likely to make such a recording challenging,
and resolving these issues may rely on the real-time movement correction methods developed in Chapter 4. This is a natural next step for this project.

In addition to these movement challenges, there are practical challenges which should be considered before seizures involving jerking movements or potentially a fall could be recorded with OP-MEG. It is not currently possible to lie down in the OP-MEG scanner-casts. This is true of the scanner-casts we use at UCL and every commercially available system. To allow tonic-clonic seizures (which involve stiffening and jerking and are what people generally think of as a seizure) in OP-MEG, not only would the system have to be able to cope with being lain upon, but would need to cope with being jerked in a range of directions (including pulling the sensors away from the cables) and being hit against the bed or chair. The scanner-cast would also have to able to be quickly removed by a clinician if necessary. Protecting the sensors is not as straightforward as placing a plastic helmet over the sensor array, as the sensors operate at a temperature over 100°C (although are approximately 41°C at the surface). This heat needs to be able to dissipate to avoid overheating. Future sensor development may overcome some of these issues. For example, the helium-4 OPMs designed by Mag4Health do not need to be heated (Fourcault et al., 2021). It is likely therefore that more ictal recordings will become possible as research in both the field of OP-MEG helmet and sensor design develops.

7.2 Outlook

Currently, on-board real-time magnetic field correction is imperfect. In our system, we found that it increased the noise floor by approximately 10 dB between 4 Hz to 40 Hz. However, we also showed that it reduced the noise by approximately 25 dB below 1 Hz and could be used to increase the range of movement in OP-MEG. As such, it has a great deal of promise to expand the questions we are able to ask with OP-MEG. It could be useful for wide ranging naturalistic experiments, in which the participant is no longer constrained to being seated. It could also help account for some of the Earth’s field when considering OP-MEG in a less heavily shielded environment.

In a clinical context, reducing the degree of magnetic shielding to record OP-MEG could have a dramatic impact. This would make MEG cheaper, mean it took up less space in a hospital, and potentially mean it could be recorded at the bedside. Allowing greater freedom of movement could also mean that the patients could more easily wear the OP-MEG system for longer. For epilepsy, this would mean a higher probability of recording interictal activity: of importance since a low number of IEDs in a recording is frequently a limiting factor in identifying the epileptogenic focus with MEG. It would also greatly increase the likelihood of observing a seizure. Even in a heavily shielded environment, due to the additional movement of seizures, real-time magnetic field correction may be useful to record and interpret MEG throughout seizures, rather than simply in the pre-movement phase. Put simply, OP-MEG in combination with real-time feedback has the potential to offer a deeper insight into the epileptogenic network and seizure progression than has been possible to date.
8 Bibliography


