

Inverse Problems and Control for Lung Dynamics

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INVERSE PROBLEMS AND CONTROL FOR LUNG DYNAMICS

A THESIS SUBMITTED TO THE UNIVERSITY OF MANCHESTER FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF SCIENCE AND ENGINEERING

2017

By Henry F.J. Tregidgo School of Mathematics

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The University of Manchester

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Mechanical ventilation is vital for the treatment of patients in respiratory intensive care and can be life saving. However, the risks of regional pressure gradients and over-distension must be balanced with the need to maintain function. For these reasons mechanical ventilation can benefit from the regional information provided by bedside imaging such as electrical impedance tomography (EIT).

In this thesis we develop and test methods to retrieve clinically meaningful measures of lung function from EIT and examine the feasibility of closing the feedback loop to enable EIT-guided control of mechanical ventilation. Working towards this goal we develop a reconstruction algorithm capable of providing fast absolute values of conductivity from EIT measurements. We couple the resulting conductivity time series to a compartmental ordinary differential equation (ODE) model of lung function in order to recover regional parameters of elastance and airway resistance. We then demonstrate how these parameters may be used to generate optimised pressure controls for mechanical ventilation that expose the lungs to minimal gradients of pressure and are stable with respect to EIT measurement errors.

The EIT reconstruction algorithm we develop is capable of producing low dimensional absolute values of conductivity in real time after a limited additional setup time. We show that this algorithm retains the ability to give fast feedback on regional lung changes. We also describe methods of improving computational efficiency for general Gauss-Newton type EIT algorithms.

In order to couple reconstructed conductivity time series to our ODE model we describe and test the recovery of regional ventilation distributions through a process of regularised differentiation. We prove that the parameters of our ODE model are recoverable from these ventilation distributions apart from the degenerate case where all compartments have the same parameters. We then test this recovery process under varying levels of simulated EIT measurement and modelling errors.

Finally we examine the ODE lung model using control theory. We prove that the ODE model is controllable for a wide range of parameter values and link controllability to observable ventilation patterns in the lungs. We demonstrate the generation and optimisation of pressure controls with minimal time gradients and provide a bound on the resulting magnitudes of these pressures. We then test the control generation process using ODE parameter values recovered through EIT simulations at varying levels of measurement noise.

Through this work we have demonstrated that EIT reconstructions can be of benefit to the control of mechanical ventilation.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Chapter 1

Introduction

In this thesis we develop novel methods for retrieving clinically meaningful measures of lung function from the use of electrical impedance tomography (*EIT*). Specifically these measures include the distribution of air flow and parameters such as airway resistance and elastance. We also propose methods for incorporating these parameters into control schemes in an attempt to tailor mechanical ventilation to the specific circumstances of individual patients. In the course of developing these techniques we examine implementations of EIT reconstruction and design a novel reconstruction algorithm capable of providing the required absolute values of conductivity on a regional basis while retaining the speed and flexibility of commonly used techniques.

The motivation for the work in this thesis comes from the vital role mechanical ventilation strategies play for the treatment of patients in respiratory intensive care units. The use of mechanical ventilation can be life saving for patients in multiple situations, for example acute lung injuries such as acute respiratory distress syndrome (ARDS) [1] or acute complications to chronic conditions such as chronic obstructive pulmonary disease (COPD). However, increased stress on lung tissue can cause ventilator induced lung injury (VILI) [2].

The need to increase recruitment and ventilation of the lungs while avoiding the risks of mechanical ventilation has encouraged the development of lung protective ventilation (LPV) techniques. These techniques attempt to optimise frequency, tidal volumes and pressure settings in order to balance the dual risks of alveolar collapse and over-distension. Despite the use of LPV, it is estimated that 33-55% of patients with ARDS still develop VILI [3]. Hence there is a pressing need to develop patient specific LPV strategies, in this case through the use of lung modelling and EIT.

Two related approaches to developing LPV strategies are to regulate both the volume of air flow and driving pressures experienced by the patient. Larger tidal volumes increase the variations in pressure between full inhalation and exhalation. One recent study [4] has shown that the magnitude of this driving pressure is strongly adversely linked with the mortality rate of patients. Additionally, modelling the process of airway opening has revealed that inducing gradients of pressure within opening airways can cause damage [5]. Hence the control procedures we use to test the feasibility of EIT guided control are focused on minimising pressure magnitudes and gradients.

In addition to monitoring variations in pressure, it is also important to set the end expiratory pressure level correctly. Because airway collapse or recruitment can cause drastic changes in the ventilation pattern of the lungs [6], the positive end expiratory pressure (*PEEP*) is set as the minimum pressure applied during expiration to keep airways open. There are multiple ways to determine an optimal PEEP setting [7], but generally a recruitment manoeuvre is performed, followed by PEEP titration using measures such as lung compliance or blood gas composition to determine when an acceptable pressure has been found [8]. These approaches, by necessity, rely upon taking measurements that can be easily accessed from the bedside, making it difficult to take into account regional variations in the structure and health of the lungs.

Mechanical ventilation can result in some lung lobes being over-distended, causing damage, while others are only partly recruited [9]. This, combined with regional variations in perfusion, can cause areas of alveolar dead space which do not assist in gas transfer [10]. It is therefore desirable to have some form of bedside imaging to recover regional ventilation distributions and inform ventilation strategies. However, radiation concerns [11] limit the frequency with which X-ray computerised tomography (CT) may be used for routine monitoring, while magnetic resonance imaging (MRI) requires expensive tracers to accurately monitor air flow [12]. Additionally, neither CT nor MRI is practical at the bedside.

1.1. THESIS STRUCTURE

These practical limitations are not shared by EIT, which has high temporal resolution and is safe to use at the bedside for extended periods [13]. It has been shown that air content of the lungs causes a high contrast in the conductivity levels of tissue [14] and so time series of EIT reconstructions can be used to monitor the regional ventilation of the lungs [15]. This has enabled clinicians to begin incorporating EIT into patient care, and techniques are being examined for such purposes as monitoring lung fluid content [16], improving PEEP titration [17] and verifying the efficacy of pressure controls [18].

For these reasons we examine the feasibility of converting high frequency regional ventilation information into objective measures of lung function based on widely known lung models. Once parameters have been recovered we examine their utility in refining ventilation strategies for the patient. The structure and content of this work is described in the following section.

1.1 Thesis structure

As described above the motivation for this thesis comes from a desire to incorporate EIT into the procedures used for mechanical ventilation. These efforts centre around coupling EIT to a simplified model of lung function and using it to modify pressure controls. One difficulty with this approach comes with the need to repeatedly update the parameter estimations during the process of mechanical ventilation. As mentioned above the actions of pressure controls can cause airway collapse and recruitment which in turn changes ventilation parameters [6]. This results in the need for a cyclical workflow, as shown in fig. 1.1, to account for the feedback from EIT guided control. In this workflow the conductivity maps generated from imaging during mechanical ventilation are combined with other ventilator measurements and a linear lung model to enable recovery of the regional ventilation distribution. This in turn is used to calculate parameters for the model of lung function which can then be used to generate control profiles to be used for further mechanical ventilation.

The first requirement of such a workflow is fast reconstruction of EIT imaging. These reconstructions must occur within a time frame that allows the results to be processed and controls to be generated at the bedside. The current algorithms allowing reconstructions within such time frames only produce images of the changes in conductivity distributions over time or are not capable of the 3D



Figure 1.1: Flowchart showing a proposed procedural workflow for implementing EIT guided control of mechanical ventilation.

imaging needed to capture the behaviour of the full lung system. Therefore, in chapter 2 we propose a new technique to provide fast 3D imaging which is capable of producing regional values of absolute conductivity. In this chapter we describe the regularisation and constraints required for such reconstructions and compare the resulting images to those produced by difference imaging when modelling assumptions are incorrect.

The second requirement of the workflow in fig. 1.1 is a suitable lung model and a method for recovering both ventilation states and parameters. In chapter 3 we describe a linear compartmental ordinary differential equation (ODE) model of ventilation for which ventilation changes occur on a scale observable through EIT. We describe methods for generating conductivity images from ventilation profiles as well as recovery of these profiles and lung parameters from the resulting conductivity time series. We prove the model used has recoverable parameters and test the recovery process under varying levels of voltage measurement noise and modelling inaccuracy.

The final requirement for the workflow in fig. 1.1 is a method for generating pressure control profiles from recovered ODE parameters. In chapter 4 we prove the controllability of our ODE lung model under a range of parameter values. We then discuss the generation of controls with minimised pressure gradients and bounded magnitudes. We also outline methods for the optimisation of these controls and perform tests of such procedures using parameters recovered from EIT over a range of measurement noise levels.

Chapter 2

Electrical Impedance Tomography

Electrical impedance tomography has been discussed as a safe method for monitoring lung function for over 30 years [19]. This stems from the fact that this is a radiation free imaging modality for which air, with its low conductivity, provides a large contrast to surrounding tissue. Additionally, despite its low spatial resolution, EIT has the advantage of high temporal resolution while remaining safe to use at the bedside for extended periods [13].

In the simplest terms, the process of EIT data acquisition may be described as exciting a current through successive pairs of attached drive electrodes in order to measure the voltage change across pairs of measurement electrodes. This combination of drive and measurement patterns then allows reconstructions to be made of the conductivity distribution within the domain.

To model the data acquisition process the equations governing voltages on the interior of the domain can be derived from the time harmonic Maxwell's equations [20] to give Kirchhoff's law,

$$\nabla \cdot \sigma(x) \nabla \phi(x) = 0, \qquad x \in \Omega, \tag{2.1}$$

where $\sigma \in L^{\infty}_{+}(\Omega)$ is the conductivity distribution, $\phi \in H^{1}(\Omega)$ is the electrical potential and Ω is the domain. Assuming that the domain has a sufficiently smooth boundary, $\partial \Omega$, the weak form of eq. (2.1) can be solved with given boundary conditions to provide interior potentials for a given conductivity distribution. These boundary conditions are given in terms of the current densities, $j \in H^{-\frac{1}{2}}(\partial \Omega)$, or

voltages, $\phi \in H^{\frac{1}{2}}(\partial \Omega)$, which obey both Ohm's Law

$$j(x) = \sigma(x)\nabla\phi(x) \cdot \mathbf{n}, \qquad x \in \partial\Omega, \qquad (2.2)$$

where \mathbf{n} is the outward facing unit normal, and the consistency condition

$$\int_{\partial\Omega} j \, \mathrm{d}S = 0. \tag{2.3}$$

Excitation of current and measurement of voltages then gives pairs of Dirichlet and Neumann boundary conditions, $\phi|_{\partial\Omega}$ and j, on the area of the domain boundary covered by the electrodes. These pairs define a *Dirichlet to Neumann map* $\Lambda_{\sigma} : \phi|_{\partial\Omega} \mapsto j$ and EIT reconstruction consists of recovering the conductivity distribution σ that generates the correct mapping.

There are many different algorithms to perform this reconstruction. These range from the early attempts with backprojection, as used by the Sheffield system [21], to linearised methods such as the GREIT algorithm [22] and even analytic methods such as d-bar [23] for 2D reconstructions. Reviews of the available algorithms and techniques for EIT reconstruction may be found in [20, 24, 25]. In this chapter we examine iterative techniques based on the Gauss-Newton optimisation algorithm. These techniques are widely used in commercial geophysics applications of EIT [24]. Here they will be discussed in the context of the specific requirements we have, both for the testing of techniques in later chapters and in order to retain the utility of our reconstructions to other avenues of research.

A review of some of these avenues of research was given by Adler et al. [26]. This review broadly defined four interesting, achievable and relevant uses of EIT:

- 1. the recovery of clinically relevant diagnostic measures,
- 2. guidance for recruitment manoeuvres in mechanical ventilation,
- 3. fast feedback for regional lung changes,
- 4. warnings for dangerous conditions.

A review of some of the more recent attempts at developments in these areas can be found in the 2016 TREND consensus paper [27].

This thesis attempts to address the first two points in the list above directly. In chapter 3 we describe our methods for recovering clinically relevant diagnostic measures and chapter 4 describes the use of lung modelling and control theory in conjunction with EIT to directly influence profiles used for control. However, the post processing techniques in chapters 3 to 4 are designed to work best with absolute values of bulk conductivity over a given 3D region. This poses a challenge for the development of a suitable reconstruction algorithm. Most iterative methods for the recovery of absolute lung values require a prohibitive amount of processing time reducing the utility of EIT for fast feedback. Similarly methods of reducing the complexity of the problem to improve reconstruction times can result in biased reconstructions, limiting the ability of EIT to provide warnings for dangerous conditions.

Balancing the need for 3D, regionally-absolute, reconstructions with the need for fast reconstruction times and maintaining the utility of the images for other purposes provides the motivation for this chapter. In this chapter we discuss the development of a *pseudo-absolute* reconstruction algorithm capable of providing regional absolute values of conductivity. This combines a single-frame, iterative absolute solve, constrained to a low-dimensional parameter space, with highdimensional difference imaging. We also investigate how the assumptions and constraints involved in this combination change the reconstructions produced by difference imaging and how to speed up reconstructions via code optimisation.

With this in mind, in section 2.1 we briefly review the well known Bayesian approach to this inverse problem. This framework is frequently used as a justification for the use of regularisation techniques in direct methods for solving inverse problems. However, it is also useful for analysing what assumptions are being made when constraints and regularisation methods are used in reconstruction. In this section we also describe the finite element meshes used for data generation and reconstruction in this thesis, as well as the *grouping constraints* placed on parameters during the reconstruction. Finally we discuss the different implementations of the discrete Laplacian for regularisation and propose modifications for use when it is desirable to apply varying levels of regularisation in different directions. In section 2.2 we review the Gauss-Newton algorithm, as applied to EIT, along with its modification to provide fast difference imaging. We also describe the proposed pseudo-absolute algorithm used in later chapters. Section 2.3 then tests the effects of using pseudo-absolute reconstruction where the imposed grouping constraints cannot accurately match the phantom used for data generation. This section also proposes a general method for quantitative comparison of difference reconstructions with the ability to account for varying quality criteria.

Finally section 2.4 discusses some additional implementation details which improve the efficiency of iterative reconstruction algorithms. These efficiency improvements have been reported at the EIT2017 conference [28].

2.1 Meshing, constraints and regularisation

One of the difficulties with EIT reconstruction, as with many inverse problems, is the fact that it is an *ill-posed* problem. The definitions of *well* and *ill* posed can be variable, although most agree that problems which have unique solutions which depend continuously on input variables are well-posed [29]. In this case we classify EIT as ill-posed due to the fact that, although existence and uniqueness of solutions have been proven for EIT [30], small errors in the measured data can result in large changes to the recovered conductivity distribution, exacerbating the effects of measurement noise and modelling inaccuracies. This is due to the existence of large, typically high spatial frequency, changes in conductivity which do not produce observable changes in the measurements. We will refer to this sensitivity as the *ill-conditioning* of the problem, a term derived from the numerical properties of matrices used in numerically solving this inverse problem.

To counteract the ill-conditioned nature of this inverse problem, a priori information is used to both constrain solutions and restate the inversion as a related problem with better conditioning in a process called *regularisation*. As the measurement noise and modelling errors can be modelled as random variables [31] it is useful to examine how constraints and regularisation affect the inverse problem from a Bayesian standpoint. Therefore in section 2.1.1 we review the Bayesian formulation of the EIT reconstruction problem as a tool for understanding the effects of assumptions in later sections. In section 2.1.2 we then discuss the constraints placed on the reconstruction through definition of the finite element meshes used for both data generation and inversion. This includes a description of the *grouping constraint method* used for the iterative absolute solve component of our pseudo-absolute algorithm as described in section 2.2. We then discuss implementations of the discrete Laplacian operator in section 2.1.3. This is the operator used to provide a regularisation term for difference reconstructions throughout this thesis. We also describe possible new implementations for use when it is desirable to apply varying levels of regularisation in different spatial directions, known as *anisotropic regularisation*.

2.1.1 Bayesian formulation

To gain a greater understanding of this problem it is possible to pose EIT reconstruction in terms of probability distributions and Bayesian conditional probability. The first step in posing the problem this way is to define the sets of possible realisations of the conductivity map and the measured data. These parameter spaces are the model space (\mathcal{M}) and the data space (\mathcal{D}) respectively. These two parameter spaces are then related via the forward solution operator F such that $F: \mathcal{M} \mapsto \mathcal{D}$. We can then understand realisations of the model and data spaces to be vectors of scalar values which are applied to a basis of functions on the modelled mesh and electrodes.

The probability density functions (PDF) for different realisations of conductivity, $\mathbf{m} \in \mathcal{M} \subset \mathbb{R}^m$, and measured data, $\mathbf{d} \in \mathcal{D} \subset \mathbb{R}^d$, can then be denoted by:

- $P_{\mathcal{D}}(\mathbf{d})$ the probability density over the data space of the data realisation \mathbf{d} ,
- $P_{\mathcal{M}}(\mathbf{m})$ the probability density over the model space of the conductivity realisation \mathbf{m} , called the *prior distribution*
- P_D(**d**|**m**) the conditional probability density over the data space of the data realisation **d** given the model realisation **m**, called the *likelihood*,
- P_M(**m**|**d**) the conditional probability density over the model space of the model realisation **m** given the data realisation **d**, called the *posterior distribution*.

In this notation solution of the inverse problem can be equated to choosing a model realisation **m** based upon its relation to the posterior distribution. Common methods for making this choice include picking the model realisation with the highest probability density or realisation corresponding to the mean of the posterior distribution. Both these methods have their own advantages and drawbacks depending on the structure of the posterior distribution itself and the cost of evaluating individual probability densities.

For this work we examine the solution which has the maximum posterior probability density of all possible reconstructions

$$\mathbf{m}_{\mathbf{MAP}} \equiv \arg \max_{\mathbf{x}} P_{\mathcal{M}}(\mathbf{x}|\mathbf{d}). \tag{2.4}$$

This is known as the maximum a posteriori probability estimate or MAP estimate. It should be noted that this estimate may not be as accurate as other estimates which can be found from an analysis of the full posterior distribution. For example taking the mean of the posterior distribution may reduce the levels of random reconstruction noise outside of regions of interest. However, due to the high dimensional model space, recovery of the full posterior distribution requires the use of sampling techniques such as Markov chain Monte Carlo methods. While these techniques allow quantification of uncertainty for features of the reconstruction [32], they are also computationally intensive. Conversely calculation of the MAP estimate can be done much more quickly as required for bedside imaging.

Under the Bayesian formulation of conditional probability we can relate the posterior distribution to the likelihood and prior [33] by the equation

$$P_{\mathcal{M}}(\mathbf{m}|\mathbf{d}) = \frac{P_{\mathcal{D}}(\mathbf{d}|\mathbf{m})P_{\mathcal{M}}(\mathbf{m})}{P_{\mathcal{D}}(\mathbf{d})}.$$
(2.5)

Commonly $P_{\mathcal{D}}(\mathbf{d})$ is simply taken to be a scaling factor leaving just the likelihood and prior to be examined. Looking first at the likelihood, it is possible to formulate the inverse problem without further information about the model space by taking $P_{\mathcal{M}}(\mathbf{m})$ to follow uniform distributions. In this case

$$P_{\mathcal{M}}(\mathbf{m}|\mathbf{d}) \propto P_{\mathcal{D}}(\mathbf{d}|\mathbf{m}) \tag{2.6}$$

giving the maximum likelihood estimate for which $P_{\mathcal{D}}(\mathbf{d}|\mathbf{m})$ is maximised.

Assuming the measured data d is the mapping of some true conductivity distribution m_{TRUE} into the data space combined with additional noise we have that

$$\mathbf{d} = F(\mathbf{m}_{\mathbf{TRUE}}) + \boldsymbol{\nu},\tag{2.7}$$

where $\boldsymbol{\nu}$ is a random variable representing errors in measurement and modelling. Under these assumptions for any given realisations **d** and **m** to be correct $\boldsymbol{\nu}$ would have to take the form

$$\boldsymbol{\nu} = \mathbf{d} - F(\mathbf{m}). \tag{2.8}$$

In this way we can repose the problem of calculating the likelihood of a given measurement as the problem of calculating the probability that the noise component ν has taken a specific realisation. This requires some assumptions about the distribution of noise inherent in the system. A list of possible errors in EIT measurement is given by [34] and an in depth analysis of these errors for a particular system is described by [35]. We note that EIT measurement systems do not measure voltage continuously but rather measurements consist of demodulation and conversion from analogue to digital signals. This conversion process includes a summation over time of the error sources within the analogue signal itself. Therefore, for a well calibrated system where the noise sources can be assumed to be independent and uncorrelated, the Central Limit Theorem (CLT) may be used to suggest that the noise distribution converges to a Gaussian Distribution. This assumes that the measurement time window is long enough to be able to discard the initial few cycles of data in order to allow for transient effects to settle, while still allowing enough remaining cycles to be averaged so that the CLT may be applied.

Assuming the measurement noise is additive Gaussian with mean zero, we can write that the conditional probability of a measurement given a specified model realisation is

$$P_{\mathcal{D}}(\mathbf{d}|\mathbf{m}) \propto \exp\left\{-\|F(\mathbf{m}) - \mathbf{d}\|_{W}^{2}\right\},\tag{2.9}$$

where W is the inverse covariance matrix for the random variable $\boldsymbol{\nu}$ and $\|\mathbf{d}\|_{W}^{2} \coloneqq \mathbf{d}^{T}W\mathbf{d}$, in matrix vector notation. Combining this formulation with eqs. (2.4) and (2.6) we see that finding the maximum likelihood estimate is equivalent to the Least Squares optimisation problem

$$\mathbf{m}_{\mathbf{L}} = \arg\min_{\mathbf{x}} \|F(\mathbf{x}) - \mathbf{d}\|_{W}^{2}.$$
(2.10)

The ill-posed nature of this problem then becomes apparent under further examination of the forward operator F. This is due to the fact that for any given level of accuracy $\epsilon > 0$ there exists an arbitrarily large perturbation to the model space δ such that $||F(\mathbf{x} + \delta) - F(\mathbf{x})|| < \epsilon$ as has been shown in the literature [36].

To describe the optimisation problem for the MAP estimate more information must be given about the prior distribution. There are many way to set this distribution, varying from a focus on reducing ill-conditioning of the problem [37] to focusing on anatomical detail [38]. A common approach, which we use in this thesis, is a condition on how smooth the reconstructions should be. In this generalised Tikhonov regularisation approach the prior distribution is taken to be

$$P_{\mathcal{M}}(\mathbf{x}) \propto \exp\left\{-\lambda \|L(\mathbf{x} - \mathbf{x}_{\mathbf{p}})\|^2\right\},\tag{2.11}$$

where λ is a regularisation hyperparameter, L is a differential operator and $\mathbf{x}_{\mathbf{p}}$ is the mean of the distribution often simply called the *prior*. Both the choice of differential operator and the hyperparameter affect the regularity enforced on members of the model space. Larger hyperparameters restrict the variance of the prior distribution ensuring that the derivatives of model space members are more closely matched to those of the prior. Similarly increasing the degree of the differential operator used enforces additional smoothness on the model. For reconstructions performed in this thesis, L has been defined as a discrete approximation to the Laplacian, which is a second order differential operator.

Using eq. (2.5) to combine the formulation of the likelihood in eq. (2.9) with the prior distribution in eq. (2.11) we arrive at a new formulation for the posterior distribution

$$P_{\mathcal{M}}(\mathbf{m}|\mathbf{d}) \propto \exp\left\{-\|F(\mathbf{m}) - \mathbf{d}\|_{W}^{2} - \lambda \|L(\mathbf{x} - \mathbf{x}_{\mathbf{p}})\|^{2}\right\}, \qquad (2.12)$$

2.1. MESHING, CONSTRAINTS AND REGULARISATION

resulting in an optimisation problem for the MAP estimate of the form

$$\mathbf{m}_{\mathbf{MAP}} = \arg\min_{\mathbf{x}} \left\{ \|F(\mathbf{x}) - \mathbf{d}\|_{W}^{2} + \lambda \|L(\mathbf{x} - \mathbf{x}_{\mathbf{p}})\|^{2} \right\}.$$
 (2.13)

This formulation will be used in later sections to interpret the consequences of meshing, constraints and regularisation decisions. In section 2.1.3 we will discuss some implementations of the discrete Laplacian used for the Tikhonov regularisation stated above. In section 2.1.2 we will discuss how the definition of the reconstruction mesh and constraints on the model space can affect reconstruction accuracy and processing time.

2.1.2 Hard priors and meshing

Having established the need for the use of prior information in the formulation of the inverse problem we now discuss regularisation techniques which we define as belonging to the categories of *hard* and *soft* priors.

As discussed by Borsic [39] we define hard and soft priors based upon the level of bias they introduce into the reconstruction. Using soft priors involves modifying the *prior* distribution $P_{\mathcal{M}}(\mathbf{m})$ to incorporate modelling information about the domain with a level of uncertainty. This increases the probability of a reconstruction matching modelling assumptions, but does not constrain the reconstruction to these assumptions. This freedom to vary from modelling assumptions is the basis for calling these regularisation techniques soft. However, as the variance of the prior distribution is lowered these priors introduce more bias and become *harder*.

The limiting case of this distribution narrowing comes when the prior distribution becomes a delta measure on a set of reconstruction realisations resulting in constraints to the reconstruction. At this point we incorporate prior knowledge into the formulation of the likelihood PDF itself through the model. It is possible to force the inverse problem to be well posed by defining a small enough spanning set of basis functions for the model space, incorporating known information about the reconstruction domain. This results in a strong bias in reconstruction towards images following the modelling assumptions, so unexpected changes or modelling errors can result in reconstructions being highly inaccurate reducing image utility for early warnings. This increased bias is the basis for calling these regularisation techniques hard. This concept of incorporating prior information into the formulation of the model space leads to our next topic of discussion. An important step in both modelling the forward problem and setting up the inverse problem is the process of assigning a discretisation of the model domain, otherwise known as meshing. In modelling of the forward problem, both the size and positioning of elements within the mesh can have an effect on the calculated potentials. For example standard results from Finite Element Analysis relate maximum edge length, h, to the convergence of the finite element solution and its derivatives towards the true function. In particular, measured potentials are highly sensitive to changes near or on electrodes, resulting in a need for both a finer mesh and increased accuracy of modelling in these areas. Generally this results in increased mesh refinement near the electrodes which will be discussed further in section 2.4.

Additionally EIT has been shown to have a high sensitivity to the shape of the domain [40], requiring an accurate description of the external boundary to increase the fidelity of the models. This poses difficulty for both forward modelling and inversion, as during ventilation the shape of the chest is continually changing. This problem has lead to many different approaches to tracking the movement of the chest and incorporating it into both forward and inverse modelling. These attempts include, but are not limited to, modification of the inverse problem to include a Fréchet derivative with respect to changes in the boundary, design of EIT measurement systems to include shape tracking and external monitoring of the boundary with additional equipment. Even with these techniques large changes in the shape of the domain require the construction of a completely separate mesh, however for small changes in shape the effects may be modelled by small deformations of the mesh leading to an additional matrix in the formulation of the inverse problem.

We have not investigated solutions to the boundary shape problem in this work. However, as shape is such an important factor in EIT we have attempted to incorporate shape information in our modelling. For this reason all the post processing procedures in this work have been tested on meshes created by extruding the outline of human thorax taken from the segmentation of a chest CT, and refining the mesh more towards electrodes as shown in fig. 2.1. The model space

 $^{^{1}{\}rm The}$ CT image is licensed under creative commons attribution 3.0 unported license (C) 2010 Josef X Brunner and segmented in EIDORS.



Figure 2.1: Human adult male thorax CT outline¹(left) and extruded mesh (right).

 \mathcal{M} defined in section 2.1.1 then consists of the space spanned by basis functions which are piecewise constant on mesh elements representing the discretisation of the domain. Using this method of discretisation, the forward problem is considered well-posed so long as the mesh is sufficiently fine in regions with high gradients of electrical potential to ensure that discretisation errors are significantly lower than measurement errors. This results in higher levels of mesh refinement in the regions around electrodes, where the gradients are highest [40, 41].

It should be noted at this point that the electrode positioning, shown in fig. 2.1, places electrodes close to the upper and lower boundaries of the mesh. For the purposes of reconstructing real data this would cause inaccuracies. It does not allow for field lines to pass outside of the region between the electrodes, as would occur on a real patient. For reconstructions of real measurements this results in the need to either extend the finite element mesh or compensate with appropriate boundary conditions on the truncated boundaries [42, 43]. However, as all testing in this thesis is performed on simulations using the same meshed volume and boundary conditions, we believe this is a reasonable first approximation to performing EIT on a patient assuming that all shape changes could be accurately modelled.

We have also explicitly defined cylindrical regions in the construction of our test meshes to represent lung regions for the tests in chapter 3 and chapter 4. Explicitly defining the lung regions in the reconstruction meshes, as shown in



Figure 2.2: Extruded mesh with highlighted cylindrical regions representing lung regions.

fig. 2.2 allows us to use a grouping constraint method (GCM) for the single-frame absolute solve required for our pseudo-absolute algorithm described in section 2.2.

Using GCM, regions of the domain are constrained to have the same conductivity based on the assumption that organs or specific divisions of organs will have homogeneous electrical properties [44]. In this way the dimensionality of the optimisation problem can be reduced significantly allowing the least squares formulation in eq. (2.10) to become overdetermined. This reduces the ill-conditioning of the inverse problem as well as the required computation time, but it also prevents variation over different divisions of the domain and does not account for shape changes in organs. Both of these present a problem in medical imaging where organs are likely to move and unexpected changes may indicate a medical problem. For these reasons we only use GCM in this work for single frames of reconstructions under the assumption of a high degree of model accuracy.

It should be noted that the fact the lung regions are explicitly segmented in our reconstruction mesh will also affect reconstructions where GCM has not been used. This is similar to the use of *basis constrained methods* (*BCM*). Basis constrained methods differ from GCM in that they do not constrain regions to the same value but rather limit the model space to the span of a set of basis vectors which are constructed to encode useful information about likely states of domain during the course of imaging [45]. This set of basis vectors can be designed to encode both variations in conductivity values and changes in organ shape within the thorax, reducing the problems of a static domain segmentation. However, this method still suffers from a hard bias towards those states which have been included in the modelling of the basis vectors.

Unlike in BCM, the difference reconstructions described in section 2.2 allow the values assigned to each mesh element to vary individually. This means that the problem is not overdetermined reducing the risk of a hard bias in reconstructions. However, concern over the possible effects of bias produced by this segmentation and the GCM method used in our absolute solves makes it necessary to test the accuracy of our reconstructions when the lung regions have not been segmented accurately. This will be examined further in section 2.3.

2.1.3 Discrete Laplacian

As mentioned in the previous two sections, when performing difference imaging we use Tikhonov regularisation with a discrete approximation to a differential operator giving the regularisation term

$$-\lambda \|L(\mathbf{x} - \mathbf{x}_{\mathbf{p}})\|^2. \tag{2.14}$$

A common discrete differential operator used for this purpose, which we use for reconstructions in this thesis, is the discrete graph Laplacian matrix. To generate this matrix L we define the dual of the reconstruction mesh to be the graph generated by replacing elements with nodes as shown in fig. 2.3. We can then define the graph Laplacian based on the connected edges in this dual mesh. Entry L(i, i) is then defined to be the degree of node i, equal to the number of connections it has, and entry L(i, j) is set to -1 when elements i and j are connected by an edge [46]. For the small mesh shown in fig. 2.3 this would produce the matrix

$$L = \begin{bmatrix} 3 & -1 & -1 & -1 \\ -1 & 1 & 0 & 0 \\ -1 & 0 & 1 & 0 \\ -1 & 0 & 0 & 1 \end{bmatrix}.$$
 (2.15)



Figure 2.3: Diagram showing a dual mesh of a regular triangulation.

Efficient implementations for generating this matrix can be written by generating an ordered list of all element edges, or faces in 3D, along with which elements they are adjacent to. This list of adjacent elements can then be used to generate the matrix. It should be noted however that the implementation of Lused for reconstructions in this thesis is actually a multiple of the graph Laplacian described here due to the implementation used in EIDORS 3.9 [47].

The rest of this section represents a discussion on possible additional methods for approximating a second order differential operator to be used in eq. (2.14). While use of the graph Laplacian operator has advantages over more complex approximations to the continuous Laplacian operator it doesn't incorporate information about the relative size of elements. Instead the same penalty is applied for variations across element boundaries in areas of high mesh refinement, such as near electrodes, as in more central regions of interest.

Another possible implementation can be derived from the formulation of Finite Volume solutions to PDEs [48]. In this implementation, for a discrete approximation $\boldsymbol{\sigma} \in \mathbb{R}^n$ of a smooth conductivity map $\sigma(x) \in H^2(\Omega)$ the operation of Lon $\boldsymbol{\sigma}$ gives

$$(L\boldsymbol{\sigma})_k \approx \int_{E_k} \nabla^2 \sigma \mathrm{d}V,$$
 (2.16)

where E_k is mesh element number k. To generate this matrix the divergence theorem is used to generate an equivalent boundary integral

$$\int_{E_k} \nabla^2 \sigma \mathrm{d}V = \int_{\partial E_k} \boldsymbol{n} \cdot \nabla \sigma \mathrm{d}S, \qquad (2.17)$$

where \boldsymbol{n} is the outward pointing unit normal for the boundary of element E_k . This can then be approximated numerically by defining the conductivity entries of $\boldsymbol{\sigma}$ to act on the nodes of the dual mesh.

Using the dual mesh in fig. 2.3 as an illustrative example, we denote the edge linking the dual mesh nodes x_0 and x_i by the vector $\mathbf{r}^{(i)} \in \mathbb{R}^2$, the edge of the element crossing $\mathbf{r}^{(i)}$ as $\partial E^{(i)}$ and the normal to $\partial E^{(i)}$ as $\mathbf{n}^{(i)}$. We can then approximate the value of $\nabla \sigma$ on $\partial E^{(i)}$ by

$$\nabla \sigma|_{\partial E_k} \approx A^{(i)} \boldsymbol{\sigma}^{(i)}$$
$$\approx \begin{bmatrix} \frac{1}{\boldsymbol{r}_1^{(i)}} & -\frac{1}{\boldsymbol{r}_1^{(i)}} \\ \frac{1}{\boldsymbol{r}_2^{(i)}} & -\frac{1}{\boldsymbol{r}_2^{(i)}} \end{bmatrix} \begin{pmatrix} \sigma_0 \\ \sigma_i \end{pmatrix}, \qquad (2.18)$$

where $\mathbf{r}_{j}^{(i)}$ is coordinate number j of vector $\mathbf{r}^{(i)}$ and σ_{i} is the conductivity value acting at node i. This allows the boundary integral to be approximated by

$$\int_{\partial E_k} \boldsymbol{n} \cdot \nabla \sigma \mathrm{d}S \approx \sum_{i=1}^3 |\partial E^{(i)}| \boldsymbol{n}^{(i)} \cdot A^{(i)} \boldsymbol{\sigma}^{(i)}.$$
(2.19)

This can be generalised to larger triangular meshes and tetrahedral meshes by assembling the $A^{(i)}$ into the matrix L.

This formulation of a *finite volume Laplacian* [49] has the potential to be a useful and flexible regularisation operator. For example it could be used to introduce anisotropy into the regularisation term by introducing an anisotropy matrix M into the integral in eq. (2.16) giving

$$(L\boldsymbol{\sigma})_k \approx \int_{E_k} \nabla \cdot M \nabla \sigma \mathrm{d}V.$$
 (2.20)
Alternatively it can be used to give an estimate of the H^2 semi-norm. Defining a diagonal vector W containing the elemental volumes and using $\|\cdot\|_{W^{-1}}$

$$\|L\boldsymbol{\sigma}\|_{W^{-1}}^2 \approx \sum_{k=1}^n \int_{E_k} |\nabla^2 \sigma|^2 \mathrm{d}V$$
(2.21)

which can be shown to be equal to the H^2 semi-norm [50].

As mentioned above these finite volume Laplacian implementations incorporate the length scales of the mesh elements used for reconstruction. This is emphasised by the comparison shown in table 2.1 of the units of the quantities produced by their action on the conductivity distribution. However, there are

Table 2.1: Table comparing the units of the quantities provided by three implementations of a Laplacian regularisation term. Units are given as L to denote length and σ to denote conductivity.

Dimension	Graph-Laplacian	$\int_{E_k} \Delta \sigma \mathrm{d} V$	$\int_{E_k} \Delta \sigma ^2 \mathrm{d} V \Big $
2D	σ	$\frac{\sigma}{L^2} \times L^2 = \sigma$	$\left \left(\frac{\sigma}{L^2} \right)^2 \times L^2 = \frac{\sigma^2}{L^2} \right $
3D	σ	$\frac{\sigma}{L^2} \times L^3 = \sigma L$	$\left \left(\frac{\sigma}{L^2} \right)^2 \times L^3 = \frac{\sigma^2}{L} \right $

additional implementation issues. For instance the choice of spatial coordinates for nodes in the dual mesh, which is complicated by the existence of multiple definitions for the centres of triangles and tetrahedra [51]. Some of these centres are shown in fig. 2.4.

Due to these implementation difficulties we have produced several versions of the Matlab code required to construct these finite volume Laplacians in EIDORS. However, because of time constraints we have not yet been able to devise and run an appropriate test to properly highlight reconstruction differences caused by their use.



Figure 2.4: Diagram showing the finite difference lines between the different centre types of two connected irregular tetrahedra. These centre types are the Circumcenter (Ocrc), the Centroid (Ocnt), the Incenter (Oin) and the Symmedian point (Os).

2.2 Gauss-Newton based reconstruction

In this section we describe three methods for reconstructing conductivity distributions from measured voltages. These method all aim to minimise the cost functional

$$f(\boldsymbol{x}) = \frac{1}{2} \|F(\boldsymbol{x}) - \boldsymbol{d}\|_{W}^{2} + \frac{1}{2} \alpha \|L(\boldsymbol{x} - \boldsymbol{x}_{p})\|^{2}, \qquad (2.22)$$

where \boldsymbol{x} , $F(\boldsymbol{x})$ and \boldsymbol{d} denote a model realisation, forward solution and measured data respectively in general inverse problems notation. Equation (2.22) is derived from the formulation of the MAP estimate given by eq. (2.13) in section 2.1.1.

The work in sections 2.2.1 to 2.2.2 represents a review of commonly used algorithms. In section 2.2.1 we describe the full iterative Gauss-Newton algorithm for reconstruction of the absolute values of conductivity for a single frame reconstruction. This is a technique which is commonly used in commercial geophysics applications of EIT [24]. In section 2.2.2 we describe a commonly used difference reconstruction algorithm based on a single step in the Gauss-Newton algorithm [37].

In section 2.2.3 we provide a novel combination of both the full iterative Gauss-Newton algorithm, using GCM as described in section 2.1.2, and the single step difference imaging technique. This combined pseudo-absolute algorithm is able to provide a regional estimate of absolute conductivity values in real time after a limited initial processing time.

2.2.1 Gauss-Newton iterative absolute

The Gauss-Newton algorithm for reconstructing absolute values of conductivity aims to minimise the cost functional in eq. (2.22) by using a linearisation of the forward operator

$$F(\boldsymbol{x} + \boldsymbol{\delta}\boldsymbol{x}) = F(\boldsymbol{x}) + DF_{\boldsymbol{x}}(\boldsymbol{\delta}\boldsymbol{x}) + O(\|\boldsymbol{\delta}\boldsymbol{x}\|^2), \qquad (2.23)$$

where $DF_{\boldsymbol{x}}(\boldsymbol{\delta x})$ denotes the Fréchet derivative of F at the point \boldsymbol{x} composed with the increment $\boldsymbol{\delta x}$. The calculation of this derivative will be examined further in section 2.4. This linearisation is used to estimate the gradient of the cost functional at a given conductivity distribution and look for a direction which reduces $f(\boldsymbol{x})$ using the necessary condition that the gradient of the cost functional must be zero at a minimum.

As both the voltages, $F(\boldsymbol{x})$ and \boldsymbol{d} , and the conductivity distributions, \boldsymbol{x} , are represented by vectors we can expand the cost functional in terms of vector and matrix products giving

$$f(\boldsymbol{x}) = \frac{1}{2} (F(\boldsymbol{x}) - \boldsymbol{d})^T W(F(\boldsymbol{x}) - \boldsymbol{d}) + \frac{1}{2} \alpha (\boldsymbol{x} - \boldsymbol{x}_p)^T L^T L(\boldsymbol{x} - \boldsymbol{x}_p).$$
(2.24)

To take the gradient of this functional with respect to \boldsymbol{x} , we use the fact W is symmetric inverse covariance matrix and denote the derivative of F by the Jacobian matrix J giving

$$\nabla f(\boldsymbol{x}) = \frac{1}{2} \{ \nabla (F(\boldsymbol{x})^T W F(\boldsymbol{x})) - 2 \nabla (F(\boldsymbol{x})^T W \boldsymbol{d}) + \alpha \nabla (\boldsymbol{x}^T L^T L \boldsymbol{x}) - 2 \alpha \nabla (\boldsymbol{x}^T L^T L \boldsymbol{x}_{\boldsymbol{p}}) \}$$
$$= J^T W F(\boldsymbol{x}) - J^T W \boldsymbol{d} + \alpha L^T L(\boldsymbol{x} - \boldsymbol{x}_{\boldsymbol{p}}).$$
(2.25)

2.2. GAUSS-NEWTON BASED RECONSTRUCTION

Using matrix vector notation eq. (2.23) can be used to relate two successive estimates \boldsymbol{x}_i and \boldsymbol{x}_{i+1} giving the relation

$$F(\boldsymbol{x}_{i+1}) - F(\boldsymbol{x}_i) \approx (J_i)(\boldsymbol{x}_{i+1} - \boldsymbol{x}_i), \qquad (2.26)$$

where $J_i = DF_{\boldsymbol{x}_i}$. Substituting this linearisation into eq. (2.25) and setting the gradient equal to zero at point \boldsymbol{x}_{i+1} gives

$$J_i^T W F(\boldsymbol{x}_{i+1}) - J_i^T W \boldsymbol{d} + \alpha L^T L(\boldsymbol{x}_{i+1} - \boldsymbol{x}_p) = 0,$$

$$J_i^T W (F(\boldsymbol{x}_i) + J_i \boldsymbol{\delta} \boldsymbol{x}) - J_i^T W \boldsymbol{d} + \alpha L^T L(\boldsymbol{x}_i + \boldsymbol{\delta} \boldsymbol{x} - \boldsymbol{x}_p) = 0.$$

This can be rearranged to give the search direction

$$(J^T W J + \alpha L^T L) \boldsymbol{\delta x} = J^T W (\boldsymbol{d} - F(\boldsymbol{x}_i)) - \alpha L^T L(\boldsymbol{x}_i - \boldsymbol{x}_p)$$

$$\boldsymbol{\delta x} = (J^T W J + \alpha L^T L)^{-1} (J^T W (\boldsymbol{d} - F(\boldsymbol{x}_i)) - \alpha L^T L(\boldsymbol{x}_i - \boldsymbol{x}_p)).$$

However, as δx is derived from a linearisation of the forward operator, $x_{i+1} = x_i + \delta x$ is unlikely to be a minimum for the cost functional. Therefore we perform an additional *line search* to find the point $x_{i+1} = x_i + \beta \delta x$ such that

$$\beta = \arg\min_{\gamma} f(\boldsymbol{x}_i + \gamma \boldsymbol{\delta} \boldsymbol{x})$$
(2.27)

With this the algorithm becomes: linearise the cost functional with the Jacobian, calculate a descent direction, perform a line search and check the residual for convergence. This is shown in algorithm 2.1.

Modifications to this algorithm provide the basis for all reconstructions performed in this thesis. The reduction of the method to work with difference EIT data is examined in section 2.2.2 and a new fast algorithm for estimating regional conductivity is shown in section 2.2.3.

Algorithm 2.1 Absolute Imaging: Gauss-Newton

1: Set initial guess x_0 2: 3: % Calculate residual 4: $R = \frac{1}{2} \|F(x_0) - d\|_W^2 + \frac{1}{2}\alpha \|L(x_0 - x_p)\|^2$ 5: 6: % Iterate to convergence while R > tol do 7: % Calculate new Jacobian 8: $J_i = J(x_i)$ 9: 10: % Calculate descent direction 11: $\delta x = (J_i^T W J_i + \alpha L^T L)^{-1} (J_i^T W (d - F(x_i)) + \alpha L^T L (x_p - x_i))$ 12:13:% Line-search. Find β such that 14: $\beta = \arg\min_{\gamma} \{ \|F(x_i + \gamma \delta x) - d\|^2 + \alpha \|L(x_i + \gamma \delta x - x_p)\|^2 \}$ 15:16: % Update estimate 17: $x_{i+1} = x_i + \beta \delta x$ 18:19:% Calculate residual 20: $R = \frac{1}{2} \|F(x_{i+1}) - d\|_W^2 + \frac{1}{2}\alpha \|L(x_{i+1} - x_p)\|^2$ 21: 22: end while

2.2.2 Difference Imaging

As mentioned in the introduction to this chapter, much of the important information in clinical uses of EIT comes from its ability to quickly indicate temporal changes occurring in the patient. However, the convergence of iterative absolute reconstruction algorithms is currently too slow for real-time imaging. For functional imaging and ventilation monitoring in later chapters something faster is needed.

Difference imaging is a technique for focusing on the changes in conductivity distribution over time rather than converging to the absolute conductivity. In this technique the relevant data is the difference between two voltage measurements. A reference measurement is chosen from the measurements and subtracted from successive measurements to provide the temporal data. This gives the equation

$$F(\boldsymbol{x}_t) = \boldsymbol{V}_0 + J_b \boldsymbol{\delta} \boldsymbol{x} + O(\|\boldsymbol{\delta} \boldsymbol{x}\|^2)$$
(2.28)

where V_0 is the reference voltage, δx is the change in conductivity and J_b is the Jacobian calculated for a background conductivity. Using the same Tikhonov formulation of the MAP estimate as in section 2.2.1, the cost functional becomes

$$f(\boldsymbol{\delta x}) = \frac{1}{2} \|\boldsymbol{V}_0 + J_b \boldsymbol{\delta x} - \boldsymbol{d}\|_W^2 + \frac{1}{2} \alpha \|L(\boldsymbol{x}_0 + \boldsymbol{\delta x} - \boldsymbol{x}_p)\|^2,$$

$$= \frac{1}{2} \|J_b \boldsymbol{\delta x} - \boldsymbol{\delta V}\|_W^2 + \frac{1}{2} \alpha \|L(\boldsymbol{x}_0 + \boldsymbol{\delta x} - \boldsymbol{x}_p)\|^2.$$
(2.29)

Here δV is the voltage difference measurement and there are three assumptions made for the process of linearisation and regularisation, giving rise to the three points:

- reference conductivity \boldsymbol{x}_0 is the assumed conductivity distribution at the reference voltage, such that $F(\boldsymbol{x}_0) \approx V_0$,
- background conductivity x_b is the conductivity distribution used to calculate the Jacobian J_b
- prior conductivity x_p is the assumed prior for regularisation.

The minimiser of the cost functional in eq. (2.29) can then be found by differentiating with respect to δx and setting the derivative equal to zero as in the full Gauss-Newton method. This gives the equation

$$(J_b^T W J_b + \alpha L^T L) \boldsymbol{\delta x} = J_b^T W \boldsymbol{\delta V} - \alpha L^T L(\boldsymbol{x}_0 - \boldsymbol{x}_p).$$
(2.30)

This formulation of the optimisation problem leads to algorithm 2.2 which is equivalent to performing a single step of the Gauss-Newton algorithm for each successive frame.

The major advantage of this algorithm is found in its speed. Pre-computation of the regularised inverse $J_{\alpha,L}^{\dagger}$ allows successive solutions to be found using a single matrix vector multiplication and a vector-vector addition. This multiplication and addition may be achieved rapidly compared to other optimisation techniques or even the more complex matrix-matrix operations. Additionally there exist efficient implementations of these forms of products to take advantage of vectorisation, parallelism and cache memory. In particular this kind of operation falls under the category of level 2 basic linear algebra subprogram (*BLAS*) [52] for which efficient implementations are available, for example in LAPACK [53].

Algorithm 2.2 Difference Imaging: GN one-step

1: Set estimate of linearisation conductivity x_0 2: Set background for Jacobian calculation x_b 3: Set prior information x_p 4: 5: % Calculate Jacobian 6: $J_b = J(x_b)$ 7:8: % Calculate generalised inverse 9: $J_{\alpha,L}^{\dagger} = (J_b^T W J_b + \alpha L^T L)^{-1} J^T W$ 10: 11: % Calculate correction for regularisation 12: $x_r = \alpha (J_b^T W J_b + \alpha L^T L)^{-1} L^T L (x_0 - x_p)$ 13:14: % Loop over time steps 15: for each time step i do 16:% Calculate difference data $\delta V_i = V_i - V_0$ 17:18:% Calculate difference image 19: $\delta x_i = J_{\alpha,L}^{\dagger} \delta V_i - x_r$ 20:21: end for

It should be noted that this speed comes at the cost of numerical stability as we have computed the inverse matrix $J^{\dagger}_{\alpha,L}$ rather than solving from a factorisation. However, as the required reconstruction frame-rate increases factorisation methods will not be as efficient as matrix vector multiplication.

In algorithm 2.2 it is important to note that \mathbf{x}_0 , \mathbf{x}_b and \mathbf{x}_p can all be selected independently. This is most evident when thinking about the difference between the reference \mathbf{x}_0 and the prior \mathbf{x}_p . Here changing the prior from the reference distribution enforces a change in the prior distribution, $P_{\mathcal{M}}(\mathbf{m})$, based on external information such as co-registered MRI or CT scans, or information on the breathing cycle. Examining the prior in this way raises the possibility of using a prior which varies in time to match the current state of the patient.

The difference between the reference distribution and the background distribution is less immediately obvious. Equating the linearisation in eq. (2.28) to the linear terms in the Taylor series expansion of voltage these would appear to refer to the same point. However, some iterative methods for non-linear optimisation problems choose to use different values for these two points, particularly where calculation of the Jacobian is computationally intensive. One such example of this is the modified Newton-Kantarovich method [54, section 2.1] in which the Jacobian is kept constant between iterations despite updating the reference distribution. However, it is important to note that for iterative methods using a separate reference and background point can adversely affect convergence rates.

In many applications of this method the x_0 , x_b and x_p are all set to be the closest fitting homogeneous distribution. This is a constant conductivity **h** normalised such that

$$\frac{\langle F(\mathbf{h}), V_0 \rangle}{\langle V_0, V_0 \rangle} = 1,$$

which allows the resulting images to be computed quickly. However, it also means that the images include a component of error due to non-convergence and so do not represent a pure difference image. This makes the combination of these images with other information inaccurate for estimation of absolute conductivity and motivates the development of a pseudo-absolute reconstruction algorithm in section 2.2.3.

2.2.3 Pseudo-Absolute

The speed with which difference imaging can be reconstructed is vital for many applications of EIT to lung monitoring. Under the assumption of a linear relationship between bulk lung impedance and air volume content, difference imaging allows an understanding of where air is moving within the lungs. However, this does not allow us to identify the amount of air in the lungs at any given time. For this we require an absolute value of conductivity and some way of calibrating the linear relationship of air to impedance. This relationship will be examined further in chapter 3 but first we need to identify a method of obtaining an absolute reconstruction in real-time.

One simple approach to finding absolute values from difference imaging is to combine the reference value with the difference image. This is equivalent to taking the value from the end of the first iteration in algorithm 2.1 at which the level of the residual is still high. This gives a quick estimate of the absolute values but the accuracy of this method will depend entirely upon the initial choice of \boldsymbol{x}_0 .

An example of a similar method to this in practice has been given by Nebuya et al. [55]. In their paper they employed a technique proposed by Brown et al. [56] to choose \boldsymbol{x}_0 by comparing V_0 to a look-up table of anatomically modelled forward solutions. These forward solutions were based on the CT scans of healthy patients and were performed with varying tissue parameters to provide a range of possible voltage measurements. The model parameters for the closest matching forward solved voltage were then added to difference images produced through filtered back projection to provide an estimate of functional absolute conductivity. However, this method does not fully account for differences between a clinical patient and the healthy reference model and cannot take into account changes in the electrode placement and contact impedance.

We propose that the natural next step in this approach is to find a more accurate approximation to the reference conductivity using a quick method of absolute imaging. This will require more time for the initial frame but allows further frames to be produced at the same rate as difference imaging. For this purpose we propose the use of strict grouping constraints for the initial absolute reconstruction to drastically reduce the dimensionality of the problem faced by algorithm 2.1. Following this full non-linear reconstruction, algorithm 2.2 can be used with a much higher spatial resolution to provide temporal information. This results in algorithm 2.3 which we call the *pseudo-absolute* reconstruction algorithm

Algorithm 2.3 Pseudo-absolute imaging: partially converged Gauss-Newton

```
    Segment domain into regions of interest (ROI)
    Constrain mesh elements to have piecewise constant values in ROIs
    Reconstruct a single absolute frame x<sub>a</sub> using algorithm 2.1
    Reconstruct a single absolute frame x<sub>a</sub> using algorithm 2.1
    Set x<sub>0</sub> = x<sub>a</sub>
    Set x<sub>b</sub> = x<sub>a</sub>
    Set prior information x<sub>p</sub>
    Recover δx(t) from algorithm 2.2
    x(t) = x<sub>a</sub> + δx(t)
```

2.2. GAUSS-NEWTON BASED RECONSTRUCTION

The use of grouping constraints for the absolute reference frame is motivated by the required use cases of the algorithm. As discussed in the introduction to this chapter we want to develop a reconstruction algorithm which is capable not only of fast feedback and early warnings, but also guidance for recruitment and recovery of clinically relevant measures. In chapters 3 to 4 we will discuss how these parameter recovery and recruitment procedures only require absolute conductivities as a bulk quantity over a region of interest. These are calculated by aggregating values from the high spatial resolution reconstructions using a volume weighted average. Hence restricting the reference reconstruction to bulk quantities should provide the required information with minimal effect on these post processing techniques.

However, as mentioned in section 2.1.2 the use of grouping constraints can be described as imposing a hard prior and introducing bias to the reconstruction. We believe that this should be acceptable in the reconstruction of the single absolute frame under the condition that the segmentations used are modelled accurately for that single frame. Ideally a second imaging modality would be used to verify these grouping constraints. The difficulty comes in identifying how the difference reconstruction may be biased by use of the converged low-dimensional absolute frame as a reference value.

It is common practice in EIDORS to set the prior equal to the reference conductivity

$$\boldsymbol{x_p} = \boldsymbol{x_0}.$$

This results in the prior distribution for the difference imaging being set as

$$P_{\mathcal{M}}(\boldsymbol{\delta x}) \propto \exp\left\{-\lambda \|L\boldsymbol{\delta x}\|^2\right\},$$
 (2.31)

resulting in the minimisation of the derivatives approximated by the operator L. Using this method with the new reference reconstruction should provide the same prior distribution for the difference imaging step as would be provided by any other reference value.

Instead the main difference is found in the log-likelihood function

$$\|V_0 + J_b \boldsymbol{\delta x} - \boldsymbol{d}\|_W^2. \tag{2.32}$$

In this function the only variable that has changed is the Jacobian, J_b , which is now calculated at a point closer to the true conductivity distribution at the reference frame. This convergence should increase the accuracy of the reconstruction and, as the grouping constraints are removed for the difference imaging they should not directly produce additional bias in the reconstruction.

We will verify in the next section that the grouping constraints do not prevent the difference imaging algorithm from detecting un-modelled changes in the domain.

2.3 Comparison of difference reconstructions

In this section we try to assess how well the pseudo-absolute reconstruction method performs compared to standard difference imaging when modelling assumptions are incorrect. To do this we examine reconstructions with inaccurate segmentations of the thorax and vary the background conductivities used to calculate the Jacobian. To aid in assessment of reconstructions we describe a quantitative method of measuring error based on inner product angles. This is used to highlight features of the reconstruction algorithm and choose frames for comparison.

When assessing the merits of different reconstruction algorithms it is useful to have some method to quantitatively rank the methods. This can be difficult with imaging methods, and inverse problems in general, as the quality of a reconstruction is highly subjective and dependent on how the resulting images will be used. In the case of EIT reconstructions some of the criteria that should be considered when judging the quality of the reconstruction are:

- 1. How well the reconstruction fits the measured data,
- 2. How closely the reconstruction follows assumptions made by any prior information included in the reconstruction method,
- 3. How well the algorithm reconstructs a known image,
- 4. How easily the reconstruction can be interpreted for its intended use.

The first two criteria already play a role in iterative reconstruction algorithms. For example when performing iterative or linearised reconstructions the data-fit can be measured as a residual by performing a forward solve of the resulting image. This residual is then part of the criteria for choosing a step length in iterative methods using a line-search. It is also important to note when calculating the data residual that different measurement electrode pairs will produce measurement errors following different distributions. This motivates the use of a covariance matrix in the Gauss Newton formulation to emphasise the more reliable measurement data.

The prior information is also included when using a generalised Tikhonov regularisation method with a differential operator to formulate the cost functional. The prior information includes assumptions about the smoothness of the resulting images. This is the method used for most of the reconstructions in this work,

The third criteria is more difficult to use for reconstructions of measured data as it requires a separate imaging modality to obtain concurrent results for comparison. However, it can be a useful tool when evaluating methods used on simulated data as in this case. When working with simulations we know what the *ground truth* state is for the reconstruction and can use it for comparison.

Even when a reliable ground truth can be obtained there may be problems with direct comparison as a means of assessing the merits of a reconstruction scheme. In comparing the recovered image to the ground truth a decision has to be made as to how the concept of "closeness" will be defined. In many use cases this may reduce to a visual confirmation, including borders or gradients for distinct features, but in more rigorous cases a norm may be defined to provide a numerical scale. Deciding upon this norm then becomes a problem as different norms will emphasise different features and qualities of the reconstruction.

Finally, quantifying the useful data content is the most subjective criteria for assessing a reconstruction method. This is often a problem with inverse problems in general as specialising a reconstruction method for certain applications can affect how good the reconstruction looks visually or how it performs for other uses. This can be particularly difficult with EIT, where the reconstructions may be used for multiple purposes such as respiratory monitoring, alerts for medical emergencies or in our case respiratory parameter fitting. The quality of a reconstruction can also be dependent on the expertise of the user. For example, changes in conductivity around the electrodes may not be found in the ground truth but they may produce large improvements in the data residual meaning these two measures of quality provide very different results. However, if experience suggests ignoring these potential artefacts, the reconstruction in regions of interest may have completely different properties and so a quantitative measure of quality could be weighted to consider these regions more strongly.

For this work our main focus is whether the reconstruction algorithms provide useful information for respiratory curve fitting, parameter fitting and control and these aspects will be investigated in chapter 3. However, while these may be our main aims for the use of these EIT algorithms, to be acceptable in a clinical setting we must show that these algorithms also reveal potentially dangerous changes outside of the criteria they have been optimised for.

As the functional EIT in this work is performed using difference imaging, providing reconstructions in arbitrary units, we decided that the quantitative measure used should be invariant for scalar multiples of the reconstruction. This is due to the fact that detection of irregular changes are more dependent on contrasts from the background in each frame than an absolute measurement of the conductivity. This leads to our choice of angles in inner product spaces to define the quality of a reconstruction as described in the following section.

2.3.1 Inner products and angles

In this section we describe methods for producing a measure of difference reconstruction quality using inner product angles. This measure is used in section 2.3.2 to compare the accuracy of reconstructions performed using different Jacobian calculations and extensions to the method are discussed in appendix A. These measures are not used in chapter 3 or chapter 4 where EIT is assessed on its ability to retrieve ventilation distributions and parameters, as well as its utility in producing custom ventilation controls. When we perform a linearised difference reconstruction or find the next update for an iterative reconstruction the vector of elemental conductivity changes produced is a vector in \mathbb{R}^n . This vector is comprised of conductivity values for each of the *n* elements in a coarse reconstruction mesh. These conductivity values can then be thought of as acting upon some basis function defined on the reconstruction elements. In this work the conductivity basis functions used are defined to be piecewise constant functions, given the value one for an individual element and zero for all other elements.

It would be useful to know not only how well the update fits the data but how close this vector is to the optimal descent direction in some quantifiable sense. A useful tool for calculation of such a measure is the definition of an angle in an inner product space. An inner product on a vector space X over a field F such that $\langle \cdot, \cdot \rangle : X \times X \to F$ defines both an associated natural norm and the definition for angles between two vectors in the space by the formulae

$$||u||_X^2 = \langle u, u \rangle, \qquad \qquad \angle (u, v) = \arccos\left(\frac{\langle u, v \rangle}{||u||_X ||v||_X}\right). \tag{2.33}$$

Inner products themselves are frequently used to assess how well two elements of a vector space match with each other, for example in the calculation of the Gaussian likelihood function described in section 2.1 using an inner product norm defined by an inverse covariance matrix. In this case we will focus on using the definition of the inner product angle due to its invariance under scalar multiplication. We do this because the reconstruction algorithms we are examining are derived from a single step of the Gauss-Newton iterative algorithm as detailed in algorithm 2.2. Use of this algorithm means that resulting images not only include components due to the change in conductivity from the reference frame as required, but also a component due to the use of an inaccurate Jacobian background. This results in a change in the relative magnitudes of reconstructions based upon the point used for Jacobian calculation. Another reason these inner product angles can be useful is the ability to adjust the inner product in order to emphasise desired qualities in the reconstructions. In fact as this angle definition is a quality of an inner product space, rather than a Banach or Sobolev space, the conditions on which inner products may be used are relatively unrestrictive. For example, as the conductivity maps have been equated to vectors in \mathbb{R}^n , many acceptable inner products may be formulated as

$$\langle u, v \rangle = u^T A v, \qquad u, v \in \mathbb{R}^n, \qquad (2.34)$$

where A is a symmetric positive definite matrix. Additionally it is possible to combine two indefinite inner products $\langle \cdot, \cdot \rangle_A$ and $\langle \cdot, \cdot \rangle_B$ in the form

$$\langle u, v \rangle_C = \alpha \langle u, v \rangle_A + \beta \langle u, v \rangle_B, \quad u, v \in \mathbb{R}^n, \quad \alpha, \beta \in \{ x \in \mathbb{R} | x > 0 \}, \quad (2.35)$$

to provide an acceptable inner product $\langle \cdot, \cdot \rangle_C$ obeying the uniqueness axiom, so long as the null spaces of $\langle \cdot, \cdot \rangle_A$ and $\langle \cdot, \cdot \rangle_B$ do not intersect. This freedom in defining the inner product to use for our measure allows us to incorporate desirable information about data-fit and modelling assumptions into our comparison with ground truth images and is discussed further in appendix A.

For the comparisons in the next section we define a diagonal matrix D whose entries are the element volumes corresponding to the conductivity values from the reconstruction mesh. Using this matrix we can compute the inner product

$$\langle u, v \rangle_D = u^T D v. \tag{2.36}$$

While this formulation does not measure any differences with respect to modelling assumptions of smoothness or gradients it does have the advantage that it generalises well with respect to mesh refinement. As the mesh is refined further this inner product approaches the inner product on the infinite dimensional function space L^2 ,

$$\langle u, v \rangle_{L^2} = \int_{\Omega} u(\mathbf{x}) v(\mathbf{x}) \mathrm{d}V.$$
 (2.37)

As this inner product is a discrete approximation to the continuous L^2 inner product it is possible to compare measures taken on different meshes. However, it should be noted that differing levels of discretisation error will affect both the quality of the reconstruction and the calculation of the inner product angle. To minimise these effects, the angles in the next section are only compared for reconstructions performed using the same Jacobian and reconstruction discretisation meshes.

There are some additional discretisation error effects in generating an approximation of the true changes in conductivity on these meshes. This is due to the fact that voltage generation is performed on meshes with a much higher number of elements to improve the accuracy of the forward problem and avoid inverse crimes. However, as the true conductivity maps are known explicitly, it is possible to generate best fitting conductivity maps on these reconstruction meshes by volume averaging for elements which are not entirely contained within a volume of constant conductivity. This represents the best possible reconstruction using these combinations of discretisations.

2.3.2 Testing procedure and results

To verify that the pseudo-absolute reconstruction algorithm allows the detection of changes not accounted for in the model, we have applied two separate testing procedures. In both of these procedures the pseudo-absolute algorithm has been applied to a set of images in which changes occur outside of the pre-segmented lung regions. Like with the parameter fitting tests described in chapter 3, we extrude a thorax CT to provide the background domain and four rings of 16 electrodes are added with the same current and measurement patterns described in section 3.2.

The first test we performed was designed to show the effects on the reconstructions of changing the linearisation conductivity distribution. For this test an ultra-fine mesh of 1.02 million elements was produced, with two cylindrical regions defined to represent lungs. These two regions were assigned a constant conductivity linked to a simple two compartment ODE lung model, described in section 3.1.1, acting under a sinusoidal pressure profile over the course of 30 seconds. At time t = 10s a growing spherical inclusion was introduced with increased conductivity to represent a bleed which had not been included in the prior modelling. To produce voltage measurements for these conductivity patterns, EIT was simulated at 20 frames per second. To do this 4 rings of 16 electrodes were meshed onto the boundary of the thorax shape and indexed from 1 to 64, where electrodes in the top ring are numbered from 1 to 16 and the further 3 rings are indexed beginning at 17, 33 and 49 respectively. EIT was simulated with pairwise current driven at an amplitude of 0.1mA and voltages measured on pairwise electrodes both with a skip of 23 so that current is driven and measurements are recorded across rings.

Reconstructions were then performed on the resulting voltage measurements using a fine mesh of 222 thousand elements to generate the Jacobian and a coarse mesh of 10 thousand elements to discretise the resulting reconstruction. These meshes also included segmented lung regions and were used for all reconstructions of this voltage dataset. To test the effect of modifying the Jacobian background x_b , as described in section 2.2, reconstructions were performed using a range of background distributions. In each case the region outside the cylinders was held at the correct value of 1, while the lung region conductivities were varied independently for each lung from 0.1 to 1 in increments of 0.1. A reconstruction was also performed using an accurate background conductivity, using lung values of 0.16 and 0.21, retrieved through absolute reconstruction of the reference frame.

To calculate errors in the reconstructions the inner product angle described in eq. (2.33) was calculated using the inner product in eq. (2.36). Denoting the true change in the phantom as $\delta\sigma$ and the reconstructions as δx this angle can be calculated as

$$\arccos\left(\frac{\langle \boldsymbol{\delta\sigma}, \boldsymbol{\delta x} \rangle_D}{\|\boldsymbol{\delta\sigma}\|_D \|\boldsymbol{\delta x}\|_D}\right)$$
(2.38)

providing a number between 0 and π radians where a smaller number indicates closer agreement of the vectors. The errors in reconstructions using a homogeneous background and at the absolute reconstructed background are shown in fig. 2.5. Errors are shown for 30s of reconstructions at 20 frames per second.

The first thing to note in understanding this graph is that the angle errors begin at slightly above 0.5 radians and become quite large for some frames. The high angles can be explained by the use of the GN one-step algorithm detailed in algorithm 2.2 for these reconstructions. This is a single step in an iterative reconstruction algorithm, providing a linear solution for a non-linear inverse problem and imposing smoothing on the solution through the use of regularisation. Hence



Figure 2.5: Comparison of the error in difference reconstructions performed with a homogeneous Jacobian background and an absolute reconstructed Jacobian. Errors are measured by taking an inner product angle.

there will be errors in the reconstruction which become worse as large changes in conductivity occur taking the inverse problem further outside the linear regime. In this case this is due to the large conductivity of the growing spherical inclusion. However, the measure could possibly be improved by modifying the inner product used and is still useful for comparing the two reconstruction types. This graph shows that, as expected, the more accurate Jacobian results in a more accurate reconstruction. However this effect is not constant for all reconstructed frames, with the difference between homogeneous and pseudo-absolute difference reconstructions becoming less pronounced at t = 15s.

To understand why this is the case we can examine the reconstructions themselves. Figure 2.6 shows a comparison between these two reconstructions and the true change in the phantom for three frames. Each of the nine images in fig. 2.6 is comprised of six 2D slices through the volume, which have been arranged to produce a representation of the 3D image using the EIDORS function show_3d_slices. These slices consist of:

- one vertical slice in the x z plane, cutting through both lung regions and the growing spherical inclusion,
- three vertical slices in the y z plane, two arranged to cut through the respective lung regions and one arranged to cut through the spherical inclusion,



Figure 2.6: Comparison between the true difference in the phantom (left), reconstructions performed with a homogeneous background (middle) and a pseudoabsolute difference reconstruction (right). Images shown for frames number 5, 330 and 585 with colormaps scaled by show_3d_slices.

• two horizontal slices in the x - y plane, arranged to show the upper and lower ends of each lung.

These slices are each shown with a black outline denoting their intersection with the mesh boundary. Changes in conductivity are shown for the intersected mesh elements on a colormap ranging from negative changes in blue to positive changes in red. This representation has been used to give a sense of the 3D positioning of features in the reconstructions without obscuring them.

The frames shown in this comparison correspond to the initial flat section of the graph in fig. 2.5, the peak at time t = 16s and the final few seconds where the absolute background appears to improve in accuracy. Comparison of these frames reveals that the pseudo-absolute background Jacobian is able to more accurately capture the shape, position and magnitude of the spherical inclusion. This is important as EIT generally has difficulty recovering changes in the centre of the domain especially with positive changes. This has been demonstrated by the inability of EIT to detect pleural effusion formation despite its ability to detect fluid withdrawal after treatment [57].

The additional reconstructions for other background conductivity distributions have been used to generate the surface plot in fig. 2.7 showing the errors produced by different Jacobians for frame number 330. The surface plot for this



Figure 2.7: Surface plot showing the error, measured as an inner-product angle, for a single frame difference reconstruction as the Jacobian background conductivities are varied for the left and right lung. The left and right lung axes show the conductivity values assigned to these regions for calculation of the Jacobian in each test. Values of conductivity are normalised such that the conductivity of regions outside the lungs is set to 1.

frame highlights the fact that, although an accurately modelled Jacobian produces better reconstructions in general, in specific situations Jacobians for other distributions can produce more accurate reconstructions in some measures. Here this is highlighted by the drop in error for the reconstructions in which the right lung was given a value of 0.1. This could be due to the particular use of regularisation in this case or the non-linear nature of the inverse problem in general. The second testing procedure was designed to highlight the effects of model mismatching on pseudo-absolute reconstruction with grouping constraints. For this test we generated an ultra-fine forward solve mesh with 1.03 million elements, including four circular cylindrical regions to approximate lung regions and segmentation. For the generation of voltage measurements the conductivity in these four lung regions is varied in proportion to the solution of the ODE lung models for a four compartment lung system as with the two compartment test above. However, in order to add modelling mismatches for the inverse problem the conductivities in these regions have been given a gradient according to the function

$$\sigma(x, y, z, t) = \sigma_0(t) f(x, y, z), \qquad (2.39)$$

$$f(x,y,z) = \left(\frac{1}{2(0.1 + \sqrt{x^2 + 2y^2})}\right) \left(\frac{1}{1 + 0.1\sqrt{(z - 0.5)^2 + 1}}\right), \quad (2.40)$$

where $\sigma_0(t)$ is the conductivity given by the ODE lung model at time t and x, y and z are Cartesian coordinates of lung mesh elements with respect to the thorax frame of reference. This results in oval shaped level sets at a given plane through the lungs and a slight gradient in the z direction. Additionally a non-segmented spherical inclusion is introduced to the mesh at t = 10 which grows until the final frame at t = 30. This inclusion has a conductivity 50% greater than that of the background and grows to intersect with the lower lung regions, simulating the growth of a bleed in the thorax.

Two sets of reconstructions were then performed using meshes where the radii of the lung cylinders had been increased by 10%. Both sets of reconstructions used the same fine mesh of 221 thousand elements to generate the Jacobian and a coarse mesh of 10 thousand elements to discretise the reconstruction, each of which had the same cylindrical regions with increased radii. The first reconstruction was a difference reconstruction using a homogeneous Jacobian background conductivity and the second was a pseudo-absolute reconstruction. The errors for the difference reconstruction and the difference component of the pseudo-absolute reconstruction are shown in fig. 2.8.

As with the plot in fig. 2.5 the angles produced for these reconstructions begin at a level above 0.5 radians. In this case these angles are higher due to the inclusion of measurement noise and modelling mismatches. Peaks in fig. 2.8 also approach, but do not reach, $\pi/2$ radians indicating that they are close to



Figure 2.8: Comparison of the error in difference reconstructions performed with a homogeneous Jacobian background and an absolute reconstructed Jacobian for reconstructions with modelling errors and an SNR of 100 (40 dB).

being perpendicular in this inner product space. This is due to the relative magnitudes of signal and noise for these frames. For the frames where the angles peak the magnitude of the voltage signal $V_t - V_0$ is comparable to the level of measurement noise used for these reconstructions. In this case it is expected that the level of inaccuracy will be high, but this is offset by the low magnitude of the reconstructions for these frames. This is not shown due to the scale invariant nature of angles as an error measure.

Using fig. 2.8 to compare the two reconstruction methods, we see that the errors in the difference imaging component of the pseudo-absolute reconstruction were worse than those from homogeneous difference imaging for most of the reconstructed time period. However, it should be noted that this increased error is offset by the added utility of providing a regional absolute conductivity value as will be discussed in chapter 3. Additionally the pseudo-absolute reconstruction becomes more accurate than the difference imaging as the spherical inclusion begins to grow as shown in the final 10 seconds.

To gain further insight into these errors we have to compare the reconstructions as shown in fig. 2.9. These images use the same 3D slice plotting arrangement as the reconstructions shown in fig. 2.6. The frames shown in this comparison correspond to the initial low error section of the graph in fig. 2.8, the dip at time t = 14s and the final few seconds where the pseudo-absolute appears to improve in accuracy. Looking at the first two reconstruction frames, for which the



Figure 2.9: Comparison between the true difference in the phantom (left), reconstructions performed with a homogeneous background (middle) and a pseudoabsolute difference reconstruction (right). Images shown for frames number 10 (top), 280 (middle) and 585 (bottom).

error shown in fig. 2.8 appear worse than the homogeneous, the reconstructions appear visually similar. In fact for frame 10 at t = 0.5s the pseudo-absolute reconstruction shows a better separation of the lung regions than the homogeneous difference reconstruction. However, there does appear to be a higher incidence of obvious noise artifacts in the pseudo-absolute reconstruction as seen in the higher number of small blue regions on the boundary. This could mean that a different inner product would be a better choice for comparison in this case as discussed in appendix A or that a comparison of the reconstructions after processing to remove noise would show a different pattern.

Comparison of the last frame shown in fig. 2.9 is more encouraging for the use of pseudo-absolute reconstructions. Here the spherical inclusion has a higher contrast and is closer to the correct positioning than in the homogeneous difference reconstruction. This again highlights the increased accuracy in the interior of the domain offered by resolving the Jacobian.

2.4 Improving reconstruction efficiency

In section 2.2 we described a new algorithm for producing fast, regionally-absolute, EIT reconstructions through the use of the pseudo-absolute algorithm in algorithm 2.3. In section 2.3 this was then shown to produce observable features with a similar quality to the general difference imaging algorithm shown in algorithm 2.2 and in section 3.5.2 we will show that regional absolute values produced are accurate enough to allow recovery of regional ventilation profiles. However, the initial frame of pseudo-absolute still requires an iterative solve which can be time consuming. Reducing the dimensionality of the problem through grouping constraints does increase the efficiency of the reconstruction algorithm, but additional software engineering techniques can improve the reconstruction time further.

To make these improvements we have identified some of the bottlenecks in execution of the Gauss-Newton reconstruction algorithm described in algorithm 2.1. In decreasing order of time consumption these are:

- forward solving to generate both boundary and interior potentials,
- generating the Jacobian matrix,
- generating a descent direction through a dense matrix inversion.

In section 2.4.1 we discuss simple modifications to the formulation of the finite element matrix for the forward solution to increase efficiency in interpreted languages such as Matlab. In section 2.4.2 we describe efficiency savings available to speed up the Jacobian calculations. Finally in section 2.4.3 we describe a possible difficulty in performing the dense matrix solve and compare the computation time for a full pseudo-absolute solve with and without these software improvements.

All timings presented in this section were measured on a 2.8GHz Intel Core i7 with 16 GB 1.6 GHz DDR3 RAM. Comparisons were made using code from EIDORS 3.8 [58] running in Matlab 2016a. The improvements described in section 2.4.1 have been incorporated into the recent EIDORS 3.9 release [47] and the other improvements described in this section have been reported in conference proceedings [28].

2.4.1 Forward solve

In order to produce the internal potentials and boundary voltage measurements require to both perform line search checks and build the Jacobian needed for algorithm 2.1 eqs. (2.1) to (2.3) must be solved numerically. This is generally done by the use of the finite element method (*FEM*).

The EIDORS default scheme for calculating the forward problem uses piecewise linear basis functions defined on a mesh such as the one shown in fig. 2.10. These basis functions ϕ_i are defined to be 1 on node *i* of the mesh, 0 on all other



Figure 2.10: Diagram showing a simplified triangular mesh. The shaded mesh elements are those required for construction of the (1, 2) element of the stiffness matrix A_M .

nodes and vary linearly across mesh elements. Electrode modelling complicates the formulation of the FEM system matrix as boundary conditions under the electrodes must be taken into account. In this work we use the complete electrode model (CEM) [59], producing the matrix system

$$A\begin{pmatrix} u\\v \end{pmatrix} = \begin{bmatrix} A_M + A_Z & A_V\\ A_V^T & A_D \end{bmatrix} \begin{pmatrix} u\\v \end{pmatrix} = \begin{pmatrix} 0\\I \end{pmatrix}, \qquad (2.41)$$

where u contains the nodal values of potentials on the mesh, v contains the effective voltages on electrodes and I contains the applied current pattern, also known as the *stimulation pattern*. The submatrices shown in eq. (2.41) are then defined by the equations

$$A_M(i,j) = \int_{\Omega} \sigma \nabla \phi_i \cdot \nabla \phi_j dV \qquad A_Z(i,j) = \sum_{l=1}^{L} \int_{e_l} \frac{1}{z_l} \phi_i \phi_j dS$$
$$A_V(i,l) = -\int_{e_l} \frac{1}{z_l} \phi_i dS \qquad A_D(s,l) = \begin{cases} \frac{1}{z_l} |e_l| & s = l\\ 0 & s \neq l \end{cases}, \qquad (2.42)$$

where i and j are indices numbering the nodal basis functions within the mesh, s and l are indices numbering the electrodes z_l and e_l refer to the contact impedance and the area under electrode l respectively [60].

This formulation produces a sparse symmetric positive-definite system to be inverted to provide the potentials and boundary voltages required. However, to allow the efficient construction of system matrices for multiple conductivity distributions on the same mesh EIDORS does not form this matrix elementwise, instead a factorisation method is used [61, 62]. This allows the CEM system matrix A to be calculated as

$$A = F^T C F, (2.43)$$

where F is a connectivity matrix defined by the mesh and C is a diagonal matrix containing the elemental conductivities. This formulation can cause the resulting system matrix A to loose its symmetry property as matrix multiplication is not associative in floating point arithmetic. This results in the matrix containing a small antisymmetric part as shown in fig. 2.11.

Efficient solution of the system in eq. (2.41) has been examined [63] and a review of direct methods for sparse linear systems is given by Davis et al. [64]. In general for a symmetric positive definite system such as this a Choleski decomposition method will be the most efficient direct method. However, when implemented in an interpreted language, the default solver will perform checks on the matrix to determine which algorithm will be used and may choose incorrectly. In Matlab the most efficient sparse solver for this problem is the CHOLMOD algorithm [65], however, Matlab will only use this algorithm when the matrix is perfectly symmetric with positive entries on the diagonal. This is prevented by



Figure 2.11: Sparsity pattern for the full CEM system matrix of a 6 k node mesh. Values shown are for a 256×256 tiling of the matrix with the maximum value taken within each sub-matrix. Non-zero sub-matrices with maximum values less than 10^{-2} are shown in orange. The antisymmetric part of the matrix has maximum entries of order 10^{-12} .

the antisymmetric contribution shown in fig. 2.11. Correcting this asymmetry can be performed by simply taking the symmetric part of the matrix A

$$A_s = \frac{1}{2}(A^T + A) \tag{2.44}$$

and performing all further calculations with A_s . Using this symmetry correction was found to provide a significant speed up for the solution of the forward problem as shown in table 2.2 and has been incorporated into EIDORS 3.9.

Table 2.2: Forward solve timings for two meshes of the same domain.

N. nodes	Unsymmetric	Symmetric	Speedup	Unsymmetric	Symmetric	Speedup
	(CPU time s)	(CPU time s)	(CPU time \times)	(elapsed time s)	(elapsed time s)	(elapsed time \times)
46k	9.83	3.47	2.83	6.55	1.09	6.03
190k	281.06	91.45	3.07	146.77	28.01	5.24

2.4.2 Jacobian

A significant component of the construction time for the Jacobian is taken up in performing multiple forward solves. Each element in the Jacobian requires the integral of a forward solved potential over a given element [20]

$$J(\sigma)_{ij} = \int_{\Delta_j} \nabla u_i(\sigma) \cdot \nabla v_i(\sigma) dV$$
(2.45)

Here the u_i and v_i are interior potentials from forward solutions using specific current patterns. In matrix notation from the definition of the CEM forward problem, the discrete representations of u_i and v_i for piecewise linear basis functions are the vectors **u** and **v** produced by solving the equations

$$\begin{bmatrix} A_M + A_Z & A_V \\ A_V^T & A_D \end{bmatrix} \begin{pmatrix} \mathbf{u} \\ y \end{pmatrix} = \begin{pmatrix} 0 \\ I_S \end{pmatrix}, \quad \begin{bmatrix} A_M + A_Z & A_V \\ A_V^T & A_D \end{bmatrix} \begin{pmatrix} \mathbf{v} \\ z \end{pmatrix} = \begin{pmatrix} 0 \\ I_M \end{pmatrix}, \quad (2.46)$$

where I_S is the stimulation pattern applied for measurement *i*, I_M consists of a 1 and a -1 on the measurement electrodes for measurement *i*, and *y* and *z* are unused electrode voltages.

The sparse system solves for each of these stimulation and measurement patterns can be completed simultaneously by grouping all the required right hand sides into a single matrix. Performing the solve in this way only requires the Choleski factorisation step to be performed once while allowing the forward and back substitutions to be performed simultaneously. However, in cases where there are a large number of stimulation or measurement patterns this can still result in long computation times. It is therefore desirable to perform the inversion on a limited basis of vectors which span both the stimulation and measurement patterns. The implementation of the forward solve in EIDORS 3.9 determines this basis through use of a QR factorisation on the matrix of stimulation patterns. However, in the calculation of the Jacobian the stimulation and measurement patterns were being solved separately.

By performing both the stimulation and measurement solves simultaneously using the symmetry corrected system matrices from section 2.4.1 a significant time saving was achieved as shown in table 2.3. Table 2.3: Jacobian build timings for two meshes. Both Jacobians were calculated using the dual mesh method, aggregating onto the same mesh.

N. nodes	Unsymmetric	Symmetric	Speedup	Unsymmetric	Symmetric	Speedup
	(CPU time s)	(CPU time s)	(CPU time \times)	(elapsed time s)	(elapsed time s)	(elapsed time \times)
46k	74.7	61.3	1.2	41.7	31.7	1.3
160k	733.9	280.0	2.6	394.5	141.3	2.8

2.4.3 Pseudo-absolute reconstruction times

The final efficiency saving listed here relates to the calculation of the generalised inverse

$$J_{\alpha,L}^{\dagger} = (J_b^T W J_b + \alpha L^T L)^{-1} J^T W, \qquad (2.47)$$

used to determine a descent direction. The implementation issue for this dense matrix solve stems from the same associativity issue noted in section 2.4.1. Again this should be a symmetric positive-definite system but numerical errors prevent default solvers from choosing symmetric algorithms. The timings in table 2.4 demonstrate the efficiency savings available by forcing this symmetric solve.

Table 2.4: Dense solve timing comparison for symmetry correction.

N. elements	Unsymmetric	Symmetric	Speedup	Unsymmetric	Symmetric	Speedup
	(CPU time s)	(CPU time s)	(CPU time \times)	(elapsed time s)	(elapsed time s)	(elapsed time \times)
10k	162.5	124.9	1.3	42.9	35.1	1.2

Combining this dense solve efficiency saving with the techniques in sections 2.4.1 to 2.4.2 provides a large speed up to the absolute reconstruction performed in the pseudo-absolute algorithm. As shown in table 2.5 this allows a 3D regionally-absolute reconstruction to be performed in under 3 minutes with further successive frames reconstructed in real time at the same frame rate as regular difference imaging.

Table 2.5: Comparison of a pseudo-absolute reconstruction times for a 4 compartment lung model.

N. elements	Unsymmetric	Symmetric	Speedup	Unsymmetric	Symmetric	Speedup
	(CPU time s)	(CPU time s)	(CPU time \times)	(elapsed time s)	(elapsed time s)	(elapsed time \times)
10k	702.9	439.5	1.6	407.4	169.4	2.4

2.5 Conclusion

In this chapter we have developed and tested a novel pseudo-absolute reconstruction algorithm. This algorithm is capable of producing reconstructions of EIT at the same rate as difference imaging with limited initial processing time. However, unlike difference imaging, these reconstructions are *regionally-absolute*. That is to say, the aggregate value of conductivity over regions of the reconstruction follow the absolute values of conductivity, allowing recovery of regional ventilation as will be shown in sections 3.2.2 to 3.5.4. This algorithm was developed not only to enable the recovery of clinically relevant diagnostics and provide guidance for mechanical ventilation but also to retain the ability of EIT to provide fast feedback and warnings.

We have also examined the effects of regularisation, including possible bias from constraints used. This discussion of regularisation led to the description possible modifications to the matrices used in Tikhonov regularisation to allow more meaningful spatial priors including the possibility of anisotropic regularisation in section 2.1.3.

Using inner-product based error measures we have provided useful quantitative information on the reconstruction quality. Crucially this comparison between difference imaging and pseudo-absolute reconstruction provided evidence that resolving the Jacobian can increase the accuracy of reconstructions in areas shadowed by the lungs, even with modelling mismatches. This will require further testing to validate, but increased sensitivity in these interior regions could have additional implications for further post processing of EIT. For example separation of the conductivity signal produced by cardiac changes [15].

Finally we have provided useful efficiency saving techniques for implementation of EIT. This allowed the reconstruction time of pseudo-absolute images to be reduced to a 3 minute setup with further reconstruction produced in real time making the use of 3D absolute EIT feasible in a clinical setting.

Chapter 3

Lung Modelling and Parameter Recovery

In this chapter we will describe models and techniques to both generate EIT measurements from ventilation models and recover ventilation distributions and parameters for those models from EIT reconstructions. This is an important innovation due to the dynamic way in which the behaviour of the lung can change as lung regions are recruited [6]. Such behaviour necessitates fast parameter recovery procedures that are capable of being repeated multiple times during recruitment manoeuvres.

In section 3.1 we derive an ordinary differential equation (ODE) model for lung function and describe how it may be solved to produce regional conductivity values for sections of lung. In section 3.2 we discuss the sources of error in EIT reconstructions and describe two methods for generating noisy conductivity timeseries for use in testing post-processing procedures. In section 3.3 we describe how to recover regional air volumes and flows which may be used by the techniques in section 3.4 to fit parameters for the ODE lung model. Finally section 3.5 examines how errors in EIT measurement and modelling can affect how well our post processing techniques work.

3.1 Lung Modelling

There are many different approaches to modelling air flow through the lungs which vary greatly in their levels of complexity and fidelity to the true structure of the lungs. At the most complex end of the spectrum are large scale computational fluid dynamics (*CFD*) models of lung function linked to co-registered 4D MRI or CT images [66]. These models attempt to accurately capture large portions of the structure and dynamics of the lungs to give general insight into their behaviour under different modes of ventilation. Even models which do not resolve the full lung system but only part of it can provide valuable insight into how the fluid structure interactions in sections of the lungs can produce damage [67]. For example the effects of pressure gradients on epithelial damage during lung recruitment [5] or how surfactant levels affect the tendency of airways to buckle and collapse [68].

Less complex approaches attempt to incorporate the general dyadic branching tree structure of the lungs without fully resolving bronchiolar and alveolar structures. For example using low dimensional models of alveolar response as termination boundary conditions for a CFD model of the bronchiolar tree [69]. Another example of attempts at this are large scale compartmental models such as the one developed by [70]. This model consists of thousands of coupled compartment models each of which solve simplified models to find ventilation levels as well as quantities such as blood gas composition and pH by finding a new equilibrium at each time step. These models, when combined with parameters from general population studies, are useful for testing new pressure control profiles numerically [71–73] due to their reduced computational complexity.

At even lower complexities there are simple ODE models with one or two parameters for lumped lung models or compartmental models with low numbers of compartments. Such models have been studied in detail [74] and expanded since they were proposed over sixty years ago [75]. Despite their low level of fidelity to the structure of the lungs they do provide qualitative insight into lung behaviour making them prevalent in standard physiology text books [76]. Their low complexity also mean that it is easier to fit parameters to them from measurements accessible at the bedside such as air volume flow at the airway opening. Hence ODE parameters such as lumped lung compliance can be used to aid in clinical procedures such as determining optimal positive end expiratory pressure (*PEEP*) during recruitment manoeuvres [77].

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There have been attempts to couple large scale CFD models to imaging through EIT. For example Roth et al. [18] were able to simulate data acquisition and reconstruction of 2D EIT images for a 4D finite element model of lung function. Using this method they proposed testing lung ventilation profiles on the CFD model and comparing the simulated EIT to measurements taken on the patient to verify that treatment is working as expected [78]. However, the complexity of these systems combined with the high number of parameters complicates the process of in-vivo parameter recovery.

This desire to recover regional lung parameters at the bedside motivates our choice of lung model for the techniques described in this chapter. The lumped lung ODE parameters mentioned above are recoverable from current ventilator measurements so we have chosen to extend these models to incorporate regional information as a natural first step in demonstrating that additional information from EIT allows regional parameter recovery. The derivation for the extended model is described in sections 3.1.1 to 3.1.2 demonstrates the numerical solution of these models for our specific test parameters and section 3.1.3 describes how the ventilation distributions generated by these ODEs are converted into conductivity values to be used in simulations of EIT.

The parameter recovery process has been examined by Crabb [79, chapter 6] under the assumption that time series of compartmental lung volumes is known explicitly. We extend this with a proof in section 3.4 that parameters are recoverable when the ventilation distribution is known and examine how the ventilation distribution may be recovered from EIT.

3.1.1 ODE model derivation

One of the most basic ODE lung models consists of a single expanding compartment with an associated *elastance* and *resistance* [75] as shown in fig. 3.1. In this model air is taken to be an incompressible fluid forced into an elastic compartment with volume V under the action of an applied pressure P. Acting against this pressure are the assumed linear elastic recoil of the lung provided by an elastance E, an airway resistance R to air flow in or out of the compartment and the pressure in the pleural cavity P_0 . As the air flow can be seen as the time derivative of the volume this results in the linear first order ODE

$$EV(t) + RV(t) = P(t) - P_0.$$
(3.1)



Figure 3.1: Diagram of a single compartment, lumped lung ODE model.

There are many possible ways to extend this basic model to more accurately describe the lungs. For example some models add a further *inertance* term [80, chapter 9], which describes the force required to accelerate the mass of air in the lungs. Addition of this term results in a second order ODE. Similarly an additional term may be added to modify the action of resistance in the lungs. In particular terms are added to more accurately capture the hysteresis of the lungs resulting in a quadratic [81] or flow direction dependent [82] resistance term. Modifications can be also made to incorporate gas exchange in the alveoli [83] or the effects of spontaneous breathing [84]. However, these methods all complicate the process of parameter recovery so they have not been implemented for this initial testing.

Instead, to add spatial information to the ODE in eq. (3.1) we have constructed a model with additional compartments. Bates [80, chapter 7] examines the case in which two lumped lung compartments branch off from a single airway. For that model each compartment has its own elastance and a resistance which acts only on the airflow into the compartment. A single resistance parameter is then applied to all air flow through the top airway. This arrangement allows the two compartments to be assigned to the two separate lungs giving some regional information. Bates notes that it is not possible to accurately recover parameters for two or more compartments when only the air flow at the top of the system is known so models with further compartments are not examined. However, with the addition of regional information from EIT we gain the ability to recover parameters for a larger number of compartments. This novel approach allows us to increase the number of compartments in our ODE model.

In section 3.4 we will prove that models with one top level resistance in series have recoverable parameters so long as the ventilation distribution can be found at multiple points in time. As EIT provides regional information, which we will convert into ventilation distributions in section 3.3, we are able to recover parameters for models with a larger number of compartments. This means that we are able to increase the number of compartments so long as each compartment can be assigned to physically distinct lung regions fed by a single branch of the airway structure.

The maximum number of compartments could feasibly be between 5 and 20. This is due to the branching dyadic tree structure of the lungs shown in fig. 3.2. In total there are five distinct regions of the lungs, known as lobes, that are fed



Figure 3.2: Diagram of the dyadic branching tree structure of the lungs. The parameter R_j^i denotes the airway resistance for bronchiole number j at bifurcation level i.

by a single branch of the airway tree. Similarly these lobes can be split into a total of 20 bronchopulmonary segments which are fed by individual segmental bronchi and comprise the functional anatomical unit of the lung [76, chapter 25]. Practically however, segmentation of CT images has only been achieved down to lobe level [85, 86], especially in the case of patients with lung problems [87], reducing the maximum feasible number of compartments to 5. Due to difficulties in meshing 5 lung compartments for later EIT simulations, we will be using an

ODE model with four compartments which correspond to upper and lower airways for the left and right lungs. This reduction from five lobes to four corresponds to treating two of the lobes from the right lung as a single compartment. This is reasonable as the airways feeding into these lobes diverge further down the bronchiolar tree structure than the split for the upper lobe. The result is that each compartment is fed from an airway starting at the second bifurcation in the tree structure shown in fig. 3.2, increasing the fidelity of the model, and the mesh generation process is simplified for the EIT simulations in section 3.2.

A diagram of our four compartmental model can be seen in fig. 3.3. This model treats air as an incompressible fluid passing through a central airway into four compartments under the action of a pressure difference. In the model, pressure drops occur as air passes through the central airway and the airways leading into each compartment under the action of airway resistance. Each airway has its own resistance parameter denoted by R_i , where *i* denotes the number assigned to the compartment each airway leads to and R_0 refers to the central airway, or tracheal, resistance. Once airway pressure drops have been accounted for the pressure difference between air within each compartment and the pleural pressure outside the lungs is counteracted by the elastance of each compartment denoted by E_i .



Figure 3.3: Compartment layout for ODE model. Compartments are labeled in the order top right, top left, bottom right, bottom left to align with an extruded chest model used to simulate EIT reconstruction.
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Using the assumption of incompressibility the volume of air in each compartment at time t is denoted as $v_i(t)$ and the volume flow at the top of the airway is taken to be the sum of the rates of change in each of these volumes due to conservation of mass. The difference between the driven pressure at time t, P(t), and the pleural pressure P_0 can be formulated as the equation

$$P(t) - P_0 = R_0 \sum_{j=1}^{4} \dot{v}_j(t) + R_i \dot{v}_i(t) + E_i v_i(t).$$
(3.2)

Equation (3.2) holds true for each of the compartments and can therefore be reformulated into the matrix ODE system

$$R\dot{\mathbf{v}}(t) + E\mathbf{v}(t) = \mathbf{p}(t), \qquad (3.3)$$

where $\mathbf{v}(t)$ is a vector containing the air volumes in each compartment at time t, $\mathbf{p}(t)$ is a vector of pressure drops, $P(t) - P_0$, across the system and E and R are now matrices with the structures

$$E = \begin{pmatrix} E_1 & 0 & 0 & 0 \\ 0 & E_2 & 0 & 0 \\ 0 & 0 & E_3 & 0 \\ 0 & 0 & 0 & E_4 \end{pmatrix},$$

$$R = \begin{pmatrix} R_1 + R_0 & R_0 & R_0 \\ R_0 & R_2 + R_0 & R_0 & R_0 \\ R_0 & R_0 & R_3 + R_0 & R_0 \\ R_0 & R_0 & R_0 & R_4 + R_0 \end{pmatrix}.$$
(3.4)

We can then solve this ODE using numerical methods as described in the next section.

3.1.2 ODE test parameters

To generate test data for the ventilation and parameter recovery techniques in section 3.3 and section 3.4, we use a fourth order explicit Runge-Kutta method to solve the ODE system in eq. (3.3). This scheme was chosen as it is fourth order convergent for smooth inputs such as the sinusoidal pressure profile used in this chapter. That is to say that local truncation errors in the resulting ventilation

profiles should be $O(dt^5)$ where dt is the step length. In the solution of general ODE systems this high degree of accuracy is often offset by an increased computational cost over other methods. However, as our system consists of a linear ODE in four variables, the cost of solving the ODE is low compared to other steps in the testing procedures. In this case each step requires 4 matrix-vector multiplications, 9 vector-vector additions, 10 scalar-vector additions and 9 scalar operations. Hence, on a 2.8GHz Intel Core i7 with 16 GB 1.6 GHz DDR3 RAM running Matlab solution of 3,000 time steps with a step length of 10 ms took approximately 25 ms. We will refer to this from now on as a *ventilation forward solve*.

For all ventilation forward solves in the rest of this work we use the ODE parameters shown in table 3.1. These parameters were chosen to be of a sim-

	Elastance cmH_2OL^{-1}	Resistance $cmH_2OL^{-1}s$
Compartment 1	10	10
Compartment 2	10	20
Compartment 3	15	5
Compartment 4	25	10
Trachea	-	5

Table 3.1: Model parameters

ilar magnitude to those provided in [80] and [82], which quote an elastance of $10cmH_2OL^{-1}$ (centimetres of water per litre) and resistances of $15cmH_2OsL^{-1}$ (centimetres of water seconds per litre). Parameters were chosen to ensure that the parameters could be recovered, as discussed in section 3.4, and that the ODE system is controllable as will be discussed in section 4.1.

Originally testing was performed using parameters with arbitrary units as all quantities were normalised to achieve tidal breathing variations consistent with filling factor values given in the literature [88]. Here filling factor (F) is defined as the ratio of air content in a region (v_i) to the volume of the rest of the matter in a given compartment (V_c) ,

$$F = \frac{v_i}{V_c}.$$

This normalisation was performed by choosing a non-dimensional maximum pressure value of 20 for which compartments with the lowest elastance value of 10 would attain a filling factor of F = 4 when held at a steady state pressure. This pressure was chosen as [89] states that the average resulting pressure after a maximal recruitment manoeuvre is 40 cmH_2O and [90] states that pressures above 28 cmH_2O result in an increased inflammatory response. The result of this normalisation is compartments with a maximum inflation volume of $v_i = 2$ and a *condensed matter volume* of $V_c = 0.5$ in generalised units. However, when these pressures are stated in cmH_2O and the volumes are stated in litres they correspond to a lung system with capacity of 8 L. For comparison the average total lung capacity of a human male is 6 L [76], so these pressures stated in units of cmH_2O and L are roughly consistent with a large mammal.

For the rest of the tests in this chapter the ventilation pattern from eq. (3.3) were generated for the parameters in table 3.1 under the action of a sinusoidal pressure pattern with values chosen such that the most compliant compartments would reach full exhalation and inhalation filling factor values if held at minimum or maximum pressures respectively. The initial conditions were chosen such that each compartment started with a filling factor of 1, simulating a lung collapsed beyond normal exhalation being re-inflated by mechanical ventilation. As the elastance values of these compartments would not usually result in these volumes at the starting pressure of 15 cmH_2O , these initial conditions correspond to an instantaneous change in ventilation parameters from $E = 30 \ cmH_2OL^{-1}$ to the values in table 3.1. This is feasible through the use of clinical interventions such as a change in patient positioning. Both the pressure profile and resulting compartmental air volumes can be seen in fig. 3.4.

In order to produce a time series with a sample rate achievable through EIT the results of the ventilation forward solve, provided at 100 frames per second for a 30 s period, were sampled at 600 time steps. This corresponds to an EIT acquisition rate of 20 frames per second, which is achievable for a 64 electrode system using a current injection frequency of 100 kHz. These 600 volume samples were then used to generate compartmental effective conductivity values as discussed in section 3.1.3.



Figure 3.4: Graphs showing the test pressure profile (left) and the resulting compartmental air volumes (right). The volume graphs are positioned according to the compartmental layout shown in fig. 3.3.

3.1.3 Conductivity generation

Solving eq. (3.3) as described in 3.1.2 gives the compartmental volumes as the pressure is varied. However to test the post processing techniques in sections 3.3 to 3.4 these air volumes must be converted to an aggregate measure of the tissue conductivity within the compartment so that the reconstructed signal from EIT may be simulated as described in section 3.2.

In the literature it has been shown that the change in impedance for a region of the lungs as measured by EIT follow an approximately linear relationship to the air content change [16]. However this relationship will be used in section 3.3 so use of this relationship to define the conductivity in this *conductivity forward solve* step would constitute an *inverse crime*. Inverse crimes occur when the same model is used to both generate and invert simulated data [91] leading to better reconstructions with simulated data as opposed to measured data. To avoid this testing bias we will use a different homogenisation method in this conductivity forward solve step. There are many possible candidates for this homogenisation method ranging from mixing laws based on simple spherical inclusions [92] up to full finite element simulations of sections of lung structure [18]. To strike a balance between accuracy and ease of implementation we have used the model described by Nopp et al. [88]. This method requires as inputs the current injection frequency for EIT, taken here to be 100 kHz, and the filling factor for the specified region as described above. The equations used are then generated by modelling alveoli as cubes with consideration of blood, cellular membrane, endothelial and epithelial cells, and extracellular and intracellular fluids. The complete equations for this model are described by Nopp in [88] where they were first developed. These equations provide estimates for both the bulk conductivity and permittivity of the lungs and the resulting estimates of bulk resistivity have a near linear relationship with filling factor at inflation levels likely within the lungs.

Applying these equations to the air volumes shown in fig. 3.4 results in the conductivity patterns shown in fig. 3.5. These conductivity values are then used in section 3.2 to generate both voltage data and the noisy reconstructed conductivity values used to test our post processing techniques.



Figure 3.5: Graphs bulk conductivity values resulting from compartmental air volumes. The graphs are positioned according to the compartmental layout shown in fig. 3.3.

3.2 EIT conductivity measurements

Using the model and homogenisation formulae from section 3.1 we can perform both a ventilation and conductivity forward solve to generate time series of effective conductivities for each compartment in our model. This constitutes what we will call the *conductivity signal* for our post processing ventilation and parameter recovery techniques in sections 3.4 to 3.3. However, to truly test how effective these techniques can be we will need to test them on conductivity time series which approximate those recoverable through EIT.

This process of generating *conductivity measurements* requires an examination of the sources of error in EIT reconstructions. In general this is a difficult task due to:

- the range of EIT reconstruction algorithms available
- the sensitivity of EIT to modelling errors and movement [40, 93],
- the sensitivity of EIT to voltage measurement noise.

These are also complicated by the need for 3D reconstructions to capture the ventilation of all functional compartments in our lung model.

Additionally we would prefer to reconstruct absolute values of conductivity. This is motivated both by the increased accuracy of the estimation of changes in bulk resistivity (ρ) assumed to be the reciprocal of conductivity as well as the approximate affine relationship between air content and bulk resistivity

$$V = \alpha \rho + \beta \tag{3.5}$$

assumed in section 3.3. This affine relationship allows the conductivity time series to be normalised to external ventilator measurements in order to provide estimates of air flow by estimating α . However, recovery of the volume within the lungs requires co-registration to other imaging modalities to calibrate β which becomes simpler when conductivity measurements from two separate EIT acquisition sessions can be compared.

In this section we propose two approaches to estimating errors in conductivity measurements as recoverable from EIT by separating out the causes of errors in EIT reconstructions. In section 3.2.1 we propose separating out the conductivity errors due to voltage measurement noise from the modelling, movement and algorithm dependent errors. This can be done using difference imaging techniques to reconstruct measurement noise to be added to the conductivity signal. Modelling error in this way allows comparison of the volume and parameter recovery techniques under varying levels of voltage measurement error assuming *ideal absolute EIT reconstruction*. For this reason this conductivity noise estimation technique has been used to provide examples for sections 3.3 to 3.4 as well as sensitivity analysis in section 3.5.

In section 3.2.2 we propose a second method for generating noisy conductivity measurements. This is done using simulated EIT measurements reconstructed using the pseudo-absolute algorithm described in section 2.2.3. These reconstructions provide a reasonable approximation to feasible EIT time-series recovery under the assumption that movement is accounted for. This technique allows the ventilation and parameter recovery methods to be tested under varying levels of modelling mismatch in section 3.5.

3.2.1 Difference imaging

This section describes the method used to generate conductivity measurements for ventilation and parameter recovery where all conductivity measurement errors are due to the inaccuracy of voltage measurements in the acquisition of EIT. Using these assumptions allows results to be independent of reconstruction algorithms and modelling techniques and is a necessary first step in testing our post processing procedures as they are unlikely to work for practical EIT if they can't work for *ideal EIT*. The method from this section will be used in sections 3.3 to 3.4 to generate demonstrative results and in section 3.5 to test the sensitivity of the techniques to noise.

To generate these ideal EIT conductivity measurements we use difference imaging, as described in chapter 2, to generate conductivity noise directly from measurement noise values. This reconstructed conductivity noise is then added directly to the conductivity signal time series as generated in section 3.1.3. This gives a reasonable approximation to the level of reconstruction error produced under the assumptions that the shape of a patient's thorax can be modelled and tracked accurately through the course of ventilation [40], electrode positioning and impedance is modelled accurately [93] and the noise in each of the voltage



Figure 3.6: Human adult male thorax CT outline (left) and extruded meshes used for voltage generation (right)

measurements follow independent, identical distributions (*IID*). Both the simulated voltage measurements and reconstructions are produced using modified code from EIDORS version 3.9 [47, 94] and reconstructions were performed using the dual mesh reconstruction method [95].

The first step in this process is to generate full 3D meshes of a thorax geometry. As it has been shown that a leading contributor to EIT inaccuracies is error in the boundary shape [40], the mesh is generated by using Netgen [96] to extrude the boundary of an adult male chest CT image shown on the left in fig. 3.6. Three meshes were produced including the ultra-fine voltage generation mesh shown in fig. 3.6 as well as the fine and coarse meshes shown in fig. 3.7. These are composed of 1.03M, 221K and 10K volume elements respectively and each contain four cylindrical inclusions. For the purposes of testing our post processing techniques and to simplify the mesh generation process the cylinders represent the four compartments in the lung model from section 3.1.

To generate a reference voltage we assign conductivities to the cylindrical inclusions corresponding to the air volume in each compartment at mid inhalation in order to perform a voltage forward solve. To calibrate the ratio of conductivities between lung and background tissues, the values given in [97] are used providing a ratio of 0.125 at full inhalation. The mid inhalation conductivities are generated by normalising the Nopp conductivity values for full inhalation, at a filling factor of 4 [88], to 0.125 and then calculating the normalised conductivities expected if the lung model were held at the median ventilation pressure.



Figure 3.7: Extruded meshes used for Jacobian calculation (left) and reconstruction aggregation (right). The finer mesh includes electrodes and both meshes show cylindrical inclusions to represent the lungs.

The fine and ultra-fine meshes include 4 rings of 16 electrodes meshed onto the outer thorax shape in order to simulate EIT. The electrodes are indexed from 1 to 64, where electrodes in the top ring are numbered from 1 to 16 and the further 3 rings are indexed beginning at 17, 33 and 49 respectively. EIT is simulated with pairwise current driven at an amplitude of 0.1mA and voltages are measured on pairwise electrodes both with a skip of 23 so that current is driven and measurements are recorded across rings. The voltages are computed on the ultra-fine mesh for the mid inhalation reference frame through a piecewise linear FE method using the complete electrode model [59].

Once these reference frame voltage measurements have been calculated they are copied with the addition of normalised IID noise for each time step at the correct signal to noise ratio (SNR). Noise values are generated using a normal distribution with a signal to noise ratio of

$$SNR = \|\phi\| / \|\epsilon\|$$

where ϕ is a vector of measured voltage differences between electrodes for a single frame and ϵ is the vector of noise values. The errors in conductivity caused by these voltage noise values are calculated using the EIDORS function inv_solve_diff_GN_one_step. This reconstructs conductivity using a single Gauss-Newton step with a Jacobian calculated using the fine mesh of the domain.

The values from this inversion are mapped to the coarse mesh to aggregate the reconstruction and reduce the dimensionality of the problem to produce reconstructions similar to the one shown in fig. 3.8. The reconstructed conductivity



Figure 3.8: Single frame of reconstructed noise from pure noise voltages.

values are then aggregated into four compartmental noise values by taking a volume weighted average within the regions of interest. These four averaged values are then added to the Nopp generated values to give a noisy sampled time series of conductivities. An example of the noisy conductivity time series at an SNR of 100 is shown on the left of fig. 3.9 along with the equivalent noisy resistance time series on the right. An SNR of 100 equates to a 1% noise level but the convention



Figure 3.9: Conductivity and resistivity profiles generated from the difference imaging noise method.

is to measure noise in decibels (dB). The formula relating SNR to dB is

$$dB = 20 \log_{10}(SNR)$$

so in decibels 100 SNR equates to a 40 dB signal, which is significantly worse than the practical upper range of accuracy in EIT measurements of approximately 100 dB [98].

To test the sensitivity of our post-processing procedures to measurement noise sections 3.3.2, 3.4.3 and 3.5.1 use the technique outlined in this section to produce noisy conductivity and resistivity profiles like those in fig. 3.9 at varying SNR levels. For each SNR level 1000 individual tests are performed, requiring the generation of a full noisy conductivity profile. Hence for each SNR the total number of draws from the random number generator is 1000 multiplied by the number of ODE time samples, multiplied by the number of voltage measurements needed for a full EIT reconstruction of a single frame.

3.2.2 Pseudo-absolute EIT

This section describes the method used to generate conductivity measurements for ventilation and parameter recovery where both the signal and noise components of the conductivity measurements are generated through EIT reconstructions. This is done through the use of a pseudo-absolute reconstruction algorithm as developed in section 2.2.3. This is a novel method of reconstruction allowing absolute values of conductivity to be produced at the same rate as difference imaging. Unlike the ideal EIT difference imaging noise generated in section 3.2.1, this pseudo-absolute method allows us to test our post-processing techniques with incorporated modelling and algorithmic bias. The method from this section will be used in section 3.5 to test the sensitivity of the post processing techniques to absolute conductivity reconstructions with incorporated errors in mesh segmentation.

For this measurement generation method a voltage forward solve is performed not only at the mid inhalation reference frame but at every time step in the conductivity time series. These forward solves are performed using the same ultra-fine mesh, stimulation and measurement patterns as used in section 3.2.1. Noise is then added to the reference frame and each frame of data acquisition individually to be used in reconstructions.

The reference voltages are then used in a low dimensional iterative absolute reconstruction algorithm in which grouping constraints have been placed on the four cylindrical lung regions and the background resulting in a five parameter reconstruction as described in section 2.2.3. A comparison of the original reference frame lung phantom to the reconstructed absolute image is shown in fig. 3.10. These reconstructed values are then used in the calculation of the Jacobian for



Figure 3.10: Comparison of the phantom reference frame (left) to its grouping constrained absolute reconstruction (right). The maximum relative error in reconstructed values was 1.5%

difference imaging of the remaining time series of voltage measurements. A comparison between the conductivity change in the phantom and the reconstructed difference image is shown for one frame in fig. 3.11.



Figure 3.11: Comparison of the conductivity difference from the phantom reference frame (left) to the reconstructed difference image (right).

The values from the difference reconstruction at each time step are then added to the corresponding elemental conductivities from the grouping constrained absolute reconstruction and a volume weighted average is taken for each cylindrical region of interest. This volume average is then taken to be the measured conductivity for the corresponding compartment at that time step. An example of the noisy conductivity time series at an SNR of 100 (40 dB) is shown on the left of fig. 3.12 along with the equivalent noisy resistance time series on the right.



Figure 3.12: Conductivity and resistivity profiles generated from the pseudoabsolute imaging noise method.

The method from this section will be used in section 3.5 to test the sensitivity of the post processing techniques the process of absolute conductivity reconstruction and errors in mesh segmentation. This is done by using a different segmentation of compartments in the fine and coarse meshes than is used in the ultra-fine voltage generation mesh. As with the ideal EIT noise generated by difference imaging, the tests with this imaging modality will be performed using a thousand realisations of IID voltage noise for each acquisition frame.

3.3 Ventilation Recovery

This section describes the recovery of the ventilation distribution, i.e. compartmental flows and volumes for the ODE model in section 3.1, from EIT images. Recovery of these ventilation distributions not only allows the recovery of regional lung parameters, as will be discussed in section 3.4, but also presents the opportunity for an easily comprehensible interface with clinicians.

The techniques in section 3.2 generate time series of homogenised or effective conductivities σ_i , that are related to air volume v_i , for each compartment but converting these back to volumes requires fitting them to measurements of air flow available from the ventilator. To do this, in section 3.3.1 we describe the recovery of interior flow and volumes by reducing the process to differentiation of the conductivity time series and fitting it to the measured flow data at the ventilator. In section 3.3.2 we test these techniques against the conductivity time series generated in section 3.2.1 at an SNR of 100.

Recovery of these ventilation distributions not only provides useful regional information about the operation of the lungs qualitatively but also provides an opportunity to recover lung model parameters to analyse their function quantitatively. The parameter recovery process will be described in section 3.4 using the volume and flow time series produced in this section.

All timings presented in this section were measured on a 2.8GHz Intel Core i7 with 16 GB 1.6 GHz DDR3 RAM.

3.3.1 Numerical differentiation and normalisation

Our examination of the recovery of ventilation distribution and model parameters when compartmental volumes are known up to a Gaussian noise distribution has been reported both in conference proceedings [99] and by Crabb [79, chapter 6]. However, we would like to be able to do the same when we only have conductivity time series data.

In [100] and [18] it is shown that there is an approximate linear relationship between the effective electrical resistivity ρ_i , and filling factor F. Here ρ_i is approximated as the reciprocal of effective conductivity, $\rho_i \approx \frac{1}{\sigma_i}$, and F is defined as the ratio of air volume content to tissue volume. So for compartment i the filling factor F_i is given by

$$F_i = \frac{v_i}{V_i},\tag{3.6}$$

where v_i is the volume of air in compartment I and V_i is the volume of lung tissue for the same compartment. Combined with the linear relationship mentioned above this results in a formula for v_i of the form

$$v_i = \alpha V_i \rho_i + \beta, \tag{3.7}$$

where α and β are constants independent of ρ_i . It is assumed that V_i can be determined from another imaging modality, and β requires co-registration of another imaging modality at a single reference frame to calibrate air volumes. When testing these procedures with the pseudo-absolute conductivity time series generated in section 3.2.2 we assume that the absolute reconstructed reference frame was acquired in conjunction with another imaging modality allowing calibration of β . To test these procedures with the difference imaging noise generated in section 3.2.1 we estimate β by computing a linear fit of values from the equations used in section 3.1.3 to generate conductivity maps.

Under the assumption of incompressibility the volume flow measured at the ventilator Q is equal to the sum of the compartmental flows. This allows α to be determined by performing a least squares fit on the equation

$$Q = \alpha \sum_{i} \frac{\mathrm{d}}{\mathrm{d}t} (V_i \rho_i) = \alpha \sum_{i} V_i \frac{\mathrm{d}}{\mathrm{d}t} \rho_i, \qquad (3.8)$$

once the ρ_i have been differentiated. Differentiation amplifies the effects of noise so the time derivative of ρ_i is posed as the inversion of an integration operator to allow explicit regularisation of the solution [101]. This gives the equation

$$\frac{d}{dt}\rho_{i} = \arg\min_{u} \|Au - \rho_{i}\|^{2} + \lambda_{i}\|Lu\|^{2}, \qquad (3.9)$$

where A is an integration matrix used in a data-fit term, λ_i is a regularisation hyperparameter and L is a second order central difference operator used to enforce a level of smoothness on the solution.

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The regularisation hyperparameters for each compartment are found using an L-curve method. L-curve methods aim to balance the data misfit with the regularisation penalty by plotting the resulting values of the residual and regularisation norms on a log-log plot [102, 103]. This graph has a characteristic L shape, as shown in fig. 3.13, and the value of λ_i corresponding to the point of maximal negative curvature, or corner, is typically used due to the transition at this point between the two straight sections. The rationale behind this is that when λ_i corresponds to the straight horizontal section of the plot, any increase in its value will cause large increases in the datafit residual without providing benefit in terms of the model's fit to the prior. Similarly, on the straight vertical section any decrease in λ_i will drastically reduce the model's fit to the prior without benefit to the datafit residual. Therefore a good candidate for λ_i is likely to be found in the interval of hyperparameters with increased curvature, corresponding to the smooth *corner* of the L-curve graph.



Figure 3.13: L-curve for regularisation parameter of compartment 3 (λ_3) during first test. Parameters labelled with crosses are the hyperparameters for which the Regularization toolbox evaluates curvature. These values increase exponentially and the curvature between each evaluation point is interpolated to find the hyperparameter corresponding to the desired curvature.

Modified versions of the functions cgsvd and l_curve from the Regularization Tools Matlab toolbox [104] are used to choose the regularisation parameter for this problem automatically. As mentioned above, in this case parameters within an interval correspond to points on the graph with negative curvature, producing a rounded corner. As such, λ_i is chosen to be the lower of the two values in this interval at points with half the maximum curvature. This is to emphasise the data-fit for the use of reconstructed flows in parameter estimation.

Once the regularisation parameter has been found for each compartment a Tikhonov regularised inverse can be found for the problem in eq. (3.9) allowing the derivative to be computed quickly. The result is a smooth approximation to the time derivative of the electrical resistivity in a given compartment. These derivatives are then summed and normalised against the volume flow measured at the mouth to give a measure of regional flow. Integrating these values with respect to time, using the matrix A from eq. (3.9), then gives a smooth approximation to the resistivity of the compartment as a function of time, which can be converted into an approximation for the air volume within a compartment.

3.3.2 Ventilation recovery from EIT at 100 SNR

In this section we demonstrate the process of ventilation distribution recovery using conductivity timeseries with noise added through the difference imaging noise techniques outlined in section 3.2.1. To do this tests were performed on the conductivity timeseries generated for ventilation by a sinusoidal pressure profile of the 4 compartment ODE lung model outlined in section 3.1. The parameters used for this ventilation and conductivity forward solve can be found in table 3.1, the pressure and ventilation profiles can be found in fig. 3.4 and the resulting conductivity timeseries can be found in fig. 3.5.

To demonstrate the behaviour of the ventilation recovery procedure outlined in section 3.3.1, 1000 tests were performed and the minimum, maximum, mean and standard deviation of error norms on the recovered ventilation profiles were examined. For each test noise was added to the conductivity signal by performing difference EIT reconstructions on measurement noise for each successive time step at an SNR of 100 (40 dB), producing noisy conductivity and resistivity timeseries as shown in fig. 3.9. For clarity, an outline of the testing procedure is shown in algorithm 3.1.

Alg	gorithm 3.1 Ventilation recovery testing procedure
1:	Set number of time samples S
2:	Set number of tests N
3:	
4:	Solve ODE for air volumes
5:	Generate conductivity time series from volumes
6:	Generate reference voltage V_0
7:	
8:	% Perform tests
9:	for $i \leq N$ do
10:	for $j \leq S$ do
11:	Generate noisy voltage V_n from V_0
12:	Perform difference EIT on $V_n - V_0$
13:	Add reconstructed noise to conductivity sample j
14:	Take reciprocal to generate noisy resistivity
15:	end for
16:	recover ventilation distribution i from noisy resistivity samples
17:	end for

In each test, the recovered flows and volumes were qualitatively close to the original simulated values as shown in figs. 3.14 to 3.15. However, differences can be seen at the edges of the flow graphs in fig. 3.14 and the vertical offsets of the graphs in fig. 3.15. These errors and their positioning in the time series flow pattern highlights one weakness in this approach to recovering flow parameters. By using Tikhonov regularisation and a high regularisation parameter additional smoothness is enforced on the flows which may obscure features that are highly localised or occur at higher frequencies. In this case the initial transient behaviour of the flows inflating compartments from a partially collapsed state is dampened during the initial frames. However, decreasing the regularisation hyperparameter too far can result in highly oscillatory solutions, motivating our use of the L-curve method to choose the hyperparameter.

This effect on the transient is demonstrated further by examining the norms of errors in the flow recovery. To examine these errors quantitatively we will look at the L^2 norm applied to the errors in both flows and volumes. This will be done for the full ventilation recovery time as well as a time interval excluding an initial transient relaxation time. We will show the distributions of these error norms including the maximum, minimum, mean and standard deviation (STD) as produced by the thousand realisations of voltage noise described in algorithm 3.1.



Figure 3.14: Graphs comparing the simulated and recovered flows in each compartment. True simulated values are shown as a dashed blue line, while reconstructed values are a solid black line.

Table 3.2 shows the distribution of the rescaled L^2 norm applied to the flow for the whole simulated time period

$$Error = \frac{\left[\int_0^{30} (\dot{v}_i - \dot{y}_i)^2 dt\right]^{\frac{1}{2}}}{\left[\int_0^{30} (\dot{y}_i)^2 dt\right]^{\frac{1}{2}}},$$
(3.10)

where \dot{v}_i is the recovered flow and \dot{y}_i is the simulated flow for compartment *i*. Examining the errors in this way it appears that there is a much greater level of relative error in compartments 3 and 4 than compartments 1 and 2. This corresponds well to the observation that the transients in these compartments were not recovered as shown in fig. 3.14. Comparing these error values to those of the flow limited to exclude the first 2.5 s emphasises that the flow recovery errors are dominated by the transient behaviour. Table 3.3 shows the distribution of the rescaled L^2 norm applied to the flow after the initial 2.5 s in which the



Figure 3.15: Graphs comparing the simulated and recovered volumes in each compartment. True simulated values are shown as a dashed blue line, while reconstructed values are a solid black line.

transient effect dominates

$$Error = \frac{\left[\int_{2.5}^{30} (\dot{v}_i - \dot{y}_i)^2 dt\right]^{\frac{1}{2}}}{\left[\int_{2.5}^{30} (\dot{y}_i)^2 dt\right]^{\frac{1}{2}}}.$$
(3.11)

While the relative errors and standard deviations appear to rise in some compartments, this can be attributed to the removal of high flow volumes in the first 2.5 seconds. In these compartments high flow volumes in the initial relaxation time disproportionately contribute to the L^2 norms of the simulated flows, which are used for normalisation. Excluding the relaxation window for the transient drops the total error in compartments 3 and 4 down to the same order of magnitude as errors in the other compartments.

Table 3.2: Distribution of the L^2 error norm applied to the recovered flows for full simulated time frame. Values have been normalised against the norm of the simulated flows for each respective compartment to aid in comparison as described by eq. (3.10).

Comp. No.	Min	Max	Mean	STD
	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$
1	4.04	10.45	6.70	1.09
2	4.06	16.60	8.73	1.80
3	14.68	19.77	16.66	0.86
4	45.03	54.63	49.48	1.55

Table 3.3: Distribution of the L^2 error norm applied to the recovered flows excluding reconstructions from relaxation time. Values have been normalised against the norm of the simulated flows for each respective compartment to aid in comparison as described by eq. (3.11).

Comp. No.	Min	Max	Mean	STD
	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$
1	2.89	12.98	7.13	1.74
2	2.74	19.87	7.64	2.07
3	2.81	13.61	6.41	1.57
4	3.84	15.45	8.45	1.75

This transient error effect is not so pronounced on volume reconstructions. Table 3.4 shows the distribution of the rescaled L^2 norm applied to the volumes for the whole simulated time period

$$Error = \frac{\left[\int_0^{30} (v_i - y_i)^2 dt\right]^{\frac{1}{2}}}{\left[\int_0^{30} (y_i)^2 dt\right]^{\frac{1}{2}}},$$
(3.12)

where v_i is the recovered volume and y_i is the simulated volume for compartment *i*. The table shows that the errors in the volume recovery are much lower than the errors found in flow recovery. This could be due to the fact that the flows

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Table 3.4: Distribution of the L^2 error norm applied to the recovered volumes for full simulated time frame. Values have been normalised against the norm of the simulated volumes for each respective compartment to aid in comparison as described by eq. (3.12).

Comp. No.	$ Min (\times 10^{-2}) $	$\max_{(\times 10^{-2})}$	$Mean (\times 10^{-2})$	$\begin{array}{c} \text{STD} \\ (\times 10^{-2}) \end{array}$
1	0.46	4.72	1.38	0.61
2	0.51	4.65	1.39	0.62
3	0.49	4.96	1.40	0.67
4	1.37	5.89	2.42	0.62

are integrated to produce the volumes, meaning that the error values shown in table 3.4 are equivalent to a rescaled evaluation of the datafit term in eq. (3.9). As the datafit term is an explicit part of the differentiation step it is expected that the errors in volume recovery should be smaller than those for flow reconstruction.

The speed with which these flows can be computed is more encouraging. Although the initial differentiation step took 0.52 seconds, possibly due to Matlab's *just-in-time compilation*, this dropped to between 113 and 198 milliseconds for all subsequent runs. Similarly the time taken to normalise the differentiated values, converting to volumes and flows, was initially 49 milliseconds but dropped to between 3.8 and 6.9 milliseconds. This implies that clinicians could be presented with visual representations of a period of regional ventilation within around 0.2 seconds of post processing time.

Both the levels of accuracy and processing time are also encouraging for the further development of the parameter recovery described in the next section as well as providing an opportunity to examine ventilation control in chapter 4.

3.4 Parameter recovery

The link between regional ventilation parameters and EIT reconstructions has been examined before. Czaplik et al. [105] compared regional tidal variations in EIT to measurements taken through endoscopic microscopy. Through comparison to regional pressure volume loops they found a link to regional compliance, which is the reciprocal of the elastance values used in this chapter. However, despite demonstrating a correlation between regional compliance changes and impedance measurements they did not attempt to use impedance to recover compliance. Therefore, given the recovered ventilation distributions found by techniques in section 3.3, the next obvious step is to attempt recovery of not only elastance but also resistance to allow patient specific modelling of mechanical ventilation.

In section 3.4.1 we present the model specific linear regression matrix required to recover parameters in the model from section 3.1. This formulation has been reported in conference proceedings [99] and by Crabb [79, chapter 6]. In section 3.4.2 we discuss the conditions under which parameters should be recoverable from EIT measurements. Specifically we present a proof that the regression matrix has full rank when at least one compartment in the model ventilates out of phase with the others. In section 3.4.3 we demonstrate the recovered parameters obtained through difference imaging modelled EIT at 100 SNR.

3.4.1 Linear regression matrix

The smoothed flows and volumes generated in section 3.3 can be used in a parameter estimation problem to find the mechanical ventilation parameters E_i and R_i for each compartment and airway through a process of multiple linear regression similar to that described in [80, section 3.2.1].

As in section 3.1 the governing equations for this inversion can be derived from eq. (3.2). However, unlike in eq. (3.3), the parameters of resistance and elastance are treated as the dependent variables while the values of compartmental flow and resistance are known parameters. This allows the system to be reformulated as a single matrix multiplication $M\mathbf{x} = \mathbf{P}$, in which the matrix M is composed of copies of the time series values of flows and volumes while entries of the target vector \mathbf{x} are the desired parameters and \mathbf{P} contains copies of the pressure series.

Using over-tilde notation to denote quantities which have been recovered in section 3.3, denote $\tilde{\mathbf{Q}}$ as a vector of length S containing the sum of the smoothed compartmental flows, and build matrices \tilde{M}_i , with dimension $S \times 2$, and vectors $\tilde{\mathbf{P}}$ of length S in the form

$$\tilde{M}_{i} = \begin{pmatrix} \tilde{v}_{i}(t_{1}) & \dot{\tilde{v}}_{i}(t_{1}) \\ \vdots & \vdots \\ \tilde{v}_{i}(t_{S}) & \dot{\tilde{v}}_{i}(t_{S}) \end{pmatrix} \qquad \tilde{\mathbf{P}} = \begin{pmatrix} P(t_{1}) - P_{0} \\ \vdots \\ P(t_{S}) - P_{0} \end{pmatrix}, \qquad (3.13)$$

with S denoting the number of time samples. Using $\tilde{\mathbf{Q}}$, \tilde{M}_i and $\tilde{\mathbf{P}}$ and block matrix notation, eq. (3.2) can be reformulated as a $4S \times 9$ overdetermined system $M\mathbf{x} = \mathbf{P}$ with the form

$$M = \begin{bmatrix} \tilde{\mathbf{Q}} & \tilde{M}_{1} & 0 & 0 & 0 \\ \tilde{\mathbf{Q}} & 0 & \tilde{M}_{2} & 0 & 0 \\ \tilde{\mathbf{Q}} & 0 & 0 & \tilde{M}_{3} & 0 \\ \tilde{\mathbf{Q}} & 0 & 0 & 0 & \tilde{M}_{4} \end{bmatrix}, \qquad \mathbf{x} = \begin{pmatrix} R_{0} \\ E_{1} \\ R_{1} \\ E_{2} \\ R_{2} \\ E_{3} \\ R_{3} \\ E_{4} \\ R_{4} \end{pmatrix}, \qquad \mathbf{P} = \begin{pmatrix} \tilde{\mathbf{P}} \\ \tilde{\mathbf{P}} \\ \tilde{\mathbf{P}} \\ \tilde{\mathbf{P}} \end{pmatrix}, \qquad (3.14)$$

which can be solved by a Moore-Penrose generalised inverse to give a least squares solution

$$\tilde{\mathbf{x}} = (M^T M)^{-1} M^T \mathbf{P}, \qquad (3.15)$$

motivated by the assumption of gaussian noise in measurements of voltage and pressure.

This formulation provides a framework for recovering parameters from ventilation measurements using a general pressure control for mechanical ventilation. However, it still remains to be determined under what circumstances this method will be guaranteed to produce a unique solution. This question is examined in section 3.4.2 which specifies criteria on the model parameters to ensure recoverability.

3.4.2 Recoverability discusion

As mentioned in section 3.1.2 one of the criteria for choosing the values of resistance and elastance used for the ventilation and parameter recovery tests in this chapter was that they be recoverable through the method in section 3.4.1. To do this they have been chosen such that the matrix in eq. (3.14) has full column rank. To find such values we have defined the following theorem. **Theorem 1.** For periodic pressure profiles the system matrix M shown in eq. (3.14) has linearly independent columns so long as the parameter pairs (R_i, E_i) are not all multiples of each other.

This theorem is important and novel as it provides the first evidence that dynamic, region-specific parameters of elastance and resistance may be recovered for lung ventilation through a non-invasive bedside imaging modality.

Proof. The simplest way to prove parameters are recoverable is to show that the system matrix retains full column rank for all possible ventilation profiles. In the case of a compartmental model with N compartments this full rank is 2N + 1. It is simple to show that the rank of this matrix must be at least N by the block structure of the matrix. We split the matrix into a tracheal section, containing copies of the time series flow at the ventilator to produce a vector of length NS

$$\begin{pmatrix}
\tilde{\mathbf{Q}} \\
\tilde{\mathbf{Q}} \\
\vdots \\
\tilde{\mathbf{Q}} \\
\tilde{\mathbf{Q}}
\end{pmatrix},$$
(3.16)

where S is the total number of time samples, and a blockwise diagonal section containing regional flow and volume series in each block

$$\begin{bmatrix} \tilde{M}_{1} & 0 & \cdots & 0 & 0 \\ 0 & \tilde{M}_{2} & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & \tilde{M}_{N-1} & 0 \\ 0 & 0 & \cdots & 0 & \tilde{M}_{N} \end{bmatrix}$$
(3.17)

Due to this block structure we see that at least N columns of the matrix must be linearly independent so long as none of the submatrices \tilde{M}_i are equal to zero. These degenerate cases correspond to compartments with resistance and elastance values so high that no air can be forced into the compartment, in which case the compartment can be identified easily and excluded from the model. In such a case N now refers to the number of recruited compartments. This argument shows that the rank of the full matrix M is at least N.

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To go further it is necessary to make assumptions on the structure of the time series samples themselves. Namely that:

- 1. the volumes and flows have components which are periodic in nature,
- 2. the sample rate is high enough to capture this periodicity and to allow us to consider each time series as approximately equal to a smooth periodic function of time.

Under these assumption, for two columns within a block M_i to be linearly dependent the time functions would have to satisfy the equation

$$a\mathbf{v_i} + b\dot{\mathbf{v}_i} = 0, \tag{3.18}$$

for real valued a and b not equal to zero. This produces a contradiction as the vector \mathbf{v}_i correspond to samples of a non-zero periodic function which cannot satisfy eq. (3.18). Therefore under the assumptions above the rank of the system matrix must be at least 2N.

Finally, using the assumptions above, it is possible to obtain conditions for the system matrix to have full rank. Under these assumptions, the equations

$$a_j \sum_{i=0}^{N} \dot{\mathbf{v}}_i + b_j \dot{\mathbf{v}}_j + c_j \mathbf{v}_j = 0,$$

where v_j is the time series vector for air volume in compartment j, cannot all hold for j = 1 : N with a_j, b_j and c_j not all zero for the columns of the system matrix to be linearly independent. By Fourier transforming this equation it can be shown that the constants c_j must always be zero as the air volumes are non negative, meaning that the functions $\mathbf{v_j}$ have non trivial zero frequency components while the other functions are derivatives and do not.

So for the columns of the system matrix to be linearly dependent the equations

$$a_j \sum_{i=0}^N \dot{\mathbf{v}}_i + b_j \dot{\mathbf{v}}_j = 0,$$

must hold for all j = 1: N. This implies that the only situation in which the system matrix does not have full rank is when all the regional flows are multiples of each other. However, this only occurs when the ODE parameters are also proportional to each other.

Theorem 1 means that, although there is not always a unique solution to eq. (3.14), we will always be able to find the regional elastance values and obtain ratios between resistances in different compartments, using any periodic pressure profile. It also means that in the most dangerous situations for lung health, where successive compartments are out of phase with each other, there will always be a unique least squares solution.

Once the system matrix is built from reconstructed flows, the problem in eq. (3.14) becomes a total least squares problem (TLS). TLS problems arise where a least squares solution is needed to a system with unknown errors in both the measured data vector and the system matrix. Unconstrained solutions to this type of problem can be computed using singular value decompositions [106]. However, applying these techniques to the problem in eq. (3.14) was found to produce larger errors in reconstructed values. This is possibly due to the block structure and sparsity of the system matrix in this case. It is possible that the use of constrained total least squares (CTLS) techniques [107, 108] may improve the parameter recovery.

In TLS techniques, the least squares estimation problem is posed on a matrix system of the form

$$(M + \Delta M)\boldsymbol{x} = \boldsymbol{b} + \boldsymbol{\Delta}\boldsymbol{b},$$

where ΔM and Δb are errors in the formulation of the system matrix and measured data respectively. In CTLS techniques, Δb and the columns of ΔM are assumed to be linear combinations of some common noise vector, with this linear relationship known explicitly. Therefore in this formulation the zero entries in our regression matrix could be specified to have no noise component, while the relationship between the errors for volumes and their derivatives could be explicitly specified. However, implementation of these techniques was deemed beyond the scope of this thesis.

3.4.3 Parameter recovery from EIT at 100 SNR

In this section we demonstrate the process of parameter recovery using conductivity timeseries with noise added through the difference imaging noise techniques outlined in section 3.2.1. To do this tests were performed on the conductivity time series generated for ventilation by a sinusoidal pressure profile of the 4 compartment ODE lung model outlined in section 3.1. The parameters used for this ventilation and conductivity forward solve can be found in table 3.1, the pressure and ventilation profiles can be found in fig. 3.4 and the resulting conductivity timeseries can be found in fig. 3.5.

As with the ventilation distribution recovery tests in section 3.3.2, 1000 tests were performed in which a noisy conductivity series was generated using difference EIT at an SNR of 100 (40 dB) and the air volumes and flows were reconstructed. The testing procedure for this ventilation reconstruction is shown in algorithm 3.1. To generate the results in this section, in each test the reconstructed volumes and flows were used to generate the system matrix shown in eq. (3.14), which in turn was used to generate recovered ventilation parameters through eq. (3.15). For clarity, an outline of the testing procedure is shown in algorithm 3.2. This testing procedure resulted in the generation of 1000 recovered parameter sets.

Alg	gorithm 3.2 Parameter recovery testing procedure
1:	Set number of time samples S
2:	Set number of tests N
3:	
4:	Solve ODE for air volumes
5:	Generate conductivity time series from volumes
6:	Generate reference voltage V_0
7:	
8:	% Perform tests
9:	for $i \leq N$ do
10:	for $j \leq S$ do
11:	Generate noisy voltage V_n from V_0
12:	Perform difference EIT on $V_n - V_0$
13:	Add reconstructed noise to conductivity sample j
14:	Take reciprocal to generate noisy resistivity
15:	end for
16:	recover ventilation distribution i from noisy resistivity samples
17:	generate regression matrix i from recovered ventilation distribution
18:	generate recovered parameter set i using the regression matrix
19:	end for

Both the simulated parameters and the distribution of the recovered parameters are shown in fig. 3.16. Elastance values were generally recovered much more



Figure 3.16: Charts showing the simulated parameter values (bars) and the distribution of their recovered values (lines). The vertical lines are marked at the minimum, maximum and mean values recovered as well as points two standard deviations from the mean.

accurately than compartmental resistance values, while the resistance values were harder to recover in compartments with higher elastance. In order to compare the recovery of these different parameters a time constant was calculated for each compartment as the total recovered series resistance leading to a compartment, including tracheal resistance, divided by the recovered compartmental elastance,

$$\frac{R_0 + R_i}{E_i}.$$
(3.19)

These time parameters have clinical relevance, as time constant ratios of flow rate to lung volume can be used as a measure of lung health [109]. The distribution of these recovered time constants is shown visually in fig. 3.17 and numerically in table 3.5.

Due to the systematic overestimation of the compartmental resistances, these time constants were overestimated by between 0.14 - 0.17 seconds. It is not clear why this overestimation has occurred as tests at higher SNR levels display the same behaviour, implying that this is not solely due to measurement errors. However, it is encouraging that the overestimation of time constants appears relatively



Figure 3.17: Time constants for SNR 100 recons.

Table 3.5: Table showing the errors in recovery of the time constant for each compartment. The standard deviation for the recovered parameters is shown as a percentage of the true values.

Comp. No.	True Value	Mean	Error	STD
1	1.5	1.64	0.14	0.058
2	2.5	2.63	0.13	0.074
3	0.67	0.84	0.17	0.060
4	0.6	0.75	0.15	0.066

consistent. The distributions of these recovered parameters display standard deviations lower than 0.08 s, less than 11% of the values for each compartment. Hence, while time constants were not recovered perfectly, the near constant bias in recovery allows the compartments relative health to be compared.

The low error ranges for elastance recovery are also encouraging as they may be easily converted to the more common measure of compliance, which is currently used for guiding recruitment manoeuvres. These regional measures were again recoverable within a short time, taking between 0.3 ms and 6.6 milliseconds to compute after the flows had been recovered. This implies that the parameter recovery technique is a natural choice for extending the volume and flow recovery in a clinical setting. However, before further development of these methods it is necessary to see how they behave with higher levels of measurement noise and increased errors in EIT reconstruction. These will be discussed in section 3.5.

3.5 Sensitivity to EIT changes

In sections 3.3 to 3.4 we have demonstrated techniques to recover both ventilation distributions and ODE model parameters from ideal EIT at an SNR of 100 (40 dB). This testing provides a first proof of concept in the coupling of EIT to ventilation modelling. The next step in verifying the feasibility of this work flow is to test its behaviour as the quality of the EIT reconstructions is lowered.

To perform this sensitivity analysis we have tested the ventilation and parameter recovery techniques against increasing levels of voltage measurement noise as well as changes to the EIT reconstruction algorithm and model segmentation. In section 3.5.1 we show the effects of changing noise levels on conductivities recoverable through the idealised EIT noise generation methods from section 3.2.1. We then focus on the conductivity time series recoverable through pseudo-absolute imaging as described in section 3.2.2.

In section 3.5.2 we show the recovered ventilation and parameter distributions from pseudo absolute reconstructions where the segmentation of compartments for the reconstruction exactly matches the mesh used for voltage generation. We then examine how errors in this segmentation effect the recovery process in sections 3.5.3 to 3.5.4.

3.5.1 Signal to Noise Ratio

In this section we test the sensitivity of the ventilation and parameter recovery techniques to EIT modelled noise. To do this, tests were performed at signal to noise ratios of 50-100 in increments of 10 SNR. Despite an SNR of 40 dB being considerably lower than the practical limit of EIT measurement accuracy of roughly 100 dB [98], the choice was made to examine lower signal qualities in order to determine when the post-processing techniques are likely to fail. While an SNR interval of 50-100 corresponds to a range of 34-40 dB it also corresponds to a doubling in the magnitudes of the noise values applied.

3.5. SENSITIVITY TO EIT CHANGES

To perform this sensitivity analysis, at each SNR reconstructions were performed for each time sample of conductivities as described in section 3.2.1. This was repeated for one thousand realisations of voltage noise for each time sample at each noise level using the Matlab pseudo-random number generator. The resulting noisy conductivity time series were used in the ventilation and parameter recovery procedures from sections 3.3 to 3.4 and we compare the resulting distributions here. Outlines of these testing procedures for individual SNR levels can be found in algorithms 3.1 and 3.2

As shown in fig. 3.18 the change between 100 SNR, as used in previous sections, and 50 SNR noise in EIT voltage measurements has a marked effect on the resulting bulk resistivity time series. However, as described in section 3.3.1, the



Figure 3.18: Comparison of the noisy resistance time series produced by reconstruction of difference EIT at both 100 SNR (left) and 50 SNR (right).

numerical differentiation techniques we are using have been designed to account for varying levels of noise through the use of L-curve methods to determine the correct regularisation hyperparameters. The effect of the rising levels of noise on the parameters chosen by this L-curve method can be seen in table 3.6. This table shows the mean hyperparameter value chosen for each compartment across the thousand tests at each noise level. As expected the higher the level of noise the more regularisation was required.

The increase in regularisation results in similar qualitative behaviour for the recovered ventilation profiles of both the volumes and flows at the varying noise levels. The qualitative behaviour of these recoveries can be seen in figs. 3.19 to 3.20 which show volume and flow recoveries for each compartment for one realisation of voltage noise. As with the ventilation recovery at 100 SNR shown

SNR	Compartment number						
	1	1 2		4			
100	1.506	1.416	1.373	1.434			
90	1.581	1.485	1.440	1.499			
80	1.668	1.565	1.519	1.566			
70	1.771	1.663	1.611	1.642			
60	1.893	1.779	1.728	1.732			
50	2.055	1.936	1.873	1.830			

Table 3.6: Comparison of mean differentiation hyperparameters required for each compartment at varying levels of noise.

in section 3.3.2 the qualitative behaviour of these recovered distributions appears similar to that of the distributions generated in the ventilation forward solve. The magnitudes of tidal variations appear similar as does the period of ventilation. Similarly to the 100 SNR tests the most apparent qualitative error is the inability of the method to accurately track the initial few seconds of large transient behaviour.

The differences between ventilation distributions recovered at each noise level become more apparent when examined quantitatively. Table 3.7 shows the distribution of the L^2 errors in the recovered volumes at each noise level. These error

Table 3.7: Comparison of L^2 errors in recovered volumes for different SNR levels. Values have been normalised against the norm of the simulated volumes as described in eq. (3.20).

SNR	$ \text{Min} \\ (\times 10^{-2}) $	$\max_{(\times 10^{-2})}$	$Mean (\times 10^{-2})$	$\begin{array}{c} \text{STD} \\ (\times 10^{-2}) \end{array}$
100	0.91	4.64	1.51	0.52
90	0.96	5.02	1.61	0.56
80	1.01	5.49	1.74	0.62
70	1.08	6.06	1.92	0.69
60	1.15	7.15	2.19	0.80
50	1.34	8.80	2.62	0.98



Figure 3.19: Graphs comparing the phantom and recovered volumes in each compartment for ideal EIT at 50 SNR. Volume values generated in the ventilation forward solve are shown as a dashed blue line, while reconstructed values are a solid black line.

norms are calculated as

$$Error = \frac{\left[\sum_{i=1}^{4} \left\{ \int_{0}^{30} (v_{i} - y_{i})^{2} dt \right\} \right]^{\frac{1}{2}}}{\left[\sum_{i=1}^{4} \left\{ \int_{0}^{30} (y_{i})^{2} dt \right\} \right]^{\frac{1}{2}}},$$
(3.20)

where v_i are the recovered volumes and y_i are the simulated volumes for compartment *i*. As expected the overall errors measured in this way show an increase as the SNR is lowered.

One encouraging feature of the values shown in table 3.7 is that the mean, standard deviation and maximum errors shown for the 50 SNR reconstructions do not reach twice the values for the 100 SNR reconstructions. In moving between 100 SNR and 50 SNR the level of voltage noise doubles so the fact that the L^2 errors don't attain that level of increase emphasises how effective the increased



Figure 3.20: Graphs comparing the phantom and recovered flows in each compartment for ideal EIT at 50 SNR. Flow values generated in the ventilation forward solve are shown as a dashed blue line, while reconstructed values are a solid black line.

regularisation has been in reducing recovery errors. However, it should be noted that the effect may become less pronounced if a larger number of voltage noise samples is taken to generate the recovered distribution or could be due to the inclusion of the transient relaxation periods in these measures.

The parameter recovery from section 3.4 behaves similarly to the ventilation recovery under increasing levels of noise. As expected from the results in section 3.4.3 the recovery of elastance values was most stable under the increasing noise values. The mean and standard deviation for each compartmental elastance value can be found in table 3.8. As expected the mean values remain close to the values used in the ventilation forward solve but the standard deviation increases from approximately 1% of the value to approximately 2% emphasising that this parameter is stable under the proposed recovery method.

A similar pattern can be seen in the recovery of the resistance parameters shown in table 3.9. Again the mean recovered values remain close to the correct value while the standard deviation nearly doubles. However, this is more of a problem with resistance than with elastance as, for the least resistive compartment, the standard deviation increases from 22% of the true value to 42%. In fact

	E_1		E_1 E_2 E_3		E	$E_3 E_4$		4
SNR	mean	STD	mean	STD	mean	STD	mean	STD
True	10.00	-	10.00	-	15.00	-	25.00	-
100	9.94	0.10	9.92	0.11	14.91	0.16	25.38	0.29
90	9.94	0.12	9.93	0.12	14.92	0.18	25.40	0.32
80	9.95	0.13	9.94	0.14	14.94	0.20	25.44	0.36
70	9.96	0.15	9.95	0.16	14.96	0.23	25.49	0.41
60	9.98	0.17	9.98	0.19	15.01	0.27	25.59	0.48
50	10.01	0.21	10.03	0.22	15.09	0.33	25.76	0.59

Table 3.8: Comparison of recovered elastances from difference runs for different levels of noise.

one instance of measurement noise produced a single negative value of resistance for this compartment. This emphasises that the recovery of resistances from these methods can be much more inaccurate than for elastance and may require more advanced parameter fitting techniques.

This does not mean that the resistance parameters cannot be useful. As mentioned in section 3.4.3 another useful measure in gauging the relative health and behaviour of compartments can be found in the time constant ratio between elastance and resistance. A comparison of these values between reconstructions at 100 SNR and 50 SNR can be seen in fig. 3.21. Similarly to the results in



Figure 3.21: Charts comparing Time constant recovery at 100 SNR (left) and 50 SNR (right).
	R	R_0		1	R	R_2		R_3		4
SNR	mean	STD	mean	STD	mean	STD	mean	STD	mean	STD
True	5.00	-	10.00	-	20.00	-	5.00	-	10	-
100	4.14	0.25	12.18	0.78	22.00	0.92	8.35	1.12	14.83	1.92
90	4.16	0.28	12.09	0.86	21.89	1.01	8.24	1.24	14.63	2.13
80	4.20	0.31	11.98	0.97	21.75	1.14	8.09	1.39	14.35	2.39
70	4.26	0.35	11.83	1.09	21.55	1.29	7.88	1.57	13.97	2.71
60	4.34	0.41	11.60	1.25	21.27	1.49	7.56	1.81	13.40	3.13
50	4.47	0.48	11.24	1.47	20.84	1.75	7.07	2.12	12.51	3.68

Table 3.9: Comparison of recovered resistances from difference runs for different levels of noise.

section 3.4.3 the time constants remain close to the correct values and most importantly stay within similar ratios to each other. Which is encouraging for the use of recovered elastance and resistance values in further modelling of lung function.

From this analysis we can see that the recovery of ventilation distributions remains stable under increasing levels of voltage measurement noise as does the recovery of both elastance values and time constants. However, the recovery of ventilatory resistance values is less stable and may impact their use in further lung modelling. This will be discussed further in section 4.5.

3.5.2 Pseudo-absolute signal recovery

This section shows the results of ventilation and parameter recovery when both the conductivity noise and signal are reconstructed through the use of pseudoabsolute EIT at an SNR of 100 as described in section 3.2.2. As with the ideal simulations of EIT in the last section the results in this section all three meshes used had four matching cylindrical inclusions defined explicitly in the mesh. This corresponds to performing EIT with an exact segmentation of the lung regions. Therefore the grouping constraints on the absolute solve and the regions used for aggregating the difference imaging match the compartments exactly.

3.5. SENSITIVITY TO EIT CHANGES

Comparing the bulk resistivity time series produced by ideal EIT and pseudoabsolute EIT at 100 SNR in fig. 3.22 it appears that the process of pseudoabsolute reconstruction actually reduces the effect of random measurement noise on the recovered time series. However, it can be seen that the time series no



Figure 3.22: Comparison of the noisy resistance time series produced by difference EIT at 100 SNR (left) and pseudo-absolute EIT at 100 SNR (right).

longer all start at the same value for time zero. This is due to the fact that the absolute reconstructed frame used as a reference was simulated at mid inhalation. Therefore errors in the linearised difference solve for the first reconstructed frame produce different aggregated values for the compartments.

Examining the qualitative behaviour of the recovered volumes and flows from these resistance time series can see similar features to the recovered flows from ideal EIT. Figures 3.23 to 3.24 show recovered volumes and flows respectively.

As with ideal EIT many of the general qualitative features have been captured, the magnitudes of the tidal volumes appear to have been recovered well in two of the four compartments and the relative magnitudes of the volumes in each compartment are close. We also see that, in a similar way to the ideal EIT tests, the first few seconds of transient behaviour in the compartmental flows do not appear to have been captured.

Unlike the ideal absolute EIT however, some features are different in the recovered ventilation distributions. For example the peaks of the volumes in some compartments seem to have been shifted slightly and the volumes in two compartments appear to differ in magnitude from the correct values. Both of these changes could be explained by the use of a smoothing Laplace prior in the difference imaging step as described in section 2.1.3. Due to this prior the



Figure 3.23: Graphs comparing the simulated and recovered volumes in each compartment for pseudo-absolute EIT with exact segmentation. True simulated values are shown as a dashed blue line, while reconstructed values are a solid black line.

relative values in neighbouring compartments can affect each other causing the phase shift. Similarly some of the conductivity changes may be moved outside of the regions used to aggregate compartmental values. These qualitative errors in the ventilation recovery result in the overall increase in the quantitative errors, as shown in table 3.10, despite the apparent noise seen in fig. 3.22.

Table 3.10: Comparison between reconstruction types of errors produced in reconstruction of compartmental volumes measured in the L^2 norm as described in eq. (3.20).

Recon Type	$ Min (\times 10^{-2}) $	$Max (\times 10^{-2})$	$Mean (\times 10^{-2})$	$\begin{array}{c} \text{STD} \\ (\times 10^{-2}) \end{array}$
Ideal	0.91	4.64	$1.51 \\ 4.93$	0.52
Absolute	1.60	12.38		1.89

As expected this increased error in the recovered ventilation distribution does affect the recovery of parameters as shown in fig. 3.25. As with the ideal re-



Figure 3.24: Graphs comparing the simulated and recovered flow rates in each compartment for pseudo-absolute EIT with exact segmentation. True simulated values are shown as a dashed blue line, while reconstructed values are a solid black line.

constructions described in the previous section the elastance values were again recovered comparatively well. The range and standard deviation of the recovered elastances was increased as expected but they remain distributed around the correct values relatively tightly. However, the resistance values were not as well recovered with Resistances less than 10% of the correct value given for R_3 in 1.6% of tests and R_4 in 1% of tests.

Even with this large error in resistances though the distribution of the time constants was still relatively well recovered as shown by the comparison of time constants recovered from ideal and pseudo-absolute EIT in fig. 3.26. As expected the range of recovered parameters for each of these time constants was increased when using pseudo-absolute reconstruction. However, the values for each compartment retain clear differences from each other allowing the relative health of compartments to be assessed with both ideal and pseudo-absolute EIT.



Figure 3.25: Charts showing the distribution of recovered elastances (left) and resistances (right).



Figure 3.26: Chart comparing the time constant recovered from ideal EIT at 100 SNR (left) and from pseudo-absolute reconstructions with exact segmentation at 100 SNR (right).

These results are encouraging for the development of ventilation and parameter recovery from EIT. The general qualitative behaviour of the recovered ventilation was captured well while elastance values and time constants were recoverable using multiple linear regression. The errors in resistance recovery is less encouraging, however, improvements could be possible under changes to the EIT reconstruction algorithm or a more advanced parameter fitting method.

We will examine some of the effects of changing the EIT reconstruction in the next section.

3.5.3 Changes to mesh segmentation

In practical EIT it is unlikely that it will be possible to exactly segment and mesh the lungs accurately for reconstruction. For this reason we examine what happens to the recovered ventilation distributions and parameters under errors in this segmentation. In particular we describe two possible segmentation errors. The first is a segmentation which has the correct shape, in this case circular cylinders, but is larger in radius by 10%. The second segmentation error is in the shape itself. To test this case we have used elliptic cylinders for the reconstruction segmentation.

Using the circular cylinder segmentation with increased radius the reconstructed ventilation distributions appear largely similar to the reconstructions with exact segmentation. The volumes shown in fig. 3.27 again follow the correct ventilation pattern quite closely. In fact, as can be seen from table 3.11, the



Figure 3.27: Graphs comparing the simulated and recovered volumes in each compartment for pseudo-absolute EIT with inexact segmentation consisting of the correct shape estimation but a radius increased by 10%.

mean and standard deviation of the L^2 errors in the volumes is decreased for this segmentation. This improvement in the volume recovery suggests that the smoothing action of the Laplace prior may be responsible for some of the errors as mentioned in the previous section.

Radius	$ \text{Min} \\ (\times 10^{-2}) $	$\max_{(\times 10^{-2})}$	$Mean (\times 10^{-2})$	$\begin{array}{c} \text{STD} \\ (\times 10^{-2}) \end{array}$
Exact	1.60	12.38	4.93	1.89
+10%	2.35	10.25	4.82	1.39

Table 3.11: Comparison of errors produced in reconstruction of compartmental volumes as measured in the L^2 norm, described in eq. (3.20), when changing the radius of the lung segmentation for reconstruction.

Some improvement can also be seen in the distributions of the recovered parameters. Figure 3.28 shows modest improvement in the distributions of the recovered elastances but the improvement is more apparent in fig. 3.29 comparing recovered resistances. While these recovered resistance values are still not



Figure 3.28: Charts comparing the elastance values recovered with exact segmentation (left) and with an inexact segmentation consisting of the correct shape with increased radius (right).

accurate, they now have a lower variance and do not become negative allowing them to more accurately show the health of the lung region. This is emphasised by the time constant values shown in fig. 3.30 which now show a more consistent bias and lower variance.



Figure 3.29: Charts comparing the resistance values recovered with exact segmentation (left) and with an inexact segmentation consisting of the correct shape with increased radius (right).



Figure 3.30: Charts comparing the time constant values recovered with exact segmentation (left) and with an inexact segmentation consisting of the correct shape with increased radius (right).



Figure 3.31: Comparison of extruded meshes with correct segmentation and incorrect segmentation consisting of elliptical cylinders.

The second change we tested to the segmentation used in the pseudo-absolute reconstructions replaced the circular cylindrical regions with elliptic cylinders. These cylinders, shown in the mesh on the right hand side of fig. 3.31, were extruded from ellipses with a minor axis equal to the radius of the true cylindrical lung region and a major axis which was 20% larger. This ensured that the segmented region included the true lung regions.

Unlike with the previous segmentation the qualitative behaviour of the volumes recovered with this elliptic segmentation, shown in fig. 3.32 appears more noticeably different from the correct ventilation profile. Examining the L^2 error distributions for the ventilation profiles recovered using this segmentation scheme, shown in table 3.12, reveals that as expected it is less accurate than an exact segmentation as measured by the mean error. However, the decrease in

Table 3.12: Comparison of errors produced in reconstruction of compartmental volumes as measured in the L^2 norm, described in eq. (3.20), when changing the shape of the lung segmentation for reconstruction.

Segmentation	$ \text{Min} \\ (\times 10^{-2}) $	$\max_{(\times 10^{-2})}$	$\begin{array}{c} \text{Mean} \\ (\times 10^{-2}) \end{array}$	$\begin{array}{c} \text{STD} \\ (\times 10^{-2}) \end{array}$
Exact	1.60 4.02	12.38 10.80	4.93 5.90	1.89

the standard deviation and the reduction in the difference between the maximum and minimum errors suggests that this is a more stable segmentation for the EIT reconstruction step.



Figure 3.32: Graphs comparing the simulated and recovered volumes in each compartment for pseudo-absolute EIT with inexact segmentation consisting of elliptic cylinders completely enclosing the true circular cylindrical lung region.

This stability is supported further by the recovered parameters. As with the increased radius cylinder the large elliptic segmentation produced a modest improvement in elastance values and more stable estimates of resistance values. This resulted in the time constant values shown in fig. 3.33 which again show a more constant bias and greater stability than those recovered from an exact segmentation.



Figure 3.33: Charts comparing the time constant values recovered with exact segmentation (left) and with an inexact segmentation consisting of elliptic cylinders (right).

3.5.4 Segmentation size comparisons

The increase in stability of recovered ventilation distributions and parameters shown in the previous section indicates that the size of the segmented region rather than the shape may be the more important factor when determining if a good segmentation has been found. To confirm this further tests of both the circular and elliptic cylinder segmentations were performed.

Table 3.13 shows a comparison of the L^2 errors in recovered air volumes using circular cylinders with varying radii. As expected from the test in the previous

Recon Type	$ \text{Min} \\ (\times 10^{-2}) $	$\max_{(\times 10^{-2})}$	$Mean (\times 10^{-2})$	$\begin{array}{c} \text{STD} \\ (\times 10^{-2}) \end{array}$
'ExactSegmentation'	1.60	12.38	4.93	1.89
'IncrRad10pct'	2.35	10.25	4.82	1.39
'IncrRad20pct'	3.42	9.63	5.18	1.07
'DecrRada10pct'	5.66	21.83	9.77	2.62
'DecrRad20pct'	17.58	3341.50	40.31	116.60

Table 3.13: Comparison of the errors in recovered volumes, measured in the L^2 norm described in eq. (3.20), for different circular cylinder segmentation sizes

section the reconstructions from segmentations with increased radii showed increased errors but greater stability, implying that overestimating the size of the lung regions may be advantageous. However, decreasing the radii of the cylinders



Figure 3.34: Graphs comparing the simulated and recovered volumes in each compartment for pseudo-absolute EIT with inexact segmentation consisting of the correct shape estimation but a radius decreased by 10%.

produced large errors in the recovered ventilation. This also resulted in loss of much of the qualitative accuracy as shown in figs. 3.34 to 3.35. Similarly decreasing the minor and major axes of the elliptic cylindrical segmentation produced larger errors as well as shown in table 3.14.

Recon Type	Min	Max	Mean	STD
	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$
'ExactSegmentation'	1.60	12.38	4.93	1.89
'EliptLarge'	4.02	10.89	5.99	1.18
'EliptSmall'	7.25	20.66	10.80	2.08

Table 3.14: Comparison of the errors in recovered volumes, measured in the L^2 norm described in eq. (3.20), for different elliptic cylinder segmentation sizes.

The effect these segmentation size changes had on the recovery of parameters can be seen in the time constant values shown in tables 3.15 to 3.16 Again the larger segmentations showed some decrease in accuracy but improved stability while smaller segmentations produced wildly inaccurate parameters.



Figure 3.35: Graphs comparing the simulated and recovered volumes in each compartment for pseudo-absolute EIT with inexact segmentation consisting of the correct shape estimation but a radius decreased by 20%.

This demonstrates that, while the techniques in sections 3.3 to 3.4 are capable of producing qualitatively useful ventilation distributions and informative ventilation parameters, the size and shape of the segmentations used will affect how accurate and stable the results are. In particular, slight overestimation of the lung region produced more stable ventilation and parameter recovery. This is encouraging information for the practical implementation of pseudo-absolute EIT, as it will not be possible to exactly segment and track the position of the lungs throughout the breathing cycle.

3.6. CONCLUSION

	T_1		T_2		T_3		T_4	
Recon Type	mean	STD	mean	STD	mean	STD	mean	STD
TrueValues	1.50	-	2.50	-	0.67	-	0.60	-
'Exact'	1.35	0.08	2.14	0.10	0.67	0.10	0.59	0.12
'IncrRad10pct'	1.70	0.07	2.60	0.09	1.07	0.06	1.00	0.06
'IncrRad20pct'	1.76	0.08	2.67	0.10	1.10	0.06	0.99	0.06
'DecrRad10pct'	-0.03	0.25	0.51	0.21	-3.60	0.72	-7.12	1.11

Table 3.15: Comparison of recovered time constants from absolute runs using as size of segmented region changes.

Table 3.16: Comparison of recovered time constants from absolute runs using as shape of segmented region changes.

	T_1		T_2		T_3		T_4	
Recon Type	mean	STD	mean	STD	mean	STD	mean	STD
TrueValues	1.50	-	2.50	-	0.67	-	0.60	-
'EliptLarge'	1.68	0.09	2.56	0.11	0.97	0.06	0.82	0.05
'EliptSmall'	-1.30	0.31	0.38	0.15	-5.03	0.76	-10.38	1.43

3.6 Conclusion

In this chapter we have described models and techniques to both generate EIT measurements from ventilation models and recover ventilation distributions and parameters for those models from EIT reconstructions. We derived an ODE model for lung function which we used to produce time series values of conductivity. We demonstrated how both ideal absolute EIT and pseudo-absolute EIT could be simulated on these conductivity values to generate noisy conductivity time-series for use in testing post processing procedures. In section 3.3 we described how to recover regional air volumes and flows and proved that they could be used by the techniques in section 3.4 to fit parameters for our ODE lung model. Finally the results in section 3.5 show that our post processing techniques are stable enough under both measurement and modelling errors in EIT to provide useful information for clinicians monitoring care.

Chapter 4

Control

In the previous chapters we have demonstrated two important techniques for the real time monitoring of lung function. First we showed that it is possible to produce pseudo-absolute reconstructions of functional EIT in real time after a limited setup time in chapter 2. Development of this technique was motivated by the desire to couple EIT reconstructions to models of lung function in an attempt to make the use of EIT more useful to clinicians working in respiratory intensive care. This lead to the second important technique, discussed in chapter 3, whereby we recover not only regional ventilation distribution but also widely used and accepted measures of lung function in the form of regional pulmonary elastance and resistance.

In this chapter we investigate how our lung model and recovered parameters may be incorporated into control of mechanical ventilation. The recovery of these ventilation distributions and parameters are of themselves useful to clinicians. For example the fact that the magnitude of tidal volumes has been linked to patient mortality [4] implies that regional data on lung volume could be a useful indicator. Similarly the current use of compliance during *PEEP titration* [77], where an acceptable positive end expiratory pressure (*PEEP*) is determined by successive lowering of the PEEP level, implies regional compliance and resistance would be useful during recruitment manoeuvres. However, use of parameters in this manner would require experience and skill on the part of the clinician. Ideally we want to provide a procedural mechanism for incorporating our information into automatic controls. To begin incorporating EIT into the control of mechanical ventilators we first examine existing control procedures. Modern ventilators rely on both user input and feedback control techniques from control theory. Chatburn lists a hierarchy for the levels of user input and feedback control in his review of computer control systems [110]. The lowest level in this hierarchy is *set-point* control, in which the user defines a set pressure to be experienced by the patient. Due to the interaction between the patient's lung and the ventilator, the applied pressures may not be the same as those experienced by the patient's airways, so the ventilator uses measurements of the airway pressure as feedback to adjust the applied pressures accordingly.

A more advanced approach in Chatburn's hierarchy is to allow the computer to modify this pressure set-point based on optimising mathematical models of lung function in a scheme known as *optimal control*. There are many different approaches to building these optimal control schemes, however the one we examine here is known as *model predictive control*. In these techniques a simple model, often a linearisation, is used to predict the behaviour of a nonlinear system. A control is generated to optimise the behaviour of the linearised system over a limited time frame ignoring the likely changes in lung parameters between the start and end of the control procedure.

One example of such a model is given by Li and Haddad [82], where they track changes in pressure, volume flows and states between breathing periods for a simulated lung system. They then use a linear compartmental reference model for the lungs to adapt their pressure control using a *repetitive model predictive control* scheme. However, model based approaches such as this are limited by the availability of patient specific model parameters and in particular regional differences within the patient. This highlights the novelty and utility of the parameters from our observable EIT lung model, we test the feasibility of a patient-specific model-based control scheme in this chapter.

In section 4.1 we examine the model from chapter 3 to determine under what circumstances we may use control theory to produce pressure controls. In section 4.2 we describe some practical methods for building controls numerically. In section 4.3 we demonstrate that control techniques can be applied quickly to reduce gradients of pressure over small sections of existing controls. This is desirable as high gradients of pressure have been linked to increased epithelial stresses in the lungs by Bilek et al. [5]. In section 4.4 we design a framework for optimising the H^1 minimal controls with respect to clinically relevant outcomes. Finally in section 4.5 we perform a sensitivity analysis on the control methods to determine how they behave with parameters recovered through EIT at varying signal to noise ratios (SNR).

Throughout chapter will use (\cdot^*) to denote conjugate transpose as well as the transpose of real valued matrices and vectors to avoid confusion with exponents of time.

4.1 Controllability

Our aim is to develop techniques from control theory to incorporate the parameters and models from chapter 3 into control schemes for mechanical ventilation. However, before these can be examined it is necessary to confirm the *controllability* of the system of ODEs we are using. An important and novel result we will demonstrate in this section is that the system of ODEs from chapter 3 is controllable under a wide range of parameter values. This controllability tells us how effective control theory techniques can be for the given model and parameters. As the lung models we are using consist of a linear system of ODEs we will use the following two equivalent definitions of controllability throughout this chapter.

Definition 1. A controllable linear system of ODEs

$$\dot{\mathbf{y}} = A\mathbf{y} + B\mathbf{u},\tag{4.1}$$

is not algebraically equivalent to any linear system in which the state variables may be separated into one set of state variables which are directly affected by an input term and one set which is not affected by this input or the other set of state variables [111].

Definition 2. A controllable system can be steered from any state \mathbf{y}_0 at time t = 0 to any other state \mathbf{y}_T at time t = T by a control \mathbf{u} . In this general case \mathbf{y} is an n-dimensional function, A is an $n \times n$ state space matrix, B is an $n \times m$ state space matrix and \mathbf{u} is an m-dimensional control function [112, section 1.2].

4.1. CONTROLLABILITY

As we will explore further in the later sections of this chapter, control theory also provides techniques for generating the controls mentioned in the definition above. The controls corresponding to given initial conditions, target states and time constraints are not unique, but there exist closed form solutions providing the controls which are optimal under a given norm. For example the control which has minimal L^2 norm,

$$||u||_{L^2} = \left(\int_0^T |u(s)|^2 \mathrm{d}s\right)^{\frac{1}{2}},\tag{4.2}$$

is specified at every time s as

$$\mathbf{u}(s) = -B^* \exp\{(T-s)A^*\}Q_T^{-1}(\exp\{TA\}\mathbf{y_0} - \mathbf{y_T}),\tag{4.3}$$

where Q_T is a Gramian matrix [112, proposition 1.1], which will be described in section 4.2.2.

The combination of formulae such as the one in eq. (4.3) with definition 2 appears to have strong implications for the application of control theory to ventilator control. However, controllability as described above does not mean that we can design useable pressure controls to take the lungs to any arbitrary inflation state. In fact some target states and control time periods cause the generated profiles to include large variations and gradients in pressure and can violate safety constraints. For this reason we will examine options for choice of the target state in later sections in order to demonstrate the feasibility of providing benefit to mechanical ventilation through the use of EIT guided control.

In this section we show that the system of ODEs produced in chapter 3 follows definition 2 of controllability under a wide range of parameter sets. In particular we link the controllability of these equations to what can be inferred about the qualitative behaviour of the lungs for particular parameter sets and examine the extension of controllability to time derivatives of the inflation states.

4.1.1 Determining Controllability

Controllability of the system in eq. (4.1) can be determined for a given set of parameters by examining the Kalman controllability matrix [112], which has the block matrix structure

$$K = \begin{bmatrix} B & AB & \cdots & A^{n-1}B \end{bmatrix}.$$
(4.4)

A necessary and sufficient condition for the system in eq. (4.1) to be controllable is for matrix K to have rank n, where n is the length of the vector \mathbf{y} [112, theorem 1.2], or in this case the number of separate compartments in the model.

To determine if the lung model in chapter 3 is controllable, eq. (3.3) is reformulated as

$$\dot{\mathbf{v}} = -R^{-1}E\mathbf{v} + R^{-1}\mathbf{b}(P(t) - P_0),$$
(4.5)

where \mathbf{v} is a vector containing the compartmental volumes, \mathbf{b} is a vector of ones, R and E are the airway resistance and elastance matrices described in eq. (3.4) and $P(t) - P_0$ gives the difference between the applied pressure and the pleural pressure at time t. The controllability matrix K can then be formed from eq. (4.4), using

$$A = -R^{-1}E,$$
 $B = R^{-1}\mathbf{b},$ $u = (P(t) - P_0).$ (4.6)

The rank of

$$K = \begin{bmatrix} R^{-1}\mathbf{b} & -R^{-1}ER^{-1}\mathbf{b} & \cdots & (-R^{-1}E)^{n-1}R^{-1}\mathbf{b} \end{bmatrix}$$
(4.7)

may then be calculated to determine if the system is controllable.

As an example of this, the parameters for the four compartment model tested in chapter 3 give

$$A = \begin{bmatrix} -0.846 & 0.077 & 0.462 & 0.385\\ 0.077 & -0.462 & 0.231 & 0.192\\ 0.308 & 0.154 & -2.077 & 0.769\\ 0.154 & 0.077 & 0.462 & -2.115 \end{bmatrix}, \qquad B = \begin{pmatrix} 0.031\\ 0.015\\ 0.062\\ 0.031 \end{pmatrix}.$$
(4.8)

Using this matrix and vector to build the Kalman controllability matrix produces

$$K = \begin{bmatrix} 0.031 & 0.015 & -0.066 & 0.144 \\ 0.015 & 0.015 & -0.033 & 0.056 \\ 0.062 & -0.092 & 0.175 & -0.369 \\ 0.031 & -0.031 & 0.026 & 0.013 \end{bmatrix}$$
(4.9)

which has full rank. Therefore, for the parameters used in chapter 3 this model is controllable.

For a low dimensional system, corresponding to few compartments with specified parameters, this rank calculation may be completed using standard techniques and packages. However, the process of finding the rank of a matrix is itself ill-posed. For example the matrix

$$\left[\begin{array}{rrr} 1 & 1 \\ 0 & \epsilon \end{array}\right],$$

has full rank for all $|\epsilon| > 0$ and is rank deficient for $\epsilon = 0$, this violates the continuity condition for problems to be well posed. This ill-posedness, combined with the numerical difficulty of taking large powers of matrices, leads to difficulty determining the controllability of larger systems in this way.

To get around this rank determination problem it is possible to examine the controllability of systems which are equivalent to the ODE system in question. That is to say checking the controllability of the system

$$\dot{\mathbf{z}} = C\mathbf{z} + D\mathbf{w},$$

where, for real valued systems, the vectors \mathbf{z} and \mathbf{w} are related to \mathbf{y} and \mathbf{u} by the nonsingular matrices $P \in \mathbb{R}^{n \times n}$ and $S \in \mathbb{R}^{m \times m}$,

$$\mathbf{z} = P\mathbf{y}, \qquad \mathbf{w} = S\mathbf{u}.$$

This gives the equivalent matrices

$$C = PAP^{-1}, \qquad \qquad D = PBS^{-1}.$$

In order to relate controllability to the structure of the compartmental model and general relations of parameters within individual models it is necessary to look at an equivalent formulation of the ODE formed using the eigenvalues of the system.

4.1.2 Controllability from eigenvalues

In this subsection we examine the ODE lung model in the basis of eigenvectors to determine general conditions for the controllability of the system. We will show that model parameters which cause regions of the lung to inflate out of phase with each other also increase the likelihood of the system being controllable. This is an important result as ventilating out of phase could cause additional strain on lung tissue.

To determine these conditions for a general set of lung parameters we will be looking at the equivalent ODE system produced by transforming to the basis of eigenvectors for the matrix $A = -R^{-1}E$ defined in eqs. (4.5) to (4.6). The equivalence is then given by the equations

$$-R^{-1}E = UDU^{-1}, \qquad R^{-1}\mathbf{b} = U\bar{\mathbf{b}}, \qquad (4.10)$$

where D is a diagonal matrix of eigenvalues, λ , and U is a matrix whose columns are the associated eigenvectors. This results in an ODE of the form

$$U^{-1}\dot{\mathbf{v}} = U^{-1}UDU^{-1}\mathbf{v} + U^{-1}R^{-1}\mathbf{b}u$$
$$\dot{\mathbf{y}} = D\mathbf{y} + \bar{\mathbf{b}}u. \tag{4.11}$$

The Kalman controllability matrix for this system can now be calculated as

$$\bar{K} = \left[\left. \bar{\mathbf{b}} \right| D \bar{\mathbf{b}} \right| \cdots \left| D^{n-1} \bar{\mathbf{b}} \right. \right],$$

which may be separated into a multiplication of two matrices

$$\bar{K} = \begin{bmatrix} \bar{b}_1 & 0 & \cdots & 0 \\ 0 & \bar{b}_2 & 0 \\ \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \bar{b}_n \end{bmatrix} \begin{bmatrix} 1 & \lambda_1 & \lambda_1^2 & \cdots & \lambda_1^{n-1} \\ 1 & \lambda_2 & \lambda_2^2 & \cdots & \lambda_2^{n-1} \\ \vdots & \vdots & \vdots & \vdots \\ 1 & \lambda_n & \lambda_n^2 & \cdots & \lambda_n^{n-1} \end{bmatrix},$$

= diag($\bar{\mathbf{b}}$) Λ . (4.12)

Using a decomposition of the Kalman controllability matrix in this form, conditions for rank deficiency can be posed dependent on the relations between eigenpairs of the system. The rank of \bar{K} must obey Sylvester's inequality [113]. In the case of two $n \times n$ square matrices this inequality states that

$$\operatorname{rank}(\operatorname{diag}(\bar{\mathbf{b}})) + \operatorname{rank}(\Lambda) - n \leq \operatorname{rank}(\operatorname{diag}(\bar{\mathbf{b}})\Lambda).$$

This implies that the matrix \bar{K} is only rank deficient when diag($\bar{\mathbf{b}}$), Λ or both are rank deficient. From example 5 given by Kalman [111] it can be seen that diag($\bar{\mathbf{b}}$) can be assumed to have full rank, hence the remaining condition for controllability is that the Vandermonde matrix Λ has full rank.

As it is well known that the determinant of the Vandermonde matrix may only be zero if one or more of the λ_i are repeated, we can see that the condition for a loss of controllability of our model is that there is at least one repeated eigenvalue for our model. To see how this condition relates to the structure and parameters for the compartmental model it is necessary to examine the eigenpairs themselves.

Finding the decomposition shown in eq. (4.10) is equivalent to solving the generalised eigenvalue problem

$$-RUD = EU. (4.13)$$

Solving this system for U and D is made simpler by the structure of R and E. Examining their definitions in eq. (3.4), E is a diagonal matrix with strictly positive entries, meaning that it is trivially positive definite, while the matrix R can be written as

$$\begin{bmatrix} R_{1} & 0 & \cdots & 0 & 0 \\ 0 & R_{2} & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & R_{n-1} & 0 \\ 0 & 0 & \cdots & 0 & R_{n} \end{bmatrix} + R_{0} \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \\ 1 \end{pmatrix} \begin{pmatrix} 1 & 1 & \cdots & 1 & 1 \end{pmatrix}, \quad (4.14)$$

which is a rank-1 perturbation to a diagonal positive definite matrix in the form $\operatorname{diag}(R_i) + R_0 \mathbf{bb}^*$.

Without the perturbation of a series resistance R_0 from the trachea, both matrices R and E are diagonal so the eigenvalues are given by

$$\lambda_i = -E_i/R_i,\tag{4.15}$$

while the eigenvectors are given by the Euclidean basis vectors. In this unperturbed case it is easy to see that the eigenvalues will all be negative, which is desirable as it ensures that initial conditions of the system will decay over time and not cause instabilities. It also means that the only reason for a system to not be controllable is if there are two compartments i and j for which

$$E_i/R_i = E_j/R_j.$$

This is to say that when the time constants for these compartments are the same and they are ventilating in phase with each other it will not be possible to control them independently.

One approach to extend these observations to the perturbed system is to examine the effects on the properties of R and E themselves. For example writing R as shown in eq. (4.14) it becomes apparent that

$$\mathbf{x}^* R \mathbf{x} = \mathbf{x}^* \operatorname{diag}(R_i) \mathbf{x} + R_0 \mathbf{x}^* \mathbf{b} \mathbf{b}^* \mathbf{x},$$

= $\mathbf{x}^* \operatorname{diag}(R_i) \mathbf{x} + R_0 (\mathbf{x}^* \mathbf{b})^2,$ (4.16)

so the matrix R must be positive definite.

By taking $\lambda = -\mu$ and noting that symmetric positive definite matrices may be split using the Cholesky decomposition, the eigenvalue problem in eq. (4.13) now becomes

$$E\mathbf{x} = \mu R\mathbf{x},$$
$$= \mu L L^* \mathbf{x},$$
(4.17)

where L is a non-singular lower triangular matrix. Equation (4.17) can then be rearranged using the substitution

$$C = L^{-1}E(L^*)^{-1}$$
 $\mathbf{y} = L^*\mathbf{x},$ (4.18)

to become

$$L^{-1}E\mathbf{x} = \mu L^{-1}R\mathbf{x},$$

$$C\mathbf{y} = \mu \mathbf{y}.$$
(4.19)

From its definition it can be seen that C is a symmetric positive definite matrix so the eigenvalues must be real valued with $\mu > 0$, implying $\lambda < 0$ to retain the original negativity constraint.

This negativity property is encouraging but to place bounds on how the perturbation affects the eigenpairs it is again necessary to reformulate the eigenproblem. Taking $\nu = -\lambda^{-1}$ the problem becomes

$$E^{-1}(\operatorname{diag}(R_i) + R_0 \mathbf{bb}^*)\mathbf{x} = \nu \mathbf{x}.$$

This allows bounds to be placed on the disturbance in the eigenvalues using the work of Kahan [114], which states that for a Hermitian matrix H and rank deficient matrix W the eigenvalues, ν , of H + W are within the union of the regions

$$\nu \in \{z \in \mathbb{C} : |z - \gamma_i| \le ||W||_2 \text{ and } |\operatorname{Im}(z)| \le ||(W - W^*)/2||_2\},$$
 (4.20)

where γ_i are the eigenvalues of matrix H. In this case, due to the equivalence with a real valued and symmetric positive definite matrix the imaginary component must be $\text{Im}(\nu) = 0$. The bound on the regions containing the new eigenvalues can be made explicit by examining the form of the low rank perturbation,

$$W = R_0 E^{-1} \mathbf{b} \mathbf{b}^*. \tag{4.21}$$

Hence the value of $||W||_2$ can be found by calculating the value of

$$W^*W = R_0^2 \mathbf{b} \mathbf{b}^* E^{-*} E^{-1} \mathbf{b} \mathbf{b}^*,$$

= $R_0^2 \operatorname{Tr} (E^{-2}) \mathbf{b} \mathbf{b}^*,$

where $\operatorname{Tr}(\cdot)$ denotes the trace of the matrix. As **b** is a vector of ones we can substitute the value of $\|\mathbf{bb}^*\| = \sqrt{n}$ so the bound on variations from the initial eigenvalues becomes

$$||W||_2 = R_0 \sqrt{n \operatorname{Tr} (E^{-2})}.$$
(4.22)

Defining the smallest difference between an eigenvalue γ_i and its nearest neighbour to be

$$\operatorname{Gap}_i \coloneqq \min_j |\gamma_i - \gamma_j|,$$

It becomes apparent that, for systems where

$$\min_{i} \operatorname{Gap}_{i} > 2R_{0}\sqrt{n \operatorname{Tr}\left(E^{-2}\right)},$$

the perturbed eigenvalues will not be able to overlap and the repeated eigenvalue condition cannot be satisfied.

It should also be noted that a stricter bound can be defined dependent upon the separation of eigenvalues. The work of Ipsen and Nadler [115] states that if

$$\operatorname{Gap}_i > 3 \|W\|_2,$$

then the region surrounding eigenvalue γ_i in which ν_i may be found is given by the bound

$$|\nu_i - \gamma_i| \le \sqrt{5} \|W \mathbf{v}_i\|.$$

In this case the resulting bound is

$$|\nu_i - \gamma_i| \le R_0 \sqrt{5 \operatorname{Tr} (E^{-2})},$$

which becomes stricter than the original bound as the number of compartments increases.

This dependence of controllability on the separation of the values R_i/E_i makes it more likely that a lung system will be controllable when compartments have differing time constants. These results are encouraging as compartments with largely different time constants will inflate to different extents at any given time increasing the stresses on lung tissue. Therefore, as conditions become worse for lung health, examination of the system's eigenvalues shows it is more likely that the lung model will be controllable and an improved control may be generated for non-degenerate target states.

The conclusion taken from this analysis is that there is evidence that the ODE lung system should be controllable when compartments are inflating out of phase with each other. Even in the cases where the system is not completely controllable some degree of control is still possible. If some eigenvectors of the system are unaffected by the control input there is still a subproblem which is controllable. As all the eigenvalues are negative for this system the uncontrollable eigenmodes will decay and the others may be controlled, allowing states in their span to be attained [112, theorem 1.5]. Alternatively, as controllability is only lost when compartments come closer to ventilating in unison with each other, the model could be modified to merge the compartments and control them as a single unit. As such it is worthwhile to calculate the controllability of systems recovered through the use of EIT.

Analysis of these eigenpairs also becomes useful for the generation of refined controls, described in section 4.2, as some calculations benefit from a change of basis to that of the eigenvectors. The analysis above proves that for controllable lung systems there will be a basis of eigenvectors spanning the whole of \mathbb{R}^n and a full set of non-repeating negative eigenvalues. Unfortunately the analysis above also proves that the eigenvectors will not be orthogonal. From eq. (4.18) and eq. (4.19) it can be seen that the eigenvector matrix U can be obtained from the eigenvector matrix Y of a symmetric positive definite matrix C by the relation

$$Y = L^* U.$$

As the eigenvectors of a symmetric positive definite matrix are orthogonal for U to be orthogonal L^* would have to be orthogonal. However, L is the Cholesky decomposition of matrix R and is strictly lower triangular. Hence the matrix of eigenvectors, U, cannot be orthogonal and calculations in section 4.2 requiring its inverse will require a matrix system to be solved.

4.1.3 Controllability of gradient

The procedures in section 4.1.1 confirm the controllability of the ODE lung system when driving the system with a variable pressure, both for general lung systems and the specific test parameters we are using. This allows use of the formula in eq. (4.3) to design a control pressure function which is minimal with respect to the L^2 norm. Minimality in this norm ensures the lung system experiences reduced exposure to high pressures on average. However, this condition does not guarantee the generated control will be suitable, as upper and lower limits are not enforced and there are no conditions placed on the continuity or gradients of pressure.

An example of this is shown in fig. 4.1. These graphs show a comparison of ventilation of the compartmental lung model using a linear increase in pressure as compared to a L^2 minimal pressure profile designed to steer the ODE to the same target state. Due to the emphasis in this norm on absolute values of pressure the L^2 minimal pressure begins at a much lower pressure and only increases towards the end of the control period. At this point the control oscillates, achieving higher pressures than the linear control with much higher gradients. If this profile were applied to a real lung it would result in lung collapse and would be likely to cause damage to the lungs.



Figure 4.1: Graphs comparing ventilation states (right) of four compartment model under ventilation by two different pressure controls (left). Black line indicates ventilation by linear pressure increase while blue line indicates an L^2 minimal control for the same initial and target conditions.

These problems with the L^2 formula necessitate a modification of the control refinement procedure. This is possible due to the fact that the controllability test can be extended to include time derivatives of the control. The result of the controllability tests in section 4.1.1 can be generalised such that if the system in eq. (4.1) is controllable then so is the system

$$\dot{\mathbf{y}} = A\mathbf{y} + B\mathbf{u},$$

$$\dot{\mathbf{u}} = \mathbf{w},$$
 (4.23)

where **w** is treated as the new input control [112, Exercise 1.7]. This allows controls to be found which minimise the H^1 semi-norm of the applied pressures,

$$\|w\|_{L^2} = \|u\|_{H^1} = \left(\int_0^T |\dot{u}(s)|^2 \mathrm{d}s\right)^{\frac{1}{2}}.$$
(4.24)

This means that a pressure profile can be constructed, which takes a linearised model of the lungs to a specified state, at a given pressure with minimised jumps and oscillations. These minimisation properties are desirable as both high frequency oscillations and large driving pressure jumps have been shown to be damaging [4, 5].

The proof of this generalisation is a consequence of writing the new system in eq. (4.23) in block matrix form

$$\begin{pmatrix} \dot{\mathbf{y}} \\ \dot{\mathbf{u}} \end{pmatrix} = \begin{bmatrix} A & B \\ 0 & 0 \end{bmatrix} \begin{pmatrix} \mathbf{y} \\ \mathbf{u} \end{pmatrix} + \begin{bmatrix} 0 \\ I \end{bmatrix} \mathbf{w}, \tag{4.25}$$

where I is the matrix identity corresponding to the dimension of both the control **u** and its time derivative **w**. To check the controllability of this system it is necessary to compute the rank of the Kalman control matrix, modified to use the new state space matrices. Calculating the Kalman controllability matrix from the formulation in eq. (4.25) gives the matrix

$$K_{1} = \begin{bmatrix} 0 & B & AB & \cdots & A^{n-1}B \\ I & 0 & 0 & \cdots & 0 \end{bmatrix},$$
$$= \begin{bmatrix} 0 & K \\ I & 0 \end{bmatrix}.$$
(4.26)

From the structure of this matrix it is evident that when matrix K has rank n then the rank of K_1 will be n + m, so both the system in eq. (4.1) and the one in eq. (4.23) will be controllable.



Figure 4.2: Graphs comparing ventilation states (right) of four compartment model under ventilation by two different pressure controls (left). Black line indicates ventilation by an L^2 minimal control while blue line indicates an H^1 minimal control for the same initial and target conditions at specified pressures.

The result of generating this H^1 minimal pressure profile is shown in fig. 4.2. These graphs show a comparison between ventilation of the compartmental lung model using an L^2 minimal pressure profile and using an H^1 minimal pressure profile. Both profiles are designed to steer from the same initial volume conditions to the same target, but the design of the H^1 control allows the initial and target pressures to be specified as well. The initial and target states and pressures were taken to be the same as those in fig. 4.1. However, as the majority of the non-zero entries for the L^2 minimal control in fig. 4.1 occurred in the second half of the control period, the control time period has been halved to 15 s. It can be seen from these graphs that the pressures and volumes stay within a more feasible region for the purposes of ventilator control. Pressures do not drop too low or vary too widely within short periods. The volumes do not decrease and so a level of recruitment could be maintained.

4.1.4 H^1 control eigenpairs

In this section we note a practical simplification of the process to generate the eigendecomposition for eq. (4.23). As discussed briefly in section 4.1.1 both the confirmation of controllability and the construction process for controls benefit from knowledge of the eigenpairs of the matrix A for the equation

$$\dot{\mathbf{v}} = A\mathbf{v} + B\mathbf{u},$$

= $-R^{-1}E\mathbf{v} + R^{-1}\mathbf{b}(P(t) - P_0).$

So far the eigenpairs for this base system have been used to imply controllability conditions on the system, but they may also be used to simplify calculation of the controllability Gramian as well as reformulating the optimal control formula as a matrix equation. In order to use these methods for the H^1 control procedure in addition to the L^2 procedure it becomes necessary to find the eigenpairs for the new system in eq. (4.25), specifically the eigenpairs for the matrix

$$\left[\begin{array}{cc} A & B \\ 0 & 0 \end{array}\right].$$

The first *n* of these may be taken directly from calculation of the L^2 eigenpairs. The eigenpair (λ, \mathbf{q}) satisfying the equation

$$A\mathbf{q} = \lambda \mathbf{q},$$

will also satisfy the equation

$$\left[\begin{array}{cc} A & B \\ 0 & 0 \end{array}\right] \left(\begin{array}{c} \mathbf{q} \\ 0 \end{array}\right) = \lambda \left(\begin{array}{c} \mathbf{q} \\ 0 \end{array}\right).$$

Hence there is only one additional eigenpair which must be calculated for the H^1 system.

This final eigenpair may also be calculated directly rather than through standard eigenproblem solvers. Noting that the matrix now has a zero row, it is evident that the final eigenvalue must be zero, so any member of the null space for the matrix may be used as the final eigenvector. An explicit formula for this can be found by examining the matrix again in terms of the Resistance and elastance matrices. In this form it can be seen that the vector

$$\left(\begin{array}{c}E^{-1}\mathbf{b}\\1\end{array}\right)$$

is a member of the null space as

$$\begin{bmatrix} -R^{-1}E & R^{-1}\mathbf{b} \\ 0 & 0 \end{bmatrix} \begin{pmatrix} E^{-1}\mathbf{b} \\ 1 \end{pmatrix} = -R^{-1}\mathbf{b} + R^{-1}\mathbf{b} = 0.$$

Here the new eigenvector has not been normalised to unit length in order to maintain the unit value of its final entry for stability of back substitution in Gaussian elimination for the inversion steps in section 4.2.

4.2 Control generation

In section 4.1 we confirmed the controllability of our lung model under a large range of parameter values, including the specific values being used for testing purposes in chapter 3. Additionally we discussed some of the technical aspects of calculating eigenpairs that may be used to generate pressure profiles for control.

4.2. CONTROL GENERATION

In this section we discuss further the specifics of generating both L^2 and H^1 minimal controls numerically. Specifically we show how generation of the controllability Gramian may be simplified as well as a formulation of the optimal control formula in eq. (4.3) which relies upon efficient matrix vector operations. This matrix formulation may be used to formulate an optimisation problem for such quantities as compartmental recruitment levels and ventilation to perfusion ratios as shown in section 4.4. The clinical reasoning behind the development of these minimal and optimal control techniques is discussed in section 4.2.1.

4.2.1 Clinical control requirements

Before designing patient specific controls from our lung model it is necessary to identify the clinical criteria that must be met to ensure the pressure profiles provide benefit. For the controls outlined in this chapter there have been three major considerations when examining possible control designs. Motivated by links to ventilator induced lung injury (*VILI*) and patient mortality, these are: the magnitude of applied pressure, gradients of pressure and relative ventilation states of different sections of lung.

The first of these considerations was the pressure applied by the ventilator during mechanical ventilation. While it has been shown that pressures above 28 cmH_2O result in an increased inflammatory response within the lungs [90] it has also been found that the average resulting pressure after a maximal recruitment manoeuvre is 40 cmH_2O [89]. This current reliance on damaging levels of pressure motivates our analysis of pressure mode controls which are minimal in the L^2 norm, as they apply the lowest magnitude pressures on average for the resulting ventilation state. It also motivates our analysis of bounds on pressure for H^1 minimal pressures in section 4.3.2.

Another important risk factor we have considered is linked to the time gradients of pressures applied by the ventilator. It has been found that tidal variations in pressure, that is the difference between inspiratory and expiratory pressure, are strongly adversely linked with mortality rates of patients [4]. In addition to this, models of airway opening have revealed that inducing gradients of pressure within opening airways can also cause damage [5]. This is evidence that not only must we be careful of damaging, high-magnitude pressures but must also minimise how much pressure varies over a breathing cycle as well as the rate of this variation. Therefore we have examined the H^1 minimal pressures profiles discussed in section 4.3, which apply the lowest average gradients of pressure for the resulting ventilation states.

The final set of criteria we have considered when designing these controls relate to the recruitment of regions of the lung, that is the extent to which lung regions have been inflated reducing the number of collapsed airways. Increasing the level of recruitment in partially collapsed regions can improve the mechanical parameters of the lungs [6]. However, mechanical ventilation can result in some regions becoming over-distended, causing damage, while others are only partly recruited [9]. This heterogeneity in the ventilation profile across the lungs is one of the factors attributed with the occurrence of VILI despite the use of lung protective ventilation [90, 116]. For this reason we have examined the possibility of optimising the inflation state of the lung through the techniques in section 4.4. These not only look at improving recruitment and optimising towards a homogeneous ventilation state but also raise the possibility of including other optimality conditions. Specifically we mention reducing the occurrence of alveolar dead space, which does not assist in gas transfer [10], through the use of regional perfusion information.

These considerations lead us to examine L^2 minimal, H^1 minimal and optimised controls in the following sections. The H^1 and optimised controls are examined in sections 4.3 and 4.4 respectively. However, before these techniques can be defined it is necessary to outline some practical implementation details for optimal controls. We begin with details of how to generate the controllability Gramian as described in section 4.2.2. This is followed in section 4.2.3 by a description of the matrix formulation for the optimal control formula we use to generate both minimal and optimised controls in later sections.

4.2.2 Gramian calculation

In this section we discuss some practical calculations we have performed to simplify the process of generating the controllability Gramian. The first step in generation of the two minimal controls mentioned above through use of eq. (4.3)is calculating the controllability Gramian

$$Q_T \coloneqq \int_0^T \exp\left\{Ar\right\} BB^* \exp\left\{A^*r\right\} \mathrm{d}r,\tag{4.27}$$

where A and B are taken from eq. (4.6). This calculation may be done analytically in the basis of eigenvectors using the definitions from eq. (4.10). In these calculations the matrix exponential is defined as

$$\exp\{A\} \coloneqq \sum_{k=0}^{\infty} \frac{A^k}{k!}.$$
(4.28)

Using the definition of the eigenvalue matrix D and the decomposition of A this exponential can be re-written as $\exp\{A\} = U \exp\{D\}U^{-1}$, with D and $\exp\{D\}$ given by

$$(D)_{ij} = \begin{cases} \lambda_i & i = j, \\ 0 & i \neq j, \end{cases} , \qquad (\exp D)_{ij} = \begin{cases} e^{\lambda_i} & i = j, \\ 0 & i \neq j. \end{cases}$$
(4.29)

Hence the Gramian may be calculated as

$$Q_{T} = U \left[\int_{0}^{T} \exp \{Dr\} U^{-1} B B^{*} U^{-*} \exp \{Dr\} dr \right] U^{*},$$

= $U \left[\int_{0}^{T} \exp \{Dr\} G \exp \{Dr\} dr \right] U^{*},$
=: $U \bar{Q}_{T} U^{*},$ (4.30)

where G is the matrix given by

$$G = \bar{\mathbf{b}}\bar{\mathbf{b}}^*. \tag{4.31}$$

Formulation of the Gramian in this way allows coefficients and exponents to be calculated separately for an element-wise integration process. Re-writing the expression to be integrated as a single matrix

$$\Gamma = \exp\left\{Dr\right\}G\exp\left\{Dr\right\},\tag{4.32}$$

elements of Γ may be calculated explicitly, giving

$$(\Gamma)_{ij} = (G)_{ij} \exp\{(\lambda_i + \lambda_j)r\}.$$
(4.33)

These elements may then be integrated explicitly with respect to time to give elements of the Gramian in the basis of eigenvectors

$$(\bar{Q}_T)_{ij} = \int_0^T (G)_{ij} \exp\left\{(\lambda_i + \lambda_j)r\right\} dr,$$

= $\frac{(G)_{ij}}{\lambda_i + \lambda_j} (\exp\left\{(\lambda_i + \lambda_j)T\right\} - 1).$

This form of the Gramian may then be used in the calculation of the L^2 refined control pressure.

In order to calculate the H^1 minimal control it is necessary to note that there is now an additional eigenvalue associated with the derivative of the control, $\lambda_{n+1} = 0$. This additional eigenvalue and associated eigenvector means that the Gramian will now be an $(n + 1) \times (n + 1)$ matrix. The zero valued eigenvalue also changes one part of the integration so that a constant value is integrated over time rather than an exponential value. This changes the general form of the Gramian to become

$$(\bar{Q}_T)_{ij} = \begin{cases} \frac{(G)_{ij}}{\lambda_i + \lambda_j} (\exp\left\{(\lambda_i + \lambda_j)T\right\} - 1) & i, j \neq n+1, \\ (G)_{ij}T & i = j = n+1. \end{cases}$$

4.2.3 Matrix formulation

In this section we describe a practical reformulation of the analytic control formula to allow fast calculation of a desired control as well as enabling us to set up an efficient optimisation problem for control in section 4.4.1.

4.2. CONTROL GENERATION

Once the Gramian has been computed the formula for each time step (s),

$$\mathbf{u}(s) = -B^* \exp\{(T-s)A^*\}Q_T^{-1}(\exp\{TA\}\mathbf{y_0} - \mathbf{y_T}),$$
(4.34)

may be used to calculate a control which is minimal for the target state in either the L^2 or H^1 norm [112, proposition 1.1]. In order to take advantage of implicit parallelism and vectorisation the above formula can be re-written as a matrix formula to compute all timesteps in one calculation. This reformulation also assists with a process of optimisation which will be explored further in section 4.4.

The first step in reformulating eq. (4.34) is to write all components and individual vector operations in the basis of eigenvectors. In this way the pressure at each time s becomes

$$u(s) = \mathbf{b}^{*} R^{-*} U^{-*} e^{D(T-s)} \bar{Q}_{T}^{-1} U^{-1} (\mathbf{y}_{\mathbf{T}} - \exp\{TA\} \mathbf{y}_{\mathbf{0}}),$$

= $\bar{\mathbf{b}}^{*} e^{D(T-s)} \bar{Q}_{T}^{-1} U^{-1} (\mathbf{y}_{\mathbf{T}} - \exp\{TA\} \mathbf{y}_{\mathbf{0}}),$
= $\mathbf{m}^{*} \bar{Q}_{T}^{-1} U^{-1} (\mathbf{y}_{\mathbf{T}} - \exp\{TA\} \mathbf{y}_{\mathbf{0}}),$ (4.35)

where $\mathbf{m} = e^{D(T-s)} \bar{\mathbf{b}}$ is the only component which depends on s. Noticing that each element of this vector \mathbf{m} is

$$m_i = \bar{b}_i e^{\lambda_i (T-s)}$$

the time step dependent part of the formula may be written as a matrix ${\cal M}$ such that

$$M = \begin{bmatrix} e^{\lambda_{1}(T-0)} & e^{\lambda_{2}(T-0)} & e^{\lambda_{3}(T-0)} & e^{\lambda_{4}(T-0)} \\ e^{\lambda_{1}(T-s_{1})} & e^{\lambda_{2}(T-s_{1})} & e^{\lambda_{3}(T-s_{1})} & e^{\lambda_{4}(T-s_{1})} \\ e^{\lambda_{1}(T-s_{2})} & e^{\lambda_{2}(T-s_{2})} & e^{\lambda_{3}(T-s_{2})} & e^{\lambda_{4}(T-s_{2})} \\ \vdots & \vdots & \vdots & \vdots \\ e^{\lambda_{1}(0)} & e^{\lambda_{2}(0)} & e^{\lambda_{3}(0)} & e^{\lambda_{4}(0)} \end{bmatrix} \begin{bmatrix} \bar{b}_{1} & 0 & 0 & 0 \\ 0 & \bar{b}_{2} & 0 & 0 \\ 0 & 0 & \bar{b}_{3} & 0 \\ 0 & 0 & 0 & \bar{b}_{4} \end{bmatrix} \bar{Q}_{T}^{-1}U^{-1}.$$

$$(4.36)$$

Hence, the control may be written as a time series vector

$$\mathbf{u} = M(\mathbf{y}_{\mathbf{T}} - \exp\{TA\}\mathbf{y}_{\mathbf{0}}),\tag{4.37}$$
which gives the optimal L^2 control for the initial condition $\mathbf{y_0}$, target condition $\mathbf{y_T}$ and target time T. The full procedure to generate an L^2 minimal control pressure for this four compartment model can be seen in algorithm 4.1. In this algorithm Matlab notation has been assumed for the concatenation of vectors and matrices, so

$$[A,B] = [A|B]$$

and

$$[A;B] = \begin{bmatrix} A\\ B \end{bmatrix}$$

Algorithm 4.1 Control: L^2 minimisation

1: Retrieve parameters R_0 , R_i and E_i for i = 1:42: Set control time T and initial and target states y_0 and y_T 3: Generate timestep vector $\mathbf{s} = 0$: dt : T 4: 5: % Find eigenvectors, U, and eigenvalues, $D = \text{diag}(\lambda_i)$ 6: $A = -R^{-1}E = UDU^{-1}$ 7: 8: % Find $\bar{\mathbf{b}}$ such that 9: $B = R^{-1}\mathbf{b} = U\bar{\mathbf{b}}$ 10: 11: % check controllability matrix \bar{K} 12: $\bar{K} = [\bar{\mathbf{b}}, D\bar{\mathbf{b}}, D^2\bar{\mathbf{b}}, D^3\bar{\mathbf{b}}]$ 13:14: if rank $\overline{K} = 4$ then 15: $G = \overline{\mathbf{b}}\overline{\mathbf{b}}^*$ 16:17:% Generate gramian \bar{Q}_T $(\bar{Q}_T)_{ij} = \frac{(G)_{ij}}{\lambda_i + \lambda_j} (\exp\{(\lambda_i + \lambda_j)T\} - 1)$ 18:19:20: %Generate time exponential vectors 21: $\mathbf{e}_{\mathbf{i}} = \exp\{\lambda_i(T-\mathbf{s})\}\$ 22: 23:% Calculate matrix formulation M24: $M = [\mathbf{e_1}, \mathbf{e_2}, \mathbf{e_3}, \mathbf{e_4}] \operatorname{diag}(\mathbf{\bar{b}}) \bar{Q}_T^{-1} U^{-1}$ 25:26:% Calculate control time series pressures 27: $\boldsymbol{u} = M(\boldsymbol{y_T} - \exp\{TA\}\boldsymbol{y_0})$ 28:29: end if

To modify eq. (4.37) to produce the H^1 optimal control requires the target and initial conditions to be extended to include the starting and ending pressure as well as calculations of the Gramian and vector $\mathbf{\bar{b}}$ to be performed using the extended eigenbasis. It also requires that the end result be integrated with respect to time giving a pressure vector in the form

$$\mathbf{u} = \tilde{M}(\mathbf{y}_{\mathbf{T}} - \exp\{T\bar{A}\}\mathbf{y}_{\mathbf{0}}) + p_0, \qquad (4.38)$$

where \tilde{M} can be calculated by applying a discrete integration operator to a matrix M calculated as above in the extended basis of eigenvectors for

$$\bar{A} = \left[\begin{array}{cc} A & B \\ 0 & 0 \end{array} \right].$$

This implementation of the analytic control formula to allow fast calculation of a desired control as well as enabling us to set up an efficient optimisation problem. However, it still remains to analyse how the H^1 minimal control profiles will affect ventilation. This is the focus of the next section.

4.3 Analysis of H^1 minimal controls

We demonstrated in the previous two sections that the lung model described in chapter 3 not only has parameters which are recoverable from EIT but is also controllable. We also discussed some of the technical details in generating controls for given initial conditions and target states.

Having presented this information, the next step to showing that the application of EIT and control theory to mechanical ventilation can provide benefit is to demonstrate the kind of profile which can be generated using these methods. There are some further issues with this, for example as mentioned above some target states and control periods can produce unacceptable profiles. One solution is to formulate a further optimisation problem as will be demonstrated in section 4.4, another is to pick a target which we know is achievable with an acceptable pressure profile. A simple method for choosing an acceptable control is to use numerical solutions to the lung model to predict the lung state after a desirable profile has been applied. For the purposes of this demonstration we will call this desirable test profile the *original* profile and then replace a section with a control segment generated to have minimal H^1 norm, which was shown to be preferable to L^2 minimal controls in section 4.1.3. This H^1 minimal profile will have the same initial state and target state but will have improved gradients. An outline of the procedure to generate this H^1 minimal profile is shown in algorithm 4.2.

After demonstrating this process in section 4.3.1 we will discuss the effects of the H^1 minimisation on the pressure magnitudes by examining the full H^1 norm in section 4.3.2.

Algorithm 4.2 Control: H^1 minimisation

1: Retrieve parameters R_0 , R_i and E_i for i = 1:42: Set control time T, initial state y_0 and initial pressure p_0 3: Generate timestep vector $\mathbf{s} = 0$: dt : T 4: 5: Set original pressure control profile **p** 6: Numerically solve ODE with control **p** to find target state y_T 7: Set target pressure p_T to final pressure entry in **p** 8: 9: % Find eigenvectors, U, and eigenvalues, $D = \text{diag}(\lambda_i)$ 10: $A = -R^{-1}E = UDU^{-1}$ 11: 12: % Find $\overline{\mathbf{b}}$ such that 13: $B = R^{-1}\mathbf{b} = U\bar{\mathbf{b}}$ 14: 15: % check controllability matrix \bar{K} 16: $\bar{K} = [\bar{\mathbf{b}}, D\bar{\mathbf{b}}, D^2\bar{\mathbf{b}}, D^3\bar{\mathbf{b}}]$ 17:if rank $\bar{K} = 4$ then 18:% Reformulate to control gradient 19: $\lambda_5 = 0$ 20: $\tilde{U} = [U, E^{-1}\mathbf{b}; 0, 1]$ 21: A = [A, B; 0, 0]22: $\tilde{\mathbf{b}} = \tilde{U}^{-1}[0;0;0;0;1]$ 23: 24:% Generate gramian \bar{Q}_T 25: $G = \tilde{\mathbf{b}}\tilde{\mathbf{b}}^*$ 26: $(\bar{Q}_T)_{ij} = \frac{(G)_{ij}}{\lambda_i + \lambda_j} (\exp\{(\lambda_i + \lambda_j)T\} - 1)$ 27: $(\bar{Q}_T)_{55} = (G)_{55}T$ 28:29:%Generate time exponential vectors 30: $\mathbf{e}_{\mathbf{i}} = \exp\{\lambda_i (T - \mathbf{s})\}$ 31: 32: % Calculate matrix formulation \dot{M} 33: $M = [\mathbf{e_1}, \mathbf{e_2}, \mathbf{e_3}, \mathbf{e_4}, 1] \operatorname{diag}(\tilde{\mathbf{b}}) \bar{Q}_T^{-1} \tilde{U}^{-1}$ 34: Construct a numerical integration matrix L, eg. composite trapezium 35: $\tilde{M} = LM$ 36: 37: % Calculate control time series pressures 38:set $\tilde{\boldsymbol{y}}_0 = [\boldsymbol{y}_0; p_0]$ and $\tilde{\boldsymbol{y}}_T = [\boldsymbol{y}_T; p_T]$ 39: 40: $\boldsymbol{u} = \tilde{M}(\tilde{\boldsymbol{y}}_T - \exp\{T\tilde{A}\}\tilde{\boldsymbol{y}}_0) + p_0$ 41: 42: **else** use control profile \mathbf{p} 43: 44: end if

4.3.1 H^1 minimisation example

For this example volumes and flows were generated under the action of a sinusoidal pressure profile with a simulated increase in pressure at 20 seconds using the techniques in chapter 3. This profile was chosen to resemble the action of a PEEP increase step common in recruitment manoeuvres, where the PEEP level is increased between breaths after a period of regular ventilation at the initial PEEP level. For this demonstration the response of the lung system to this pressure profile was calculated using the parameters from chapter 3.

To generate the new H^1 minimal pressure profile the pressure patterns for first 5 and last 2 breaths were retained. The ventilator pressure and compartmental volumes taken at time 15 as initial condition for H^1 control, while the pressure and volumes taken at time 25 were taken as a target for steering.

Figure 4.3 shows both the original and H^1 optimised pressure profile for this increase in PEEP. Figure 4.4 shows the responses of the system to both PEEP in-



Figure 4.3: Original (solid line) and H^1 minimal (dotted line) pressure profile including an increase in PEEP level.

creases, where the initial volumes of each compartment correspond to the steady state volumes of these compartments when held at the initial pressure. As expected the initial five and final two breaths proceed exactly the same under the action of both pressure profiles. The only differences are found during the controlled section. In the controlled case, the rate of pressure increase is slower, while the flow spikes visible for the original pressure profile are smoothed out reducing stress on the lungs.



Figure 4.4: Flow (left) and volume (right) responses of the system to both a step increase in pressure (solid lines) and H^1 minimal control pressure (dashed line).

The process of predicting a flow for the given pressure profile, obtaining initial and target conditions, generating a control and recombining to give an optimised pressure profile took 10.9 milliseconds on a 2.8GHz Intel Core i7 with 16 GB 1.6 GHz DDR3 RAM.. This demonstrates that by combining regional information with control theory, it may be possible to derive patient specific pressure controls which attain the same results as classical techniques while reducing exposure to the pressure gradient risk factor.

The fact that this kind of profile may be constructed so quickly and provide noticeable changes to the ventilation control is encouraging. However, it is still necessary to check both the sensitivity of the controls generated to noise in parameters recoverable through EIT and also that the magnitude of the pressures produced is in some way bounded. The sensitivity of these profiles to noise will be examined in section 4.5 but we provide an analysis of the pressure magnitudes in section 4.3.2 by examining the equivalences between the H^1 semi-norm and H^1 norm.

4.3.2 H^1 seminorm and norm equivalence

In previous sections it has been shown that we can reduce exposure of the lungs to pressure gradients by generating an H^1 minimal control profile. In this section we show that the magnitudes of these pressure profiles are also bounded. As there are many control functions taking the state of a controllable ODE to a target state in time T we can define a set S of control functions taking the system in the ODE from state \mathbf{x}_0 at time t = 0 to \mathbf{x}_T at time t = T. We can also define that every element of S must have a specified initial value p_0 and a specified final pressure p_T giving the relation

$$S \subset \{f \in H^1([0,T]) | f(0) = p_0, f(T) = p_T\}.$$

The result of the H^1 optimised control procedure, u, must then be an element of this set. However, we have so far only proven that this function is minimal in the H^1 semi-norm. This means that for any other control function $f \in S$

$$\|u'\|_{L^2} \le \|f'\|_{L^2}. \tag{4.39}$$

This only allows us to ensure that the time derivatives of our applied pressures will be minimised in a least squares sense, but it does not directly enforce conditions on the magnitude of the pressures applied.

To relate this result to a measure taking into account both magnitudes and time derivatives we must introduce the full H^1 norm for the function,

$$||f||_{H^1} = \left(\int_0^T [(u(t))^2 + (u'(t))^2]\right)^{\frac{1}{2}}.$$
(4.40)

While the H^1 control method does not ensure that

$$\|u\|_{H^1} \le \|f\|_{H^1} \tag{4.41}$$

for $f \in S$, we will show that it does ensure

$$\|u - v\|_{H^1} \le K \|f - v\|_{H^1} \tag{4.42}$$

where v(t) is defined as the linear function passing through p_0 at time t = 0 and p_T at time t = T,

$$v(t) = at + p_0,$$

$$a = \frac{(p_T - p_0)}{T}.$$
(4.43)

and K is a constant dependent only on T. This forces our control to be the pressure profile taking \mathbf{x}_0 to \mathbf{x}_T which is closest, in gradient, to a linear increase in pressure between p_0 and p_T with a bounded difference in magnitude.

To prove that this is true, for any function $f \in S$ we define the H^1 seminorm for the difference between f and v as

$$||f' - v'||_{L^2}^2 = \int_0^T (f' - v')^2 \mathrm{d}t.$$
(4.44)

The expression in eq. (4.44) can be expanded to give

$$\|f' - v'\|_{L^2}^2 = \int_0^T [(f')^2 - 2f'v' + (v')^2] dt,$$

= $\|f'\|_{L^2}^2 - \int_0^T [2f'v' - (v')^2] dt.$ (4.45)

This can be simplified further by noting that v' = a for the linear function v, giving

$$\|f' - v'\|_{L^{2}}^{2} = \|f'\|_{L^{2}}^{2} - a \int_{0}^{T} [2f' - a] dt,$$

$$= \|f'\|_{L^{2}}^{2} - a \int_{0}^{T} [f' - a] dt - a \int_{0}^{T} f' dt,$$

$$= \|f'\|_{L^{2}}^{2} - a \int_{0}^{T} f' dt,$$
 (4.46)

as $f(0) = v(0) = p_0$ and $f(T) = v(T) = p_T$. Furthermore, by these definitions, eq. (4.46) can be reduced further to

$$||f' - v'||_{L^2}^2 = ||f'||_{L^2}^2 - a(p_T - p_0),$$

= $||f'||_{L^2}^2 - a^2 T,$
= $||f'||_{L^2}^2 - ||v'||_{L^2}^2.$ (4.47)

As $u \in S$ and $||v'||_{L^2}$ is a constant, dependent only on the boundary conditions and target control time, eq. (4.47) shows that eq. (4.39) directly implies

$$||u' - v'||_{L^2} \le ||f' - v'||_{L^2}, \tag{4.48}$$

for the optimal control $u \in S$ and any other $f \in S$. To extend this to the stronger H^1 norm inequality given in eq. (4.42) it must be noted that for $u, f \in S$, the functions $\bar{u} = (u - v)$ and $\bar{f} = (f - v)$ are in the space

$$H_0^1([0,T]) = \{g \in H^1([0,T]) | g(0) = g(T) = 0\}.$$

This allows the Poincaré-Friedrichs inequality [117] to be used to show that

$$\|\bar{f}\|_{L^2} \le C \|\bar{f}'\|_{L^2},\tag{4.49}$$

for some constant C which is only dependent on the domain [0, T]. Combining this with the fact that

$$\|\bar{f}\|_{H^1}^2 = \|\bar{f}\|_{L^2}^2 + \|\bar{f}'\|_{L^2}^2, \qquad (4.50)$$

we have that

$$\|\bar{f}'\|_{L^2}^2 \le \|\bar{f}\|_{H^1}^2 \le (C^2 + 1) \|\bar{f}'\|_{L^2}^2, \tag{4.51}$$

so by definition the H^1 seminorm and H^1 norm are equivalent on H^1_0 . Therefore we have the three inequalities

$$\|\bar{u}\|_{H^1} \le K \|\bar{u}'\|_{L^2}, \qquad \|\bar{u}'\|_{L^2} \le \|\bar{f}'\|_{L^2}, \qquad \|\bar{f}'\|_{L^2} \le \|\bar{f}\|_{H^1}, \qquad (4.52)$$

which can be combined to give

$$\|\bar{u}\|_{H^1} \le K \|\bar{f}\|_{H^1},\tag{4.53}$$

where $K = (C^2 + 1)^{1/2}$.

The value of K can be found using techniques from [118]. To do this we use eq. (4.49) and the definitions of the above norms to set

-

$$\frac{1}{C^2} = \min_{\bar{f}|_{0,T}=0} \frac{\int_0^T (\bar{f}')^2 \mathrm{d}t}{\int_0^T (\bar{f})^2 \mathrm{d}t}.$$
(4.54)

This can be reformulated using integration by parts and written in terms of inner products to give

$$\frac{1}{C^2} = \min_{\bar{f}|_{0,T}=0} \frac{-\langle \bar{f}'', \bar{f} \rangle}{\langle \bar{f}, \bar{f} \rangle}.$$
(4.55)

This is equivalent to the smallest value of λ such that

$$\bar{f}'' = -\lambda \bar{f}, \quad \bar{f}(0) = \bar{f}(T) = 0.$$
 (4.56)

Solving this differential equation, we find that the smallest valid value of λ is π^2/T^2 , so K is given by

$$K = \left(\frac{T^2}{\pi^2} + 1\right)^{\frac{1}{2}},\tag{4.57}$$

and eq. (4.42) becomes

$$\|u - v\|_{H^1} \le \left(\frac{T^2}{\pi^2} + 1\right)^{\frac{1}{2}} \|f - v\|_{H^1}.$$
(4.58)

While the bound in eq. (4.58) holds for any $f \in S$, we can be more specific when examining how the norm of the minimal control will relate to the norm of the reference control. As one step in calculating the optimal control is numerically integrating its derivative, it is simple to calculate its H^1 seminorm. We can therefore calculate the ratio between the seminorms of the refined and unrefined controls as

$$\beta = \frac{\|u' - v'\|_{L^2}}{\|f'_0 - v'\|_{L^2}},\tag{4.59}$$

where f_0 is the pressure waveform used to generate the target state for our control. This value of β will always be less than or equal to 1 due to the optimality of the generated control.

Combining eq. (4.59) with eq. (4.53) and eq. (4.58) we get that

$$\|u - v\|_{H^1} \le \beta \left(\frac{T^2}{\pi^2} + 1\right)^{\frac{1}{2}} \|f_0 - v\|_{H^1}.$$
(4.60)

Therefore, if the H^1 seminorm of control u decreases enough from that of f_0 , \bar{u} will have a smaller H^1 norm than \bar{f}_0 as well. Hence, while the pressure gradients applied are guaranteed to be minimal in the least squares sense, the magnitudes of pressure controls generated in this way will be also be bounded reducing the likelihood of damaging excessive driving pressures.

4.4 Control Optimisation

One issue with the H^1 minimal control formula is its dependence on the target state the control function is steering towards. The controllability of the system implies that any target state is achievable within a defined time period, however, some target states will require control pressures with higher magnitudes and greater variability than others.

For example the same target state achieved in a shorter time will require a higher pressure gradients. This can be seen in fig. 4.5 which shows ventilation states of the same four compartment model over three different time scales. The



Figure 4.5: Graphs comparing ventilation states (right) of four compartment model under ventilation by pressure controls (left) over 15 seconds (blue) 30 seconds (black) and 45 seconds (red).

 H^1 minimal pressure controls in these graphs are designed to raise in pressure from a value of 15 to a value of 20 over the course of 15, 30 and 45 seconds respectively, while the target inflation state is that achieved by a linear increase in pressure over 30 seconds. The L^2 norm and H^1 seminorm of these pressures

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can be seen in table 4.1 along with the measures

$$\frac{\|u\|_{L^2}}{\sqrt{T}} = \left(\frac{1}{T}\int_0^T u^2(r)\mathrm{d}r\right)^{\frac{1}{2}}, \qquad \frac{\|u\|_{H^1}}{\sqrt{T}} = \left(\frac{1}{T}\int_0^T \dot{u}^2(r)\mathrm{d}r\right)^{\frac{1}{2}}, \qquad (4.61)$$

which give a description of the average norm over the control period. This table

Time $T(s)$	$\ \cdot\ _{L^2}$	$\ \cdot\ _{L^2}/\sqrt{T}$	$\ \cdot\ _{H^1}$	$\ \cdot\ _{H^1}/\sqrt{T}$
15	71.46	18.45	1.59	0.41
30	96.26	17.57	0.91	0.17
45	115.86	17.27	0.77	0.12

Table 4.1: Table comparing the H^1 minimal controls for the same target state over varying time scales. Both the L^2 norm and H^1 seminorm are shown, both unnormalised and weighted by control time.

shows that increasing the control time lowers the average L^2 as well as both the averaged and un-averaged H^1 norms. However, moving from 15 to 30 seconds has a much larger impact on these measures than moving from 30 to 45 seconds. This, in combination with the need to complete ventilation manoeuvres within a specified time frame, suggests there may be some room to optimise the control time frame.

The magnitude and time derivatives of an optimal control also depend on how feasible a target state is. If a target state is chosen which requires too much energy to be added to one mode of the system while reducing the energy in others then all controls achieving the target state will have high L^2 and H^1 norms and instantaneous values may exceed safe or feasible bounds on pressure. An example of this is shown in fig. 4.6. These graphs compare the ventilation profiles generated by optimal controls aiming at two different target inflation states. The straight line indicates a linear increase in pressure from 15 to 20 while the curved lines indicate an H^1 optimal control aimed at bringing all compartments to the same volume. This target is possible to achieve due to the controllability of the ODE model, but all pressure controls achieving this result lie outside of the feasibility set for clinically acceptable pressures, resulting in both negative pressures and pressures thousands of times the magnitude for a feasible target.



Figure 4.6: Graphs comparing ventilation states (right) of four compartment model under ventilation by two different pressure controls (left). Black line indicates ventilation by an linear increase in pressure while blue line indicates an H^1 minimal control for an infeasible target condition at specified pressures.

One solution to this difficulty is to use the optimal control formulae to improve upon an existing control as stated in section 4.3. By using the optimal control formula to minimise a given naive pressure control the problem of choosing a feasible target point is removed. However, it is desirable to not only refine the controls for a specified target inflation, but also to improve the level of recruitment and limit the generated pressure controls to be within some feasibility set. This leads to a formulation of the problem as an optimisation of some cost functional $F(\mathbf{x}_T)$ subject to inequality constraints.

4.4.1 Compartment weighted optimisation

When optimising the targets for a control procedure, it is necessary to choose an optimality criteria. Two possible candidate are the mismatch of compartmental filling factors (FF) from ideal values or the ratio of ventilation to perfusion, known as the VQ ratio, in a region. The ratio of air volume to tissue content gives a measure of both the recruitment and stress present in the compartment. Both low and high VQ ratios are undesirable. A low ratio results in low gas transfer and a high value results in alveolar dead space and increased risk of overdistension without accompanying gas transfer.

Optimising towards either optimal FF or VQ ratios results in a cost functional of the form

$$F = \left\| V^{-1} \mathbf{x}_T - \mathbf{r} \right\|^2 \tag{4.62}$$

where \mathbf{x}_T is the target ventilation state, V is a diagonal matrix of compartmental weightings and \mathbf{r} is a vector of target ratios. In FF optimisation the entries in V will be compartmental tissue volumes while they will be perfusion values for VQ optimisation. In an unconstrained problem the minimiser of this functional is trivial, however, as shown in fig. 4.6, the pressure profiles required to attain these solutions may be infeasible.

Constraining the problem to targets attained through feasible pressure controls may be performed in one of two ways. The first is to reformulate the cost functional in eq. (4.62), substituting $\mathbf{x_T}$ with the pressure profile **u** using the formula

$$\mathbf{x}_T = e^{AT} \mathbf{x}_0 + \int_0^T e^{(T-s)A} \mathbf{b} u(s) \mathrm{d}s,$$

and optimise with respect to the time samples of \mathbf{u} . This approach has the advantage of simplifying the constraints to the linear inequalities

$$\max(\mathbf{u}) \le P_{max},$$

$$\min(\mathbf{u}) \ge P_{min},$$
(4.63)

with the possible equality constraint

$$u(T) = p(T) \tag{4.64}$$

in the case that a final pressure has been defined. However, this approach also increases the dimensionality of the optimisation problem, does not ensure any smoothness properties of the resulting pressure profile and solvers will not be guaranteed to find a global minimum to the cost functional as multiple pressure profiles may attain the same final inflation state.

Instead the approach we use is to reformulate the constraints in terms of the inflation target \mathbf{x}_T . This can be done using the matrix form of the H^1 refined control from eq. (4.38), resulting in the new inequality constraint

$$P_{min} \leq \tilde{M} \left[\begin{pmatrix} \mathbf{x}_T \\ p_T \end{pmatrix} - \exp\left\{ T \begin{pmatrix} A & \mathbf{b} \\ 0 & 0 \end{pmatrix} \right\} \begin{pmatrix} \mathbf{x}_0 \\ p_0 \end{pmatrix} \right] + p_0 \begin{pmatrix} \mathbf{1} \\ \mathbf{1} \end{pmatrix} \leq P_{max}.$$
(4.65)

This inequality may now be rearranged into the single linear matrix inquality

$$\begin{bmatrix} \tilde{M} \\ -\tilde{M} \end{bmatrix} \begin{pmatrix} \mathbf{x}_T \\ p_T \end{bmatrix} \leq \begin{pmatrix} \mathbf{p}_{max} - p_0 \\ p_0 - \mathbf{p}_{min} \end{pmatrix} + \begin{bmatrix} \tilde{M} \\ -\tilde{M} \end{bmatrix} \exp\left\{T \begin{pmatrix} A & \mathbf{b} \\ 0 & 0 \end{pmatrix}\right\} \begin{pmatrix} \mathbf{x}_0 \\ p_0 \end{pmatrix}$$

where \mathbf{p}_{max} and \mathbf{p}_{min} are vectors with dimensions corresponding to the number of time steps in the pressure control, containing the maximum and minimum allowable pressures respectively.

Hence the optimisation problem becomes

$$\mathbf{x}_{T} = \arg\min_{\mathbf{x}} \left[\mathbf{x}^{*} V^{-2} \mathbf{x} - \mathbf{r}^{*} V^{-1} \mathbf{x} \right],$$
$$\begin{pmatrix} \tilde{M}_{x} \\ -\tilde{M}_{x} \end{pmatrix} \mathbf{x} \leq \begin{pmatrix} \mathbf{p}_{\max} \\ -\mathbf{p}_{\min} \end{pmatrix} + \mathbf{f}(\mathbf{x}_{0}, p_{0}, p_{T}, T), \qquad (4.66)$$

where \tilde{M}_x is the component of matrix \tilde{M} which corresponds to the entries in \mathbf{x}_T and \mathbf{f} is a vector function of the control time, initial conditions and target pressure. This is a classic quadratic programming problem with inequality constraints and may be solved using standard techniques such as interior point methods for convex problems [119, Chapter 16]. An outline of the procedure to generate this optimised profile is shown in algorithm 4.3.

The reformulated bounds approach has the advantages that it reduces the dimensionality and ensures the convexity of the problem. Also, using the H^1 refinement formula for the pressure control combines the pressure limits of the optimisation approach with the guarantee of reduced pressure gradients of the refinement approach. However, it does not guarantee that there isn't another acceptable pressure profile which would not achieve a better end inflation state. For example a ventilation state generated by an acceptable pressure profile may have an optimal H^1 control which requires pressures to move outside of the acceptable range.

The results of this method can be seen in fig. 4.7. These graphs compare the ventilation profiles of the four compartment model under three different pressure controls. The first of these is a sinusoidal ventilation profile with a PEEP step simulated by a smoothed Heaviside function shown as a solid black line. The second is a profile, shown as a blue dashed line, in which a section of the original profile has been replaced with an H^1 minimal control. In this profile a 10 s



Figure 4.7: Graphs comparing ventilation states (right) of four compartment model under ventilation by three different pressure controls (left): smoothed Heaviside increase in pressure (black), H^1 refined control (blue), Target optimised control (red).

section of the first profile, shown between two vertical dashed lines in the figure, have been replaced with the H^1 minimal profile attaining the same pressures and volumes as the original profile at times t = 15 and t = 25. This is the same profile as was shown in figs. 4.3 and 4.4 and discussed in section 4.3.1.

The final profile shown as a red dotted line in fig. 4.7 is a control in which the 10 s control period has been replaced with an optimised control produced using algorithm 4.3. For the generation of this 10 s control, the initial pressure and volume conditions were set to be those achieved by the original profile as was the final pressure. The minimum allowable pressure was set at $P_{min} = 14$ and the maximum allowable pressure was set at $P_{max} = 20$ in accordance with the minimum and maximum pressures attained by the original profile. Finally the matrix V was set as a diagonal matrix containing the compartmental tissue volumes and the target ratio vector \mathbf{r} was a filling factor vector with each entry set to 4. This corresponds to optimising the final compartmental filling factors towards a maximum inhalation filling factor of 4.

The choice to optimise each compartment to the same filling factor was taken as inhomogeneity in the pattern of lung ventilation is considered a significant factor contributing to ventilator induced lung injury (*VILI*) and is one of the factors attributed with the occurrence of VILI despite the use of lung protective ventilation [90, 116]. However, as shown in fig. 4.6 simply setting each compartment to the same volume in the target ventilation state for H^1 control can result in pressures greatly exceeding safe levels. Therefore this technique appears to have great utility as it is able to optimise towards this state while staying within safe bounds of pressure and guaranteeing that no other profile could attain the same ventilation state with lower gradients in pressure. In fact, fig. 4.7 demonstrates that this optimal control attains a greater recruitment in every compartment during the PEEP step, as shown by the higher volumes in these compartments. This effect persists past the end of the control segment and is beneficial as greater recruitment in under-recruited regions can improved the mechanical parameters of the lungs in a clinical setting [6].

Algorithm 4.3 Control: Target Optimisation

1: Retrieve parameters R_0 , R_i and E_i for i = 1:42: Set control time T, initial state y_0 , initial pressure p_0 and target pressure p_T 3: Set minimum and maximum allowable pressures P_{min} and P_{max} 4: Set compartmental weighting matrix V and target ratio vector \mathbf{r} 5: Generate timestep vector $\mathbf{s} = 0$: dt : T 6: 7: % Find eigenvectors, U, and eigenvalues, $D = \text{diag}(\lambda_i)$ 8: $A = -R^{-1}E = UDU^{-1}$ 9: 10: % Find $\mathbf{\bar{b}}$ such that 11: $B = R^{-1}\mathbf{b} = U\bar{\mathbf{b}}$ 12:13: % check controllability matrix \bar{K} 14: $\bar{K} = [\bar{\mathbf{b}}, D\bar{\mathbf{b}}, D^2\bar{\mathbf{b}}, D^3\bar{\mathbf{b}}]$ 15:16: if rank $\overline{K} = 4$ then % Reformulate to control gradient 17: $\lambda_5 = 0$ 18: $\tilde{U} = [U, E^{-1}\mathbf{b}; 0, 1]$ 19: $\tilde{A} = [A, B; 0, 0]$ 20: $\tilde{\mathbf{b}} = \tilde{U}^{-1}[0;0;0;0;1]$ 21: 22: % Generate gramian \bar{Q}_T 23: $G = \mathbf{b}\mathbf{b}^*$ 24: $(\bar{Q}_T)_{ij} = \frac{(G)_{ij}}{\lambda_i + \lambda_j} (\exp\{(\lambda_i + \lambda_j)T\} - 1)$ 25: $(\bar{Q}_T)_{55} = (G)_{55}T$ 26:27:%Generate time exponential vectors 28: $\mathbf{e}_{\mathbf{i}} = \exp\{\lambda_i (T - \mathbf{s})\}$ 29:30: 31: % Calculate matrix formulation M $M = [\mathbf{e_1}, \mathbf{e_2}, \mathbf{e_3}, \mathbf{e_4}, 1] \operatorname{diag}(\mathbf{b}) \bar{Q}_T^{-1} \tilde{U}^{-1}$ 32: Construct a numerical integration matrix L, eg. composite trapezium 33: $M = [M_x, \mathbf{m}_p] = LM$ 34: 35: % Solve quadratic optimisation problem 36: $\boldsymbol{y_T} = \arg\min_{\boldsymbol{x}} [\boldsymbol{x}^* V^{-2} \boldsymbol{x} - \mathbf{r} V^{-1} \boldsymbol{x}]$ 37: % Subject to linear constraints 38: $[\tilde{M}_x; -\tilde{M}_x] \mathbf{x} \le [P_{max} - p_o; p_0 - P_{min}] + [\tilde{M}, -\tilde{M}] \exp\{T\tilde{A}\}[\mathbf{y_0}; p_0] + p_T[-\mathbf{m_p}; \mathbf{m_p}]$ 39: 40: % Generate control 41: $\boldsymbol{u} = \tilde{M}([\mathbf{y}_{\mathbf{T}}; p_T] - \exp\{T\tilde{A}\}[\boldsymbol{y}_0; p_0]) + p_0$ 42: 43: end if

4.4.2 Breath to breath optimisation

The techniques mentioned in section 4.4.1 are not limited to isolated individual segments of pressure control generation. The same approach can be applied to the generation of multiple connected control segments and even the optimisation of individual breaths. To do this the first step is to define when breathing sections will occur and what the pressures should be at the beginning and end of these segments. The next step is to optimise the target volumes of the first segment, after which the results of the preceding optimisation can be used as the initial conditions for the next segment and another optimisation. By specifying that the target pressure is the same as the initial pressure within a given segment the resulting control can be made to cause a single inhalation and exhalation. An outline for this procedure is shown in algorithm 4.4.

Algorithm 4.4 Control: Multiple Optimisation

1:	Set number of control periods N
2:	Set times for beginning and end of control sections t_i for $i = 0, 1,, N$
3:	Set desired pressures at these times $p(t_i) = p_i$
4:	Set initial volume as $\boldsymbol{v}(t_0) = \boldsymbol{v_0}$
5:	
6:	for $i = 1, 2,, N$ do
7:	Set initial volume conditions for optimisation to $\boldsymbol{v_{i-1}}$
8:	Set initial pressure conditions for optimisation to p_{i-1}
9:	Set final pressure conditions for optimisation to p_i
10:	
11:	$\%$ Generate next target volume $\boldsymbol{v_i}$
12:	Generate volume using algorithm 4.3
13:	end for
14:	
15:	Generate full control pressure with targets given by p_i and $\boldsymbol{v_i}$

Figure 4.8 shows a demonstration of this multiple optimisation process, combining optimised regular breathing with an optimised PEEP step as demonstrated in the previous section. For this figure a sinusoidal pressure profile with smoothed PEEP step is compared to a fully optimised breathing cycle. To generate the optimised pressure control shown in blue on the figure, 10 separate control optimisation intervals were defined for use in algorithm 4.4. For the first 6 and last 3 intervals the initial pressure, target pressure and minimum bound for pressure were set to the minimum value attained by the sinusoidal pressure for the same



Figure 4.8: Graphs comparing a sinusoidal pressure profile with smoothed heaviside PEEP jump to a fully optimised breathing cycle with optimised PEEP step.

time periods. At the same time the maximum bound on the pressure was set to the maximum pressure attained by the sinusoidal profile. This choice was made to allow the optimisation algorithm to pick target states corresponding to raises in pressure which would not exceed the range of the sinusoidal profile and would return to PEEP level giving an inhalation and exhalation phase. The seventh interval was the longest, taking place over the length of 3 breaths in the sinusoidal profile. The target pressure for this interval was set to the new PEEP level to generate an optimised PEEP step as demonstrated in fig. 4.7.

As with the example in the previous section the optimisation of each segment in this profile required a choice of compartmental weighting given in matrix Vand target ratio r. These were chosen to be the same weighting and ratio as used to generate fig. 4.7. For each breath the optimisation was performed using the resulting target from the previous breath as the next initial condition.

The optimisations performed for the *regular breathing* segments, excluding the PEEP step in segment 7, resulted in pressures rising quickly in each segment to achieved the upper boundaries placed on pressure. This rise was followed by a small oscillation and a quick return to exhalation pressure. The fact these optimisations achieved the bounds placed on pressure is unsurprising. These controls result from a quadratic minimisation problem for which the true minimum is known to be outside of the feasibility set, implying that the constrained minimum will be on the boundary. Of more interest is the similarity between these optimised breaths and a form of ventilation currently in use in clinical settings called airway pressure release ventilation (APRV). In this mode of ventilation, pressures are held at a constant positive airway pressure (CPAP) for a large proportion of each breath followed by a short period in which the pressure is dropped sharply to PEEP level before being returned to CPAP [120]. It is also common during CPAP to have small oscillations in pressure which are attributed to the need for spontaneous breathing [121].

The pressures and resulting ventilation profiles in fig. 4.8 are encouraging for the use of these control optimisation procedures in a clinical setting. The ventilation profiles show increases in recruitment even during regular breathing phases. This combined with the fact that they can be optimised to reduce risk factors such as lung heterogeneity [90, 116], through filling factor optimisation, and alveolar dead space [10], through VQ optimisation, suggests they can provide benefit to ventilator patients. Finally, the fact that the resulting profiles show similarities to currently used techniques raises the prospect that further research will be able to modify the optimisation algorithms to include further, clinicallyrequired features.

4.5 Control from recovered parameters

Through this chapter we have addressed many of the concerns which may prevent the use of EIT as a feedback mechanism for mechanical ventilation in a clinical setting. In section 4.1 we deduced that the model in chapter 3 is controllable for a wide range of lung parameters, hence it is feasible to start designing control schemes from EIT recoverable parameters. In section 4.3 we demonstrated that control techniques can be applied quickly to improve gradients of pressure over small sections of existing controls through a process of H^1 minimisation. In section 4.4 we designed a framework for optimising the H^1 minimal controls with respect to clinically relevant outcomes. The largest remaining obstacle to declaring EIT guided control feasible in this setting is an analysis of the controls under varying levels of error.

The two forms of error most likely to affect the resulting state of the ODE lung model are errors in the pressure controls applied to the system, due to mechanical limitations of the ventilators, and errors in the formulation of the pressure controls, caused by using inaccurately recovered lung parameters. All modern ventilators use closed-loop control to adjust their applied pressures and flow rate towards the *set point*, in this case a pressure waveform, defined by the clinician [110]. This means that measurements are taken at the airway to monitor pressure and flow, and the ventilator compensates to ensure the pressures do not deviate too far from the desired profile. Hence, for our sensitivity analysis we have focussed on errors in the generation of the pressure profiles themselves.

In this section we examine the quantitative and qualitative changes to generated control profiles when they are constructed not from the parameters used for numerically solving the governing ODEs, but from the parameters recovered through EIT. To do this we use the EIT difference imaging set up from chapter 3 to simulate best case EIT for six noise levels ranging from 50-100 SNR. At each of these noise levels we take one thousand realisations of the noise distribution and recover the model parameters as shown in chapter 3 then analyse both the distribution of recovered eigenvalues and the subsequent generated control profiles. Section 4.5.1 examines the difference in eigenvalues, controls and resulting ventilation distributions between using the true parameters and those recovered from EIT at 100 SNR as shown in section 3.4.3. Section 4.5.2 compares the successive changes in control as the noise level increases.

4.5.1 Control from EIT at 100 SNR

First we examine the construction of both H^1 minimal and optimised pressure controls from parameters recovered through EIT at 100 SNR. The recovery of these parameters and their sensitivity to noise and other changes are examined in section 3.5.

Before constructing the controls themselves it is important to check that the controllability property still holds. As discussed in section 4.1 this controllability relies on recovering distinct negative eigenvalues for the lung ODE model. The distribution of the eigenvalues produced from the parameters at this noise level are shown in fig. 4.9. This chart shows the minimum, maximum and mean absolute values of the recovered negative eigenvalues and indicates the range containing two standard deviations from the mean. The algorithm used to generate these values listed them in descending order, this means that the absolute value of eigenvalue 2 was always smaller than that of eigenvalue 1.



Figure 4.9: Chart comparing the distribution of recovered eigenvalues at 100 SNR to the values used in the forward problem. The bars indicated original values while the vertical lines are marked at the minimum, maximum, mean and two standard deviations from the mean.

From the chart in fig. 4.9 it is apparent that the less negative eigenvalues were recovered more accurately than the more negative ones. However, crucially, the eigenvalues remained distinct for each of the thousand tests at this noise level and all parameter sets were found to be controllable.

As the new recovered parameters were controllable we were able to compare their H^1 minimal and optimised pressure controls to those produced by true values from the system. To do this the PEEP step H^1 minimisation process from section 4.3 and a perfusion weighted PEEP step optimisation process, described in section 4.4, were repeated for each recovered parameter set. Quantitative comparisons of these recovered parameter control profiles can be found in table 4.2 and table 4.3.

4.5. CONTROL FROM RECOVERED PARAMETERS

Table 4.2 shows the difference between the pressure controls, $\bar{\mathbf{p}}$, generated with recovered parameters from the corresponding controls \mathbf{p} generated with the accurate parameter set. This error is measured in the L^2 norm and is normalised against the L^2 norm of \mathbf{p} ,

$$Error = \frac{\|\bar{\mathbf{p}} - \mathbf{p}\|_2}{\|\mathbf{p}\|_2}.$$
(4.67)

The maximum and minimum deviations from the accurate controls are given along with the mean change and standard deviation over the thousand reconstructions. The values in this table show that, at this noise level, it is possible to

Table 4.2: Errors in controls generated from recovered parameters relative to controls generated from accurate parameters. Errors are given measured using the L^2 norm as described in eq. (4.67).

Control Type	Min	Mean	Max	STD
	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$
H1	0.10	1.70	2.98	0.53
Optimised	0.01	0.41	1.00	0.18

generate pressure controls which are quantitatively close to the accurately calculated controls. However it is evident from the difference between the error values for the H^1 minimisation and the optimisation process that the optimised pressure controls are more stable with respect to noise in the recovered parameters.

This relative stability is emphasised further when we examine the change in the gradients present in the generated pressure controls. Table 4.3 shows the relative changes in the H^1 semi-norm for the generated controls. These changes are normalised against $|\mathbf{p}|_{H^1}$ to emphasise where using the wrong parameters can make large differences to the gradients of generated controls, giving the measure

$$Change = \frac{|\bar{\mathbf{p}}|_{H^1} - |\mathbf{p}|_{H^1}}{|\mathbf{p}|_{H^1}}.$$
(4.68)

In this table it is evident that both methods of control generation from recovered

Control Type	$ \text{Min} \\ (\times 10^{-2}) $	$Mean (\times 10^{-2})$	$\max_{(\times 10^{-2})}$	$\begin{array}{c} \text{STD} \\ (\times 10^{-2}) \end{array}$
H1	-0.93	14.67	28.72	5.50
Optimised	-3.21	-2.15	0.59	0.55

Table 4.3: Distribution of changes to the H^1 semi-norm of produced controls due to using the wrong eigenvalues. Values are given as calculated by the formula in eq. (4.68).

parameters can get close to the minimal H^1 properties of the accurately calculated controls. In some cases the gradients produced were in fact lower than those of the accurate controls, offsetting the fact that the resulting ventilation states will be changed. However, the optimised control gradients stay substantially more stable than the H^1 minimised gradients.

The relative stabilities of both approaches to control are also demonstrated when examining the qualitative behaviour of controls when constructed with reconstructed parameters. Figure 4.10 compares the H^1 minimal control generated using the true parameters to four other pressure controls generated from recovered parameters. These comparison controls are the controls which attained the minimum and maximum recruitment levels when used to steer the ODE lung models, along with the profile which came closest to the mean recruitment and the profile which was most different to the true profile as measured in the L^2 norm.

Qualitatively the profile attaining the maximum recruitment appears closest to the true profile, while both the minimum and mean recruitment levels appear similar. However, fig. 4.11 shows the ventilation pattern generated by the final profile which was most different from the true control as measured in the L^2 norm. Examining, these ventilation graphs show that even this profile results in a similar ventilation profile towards the end of the control period.

Figure 4.12 shows a similar qualitative comparison for the optimised controls. As the true parameter control generated by this method was calculated to have the optimum possible ventilation to perfusion ration, the comparison profiles for this figure were chosen to have the minimum, mean and maximum deviation from the optimised recruitment. The final profile again shows the maximum change in the profile as measured in the L^2 norm.



Figure 4.10: Graph comparing the generated H^1 minimal control profiles for different realisations of EIT at 100 SNR.

All the profiles shown here appear much more qualitatively similar than those shown for the H^1 minimisation process. This is demonstrated further by the ventilation pattern, shown in fig. 4.13, produced by the control with the largest deviation from the accurately optimised control. This ventilation profile only deviates slightly from the true optimum profile, emphasising the stability of this control generation method.

This analysis confirms that both the H^1 minimised and optimised control processes can produce acceptable controls when using recovered parameters. However, the controls generated through an optimisation process appear much more robust when it comes to EIT generated parameter noise. For this reason in section 4.5.2 we will primarily use the optimised control profiles to compare the effectiveness of control procedures at successively decreasing signal quality.



Figure 4.11: Graphs comparing the air volumes in each compartment under the action of H^1 minimal controls generated from true and recovered parameters. The blue dotted line was generated from the true parameters and the black line from the noise realisation generating the most different control profile as measured in the L^2 norm.



Figure 4.12: Graph comparing the generated optimised control profiles for different realisations of EIT at 100 SNR.



Figure 4.13: Graphs comparing the air volumes in each compartment under the action optimised controls generated from true and recovered parameters. The blue dotted line was generated from the true parameters and the black line from the noise realisation generating the most different control profile as measured in the L^2 norm.

4.5.2 Noise level comparisons

The analysis in section 4.5.1 shows that the optimised controls generated using parameters recovered by EIT at 100 SNR are not substantially changed from those generated using accurate parameters. This is encouraging for the development of EIT guided control, especially considering the fact 100 SNR is considerably lower than the practical maximum accuracy of EIT measurements. However, it is still necessary to examine the behaviour of our control generation schemes under rising levels of measurement noise in order to determine when they will no longer be feasible. To do this we used the same arrangement as in section 4.5.1 at 6 equispaced noise levels from 50-100 SNR. For each noise level parameters were recovered for one thousand realisations of measurement noise using a simulation of best case EIT from difference imaging as examined in section 3.5.

As in section 4.5.1 the first step in analysing the controls at these noise levels is to check eigenvalues and controllability. Through all the noise tests there was only a single instance of a negative recovered resistance. With this parameter set the system was in fact still analytically controllable as tested by the Kalman rank condition. However, the separation of eigenvalues was so small that the condition numbers for matrices requiring inversion were too high to numerically generate an optimised control. Every other test provided a system with good enough conditioning for the optimisation process.

The mean and standard deviation of the calculated eigenvalues at each noise level are shown in table 4.4 excluding the single experiment at 50 SNR for which a negative resistance value was recovered. This table shows that the mean recovered values for each eigenvalue remain separated and even become closer to their true values as the signal level decreases. However, the increased variance at successive noise levels is less encouraging. At 50 SNR the separation between eigenvalues can become small in the worst cases. Even in these cases the controllability of the system was maintained and optimised controls were generated.

The quantitative differences between these generated controls and the accurate optimal control can be seen in 4.5. This table shows the minimum, maximum, mean and standard deviation for the L^2 difference between the optimised controls generated with recovered parameters and the control generated with accurate parameters. All values are calculated and normalised according to the formula in eq. (4.67).

	Eigenv	alue 1	Eigenv	alue 2	Eigenv	alue 3	Eigenv	alue 4
SNR	mean	STD	mean	STD	mean	STD	mean	STD
TRUE	-2.698	-	-1.740	-	-0.721	-	-0.341	-
100	-1.774	0.236	-1.307	0.118	-0.638	0.027	-0.340	0.005
90	-1.809	0.275	-1.323	0.134	-0.642	0.030	-0.340	0.006
80	-1.861	0.332	-1.345	0.156	-0.647	0.034	-0.341	0.006
70	-1.940	0.423	-1.378	0.188	-0.654	0.040	-0.342	0.007
60	-2.079	0.609	-1.431	0.238	-0.665	0.048	-0.344	0.008
50	-2.352	1.025	-1.523	0.321	-0.684	0.059	-0.346	0.010

Table 4.4: Eigenvalue recovery from noisy difference data at varying SNR

Table 4.5: Comparison of computed optimal controls as measured in the L^2 norm according to the formula in eq. (4.67).

SNR	Min	Max	Mean	STD
	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$	$(\times 10^{-2})$
100	0.01	1.00	0.41	0.18
90	0.02	0.98	0.40	0.19
80	0.03	1.05	0.38	0.20
70	0.02	1.14	0.36	0.21
60	0.02	1.26	0.35	0.22
50	0.01	2.28	0.36	0.26

The fact that the minimum and mean changes in the optimised controls remain near constant across the noise levels is encouraging. This implies that the desirable properties of control from section 4.4 may be achieved even at lower signal levels. However, as expected the maximum error and variance generally increase with noise level.

To check how effective the optimised controls will be at decreased signal qualities we need to check the resulting ventilation profiles for the controls generated at these noise levels. As the optimisation process used optimised towards a target VQ ratio we will use the difference from this optimal ratio to measure control quality. To do this we calculate the VQ ratio vector at the end of the control segment as

$$\mathbf{r} = \left(\frac{v_1}{q_1}, \frac{v_2}{q_2}, \frac{v_3}{q_3}, \frac{v_4}{q_4}\right),\tag{4.69}$$

where v_i is the air content of compartment *i* at the end of the control segment and q_i is the perfusion level for the compartment as provided for the optimisation process. The reduction in quality between the VQ ratio for the accurate parameter set, **r**, and the ratio for the recovered parameter set $\bar{\mathbf{r}}$, is then measured as

$$Error = \frac{\|\bar{\mathbf{r}} - \mathbf{r}\|_2}{\|\mathbf{r}\|_2},\tag{4.70}$$

where values have been normalised against $\|\mathbf{r}\|_2$ to aid in comparison. The minimum, maximum and mean values for this measure are shown in table 4.6.

Table 4.6: Comparison of attained ventilation perfusion levels. Values given are calculated according to eq. (4.70).

SNR	Min	Max	Mean $(\times 10^{-2})$	STD
	(×10)	(×10)	(×10)	(×10)
100	0.001	0.209	0.105	0.039
90	0.005	0.226	0.100	0.043
80	0.006	0.239	0.095	0.046
70	0.003	0.248	0.089	0.048
60	0.002	0.253	0.085	0.051
50	0.004	0.623	0.086	0.058

Similarly to the previous measure of control quality, the small percentage changes shown in this table emphasise the stability of the control optimisation process to EIT measurement noise. As expected both the maximum reduction in VQ ratio and the standard deviation increase as the signal quality decreases. However, the mean VQ reduction appears to decrease for lower SNR values.

4.5. CONTROL FROM RECOVERED PARAMETERS

To try and explain these VQ results we examine the qualitative behaviour of the controls. Both fig. 4.14 and fig. 4.15 compare optimised control profiles generated at the 6 SNR levels to the optimised control generated with accurate parameters. Figure 4.14 shows the profile for each SNR level which decreased the VQ ratio the most. Figure 4.15 shows the profile at each SNR which came closest to producing the mean VQ ratio for the level.



Figure 4.14: Graph comparing profiles generated in a control optimisation procedure from EIT at 6 levels of SNR. The profiles shown are those which deviated the most from the true optimal profile as indicated by the black dotted line.

Both graphs show that the controls appear to follow a similar profile to the accurate control which has been shifted slightly. The distribution in fig. 4.15 appear to follow the accurate control more closely confirming the results shown in table 4.5 and table 4.6. The plots of the mean profiles for SNR levels 50 and 60 are plotted on top of each other and appear to more closely follow the path of the final few seconds of the accurate control. This could account for the improved mean VQ ratios at these noise levels.



Figure 4.15: Graph comparing the mean profiles generated in a control optimisation procedure from EIT at 6 levels of SNR. The Black dotted line indicates the pressure control generated from the true parameters.

A possible explanation for this behaviour is the increased mean magnitudes of the recovered eigenvalues as shown in table 4.4. These larger negative eigenvalues would result in faster decaying eigenmodes and would require greater change to the ventilation pattern to occur towards the end of the control sequence.

4.6 Conclusion

This chapter has addressed many of the concerns which may prevent the use of EIT as a feedback mechanism for mechanical ventilation in a clinical setting. In section 4.1 we deduced that the model in chapter 3 is controllable for a wide range of lung parameters, hence it is feasible to start designing control schemes from EIT recoverable parameters.

In section 4.3 we demonstrated that control techniques can be applied quickly to improve gradients of pressure over small sections of existing controls through a process of H^1 minimisation. In section 4.4 we designed a framework for optimising the H^1 minimal controls with respect to clinically relevant outcomes. Finally in section 4.5 we confirm that optimised controls may be generated from EIT recovered lung parameters at a range of signal qualities and still provide benefit to the ventilation of the patient.

There remain several hurdles before attempting practical implementation of these techniques in a clinical setting. For example the sensitivity analysis in section 4.5 was performed using simulated best case EIT, these techniques will have to be tested with more practical implementations of EIT. Similarly for these tests the ventilation profiles used to generate the EIT signal were produced using the same model used for parameter recovery, control and control testing. An important next step in testing this workflow is to attempt parameter recovery on ventilation profiles which have been generated using a more advanced lung model. Additionally work could be done on determining the best optimisation criteria for the techniques in section 4.4 to more closely link control objectives with desirable clinical outcomes.

Even though these further steps will be required before clinical testing may begin, this chapter represents an important step in determining the utility of EIT to not only inform patient care but actively design ventilator controls. We have shown that EIT can be combined with simple modelling and standard control theory techniques to actively optimise patient care.

Chapter 5

Conclusion

The work in this thesis was motivated by an observed need for improved bedside monitoring and control of ventilation in respiratory intensive care. The use of EIT for this monitoring has been studied for over 30 years due to its ability to safely provide long term monitoring at the bedside. Building on this work we have produced a novel framework to not only retrieve regional ventilation profiles and meaningful lung parameters, but also include EIT directly into the control of mechanical ventilation. This represents the first time that the feedback loop between ventilation and EIT has been closed.

With the aim of providing a framework for the retrieval of lung parameters and production of pressure control profiles three important tasks have been achieved. The first, described in chapter 2, was to produce an EIT reconstruction algorithm capable of providing 3D, regionally-absolute values of conductivity in real time. The second, described in chapter 3, was to design a coupling method between EIT and lung modelling allowing the recovery of ventilation distributions and lung parameters in a clinically meaningful capacity. The final task, described in chapter 4, was to determine under what conditions recovered parameters could be used to procedurally construct pressure controls and determine how they might produce clinical benefits to the patient.

The novel pseudo-absolute algorithm developed in chapter 2 is a fast, regionallyabsolute reconstruction method for clinical EIT. In chapter 2 we additionally showed that, despite a reliance on grouping constraints, the pseudo-absolute algorithm still provides benefit when there are errors in the segmentation, meshing and modelling assumptions. In particular the increased accuracy in reconstruction of interior conductivity changes in between the lungs merits further research. In chapter 3 we developed a lung model for which ventilation states are observable on a scale which is feasible for segmentation and reconstruction through EIT. We were able to show in chapter 3 that, with extremely limited post-processing time, it is possible to estimate not only regional air volumes and flows but also regional measures of elastance and airway resistance from EIT. This parameter estimation was proven to be feasible for periodic pressure controls so long as there are regional phase differences in the ventilation distribution. We also showed that the recovered elastance parameters and time constants are reasonably robust with respect to both EIT measurement noise and modelling errors in the reconstruction process.

Finally in chapter 4 we used the same ventilation model as above to demonstrate a method generating pressure controls for mechanical ventilation. These profiles were shown to have minimal gradients as measured in the H^1 semi-norm and could be used to define an optimisation scheme to maximise recruitment while constraining tidal pressure variations. The ability to produce these pressure controls was linked to the controllability of the parameters for the ODE lung model. Crucially we proved that the system is more likely to be controllable the more regions of the lung ventilate out of phase with each other.

5.1 Further work

The work in this thesis highlights many further avenues for research. In the first instance there are smaller improvements to the current work. For example testing the post-processing techniques in chapters 3 to 4 with a larger range of parameter values, or modifying the parameter recovery process to more accurately model error in the reconstructed ventilation distributions through the use of constrained total least squares [107, 108].

Similarly there are interesting potential directions of research opened up by the formulation of the pseudo-absolute reconstruction algorithm. For example the evidence of greater sensitivity to interior changes shielded by the lungs suggests it may be useful for separating out cardiac signals in EIT. However, the research directions we find of particular interest are further performance enhancements for Gauss-Newton type EIT reconstructions, validation of the pseudo-absolute algorithm on a wider range of datasets and verification of the post-processing techniques on more advanced lung models.
The efficiency savings described in section 2.4, while useful, do not represent a complete list of available performance enhancements for Gauss-Newton type EIT reconstructions. Savings may still be made by balancing the need for accuracy at specific stages of the algorithm with the need for speed. For example during the line search forward solves require less accuracy, allowing the use of iterative methods with relaxed convergence tolerances. Such techniques include the conjugate gradient method [122] or other Lanczos-type Krylov subspace methods [123, 124] in the case of complex admittance. Alternatively, solutions using different formulations of the problem can allow the same level of accuracy with lower computational cost. For example higher order FEM solutions to the forward problem have been shown to generate the same level of accuracy in different norms in less computational time for 2D reconstructions [125].

Additionally, testing of the pseudo-absolute reconstruction algorithm in this thesis was performed without including deformation of the chest or movement of the lungs and electrodes. This was a reasonable simplification of the system to allow for testing of the post-processing techniques under the assumption that domain deformation and electrode movement could be measured and modelled during data acquisition. However, it does raise the question of how the algorithm will perform on models including these additional parameters and ultimately how it will perform on real data. Further work could therefore consist of testing the pseudo-absolute reconstruction algorithm on animal datasets or patient datasets for which there exist general lung shape models.

The most important piece of further work is to test how the parameter recovery and control procedures behave under changes to the underlying lung model. In this thesis the same ODE model has been used for the ventilation forward solve as for the parameter recovery and control generation. Therefore these techniques still need to be validated against more accurate models of lung function such as those with a much higher number of compartments or CFD models.

Appendix A

Additional inner-product spaces

The freedom in defining the inner product to use for our measure allows us to incorporate desirable information about data-fit and modelling assumptions into our comparison with ground truth images. Additionally the measure can be weighted depending on the intended use of the reconstructions. Hence, by careful choice of the inner products used we can incorporate all four criteria for judgement of a reconstruction as mentioned in section 2.3.1.

Three examples of interesting inner products are:

- 1. the matrix inner product on \mathbb{R}^n with the diagonal matrix containing volume of each element,
- 2. a combination of the previous inner product with a matrix inner product approximating a differential operator,
- 3. an inner product defined by the objective function used in formulating the linearised difference reconstruction.

The first inner product listed has been discussed in section 2.3.1. The main issue with inner product one is the lack of any modelling information. This can be addressed by introducing an approximate differential operator matrix R such that the inner product becomes

$$\langle u, v \rangle_{DR} = \langle u, v \rangle_D + \alpha u^T R^T R v, \qquad \alpha \in \{ x \in \mathbb{R} | x > 0 \}$$

= $u^T (D + \alpha R^T R) v.$ (A.1)

The choice of operator R then depends on the modelling assumptions of the reconstruction. Emphasis on the smoothness of the solution can be increased or decreased by adjusting the regularisation hyper-parameter α . The difficulties and advantages of implementing different matrix approximations to differential operators have been discussed in another section. The two which have been examined in this thesis are the Adjoint Graph Laplacian and the Finite Volume Laplacian.

The Adjoint Graph Laplacian operator works by taking the difference between two nodes on the adjoint graph to the reconstruction mesh but does not take into account the varying sizes of neighbouring elements. As such, where another differential operator might penalise variations between elements differently depending on the length scale at that point in the mesh, this operator applies the same weighting to changes in areas of both high and low mesh refinement. Depending on the assumed regularity of the problem this can be advantageous for regularisation especially when the mesh is assumed to be deformed as in reconstructions accounting for domain shape changes. This operator has been used to regularise many of the reconstructions in this work, making it the natural differential operator to use as part of our inner product. However, this inner product relies explicitly on the discretisation of the domain and does not directly relate to biological qualities or assumptions on the spatial smoothness of the conductivity maps.

The Finite Volume approximation to the Laplacian has the advantage that it approximates a spatial Laplacian in Cartesian coordinates rather than the Graph-Laplacian. Application of this operator R to the vector of conductivity values ugives a vector containing the integrals of the Laplacian on each element of the mesh,

$$(Ru)_k \approx \int_{E_k} \Delta u(\mathbf{x}) \mathrm{d}V.$$
 (A.2)

So formulating the inner product as above we get

$$\langle u, v \rangle_{DR} = \langle u, v \rangle_D + \alpha u^T R^T R v,$$

= $\langle u, v \rangle_D + \alpha \sum_{k=1}^n \left[\int_{E_k} \Delta u(\mathbf{x}) dV \right] \left[\int_{E_k} \Delta v(\mathbf{x}) dV \right].$ (A.3)

This formulation of the inner product now explicitly contains information on the length scales over which the conductivity maps are changing. However, this measure is not the only possible use of the Finite Volume Laplacian to define an inner product.

It is possible to find a formulation of the inner product which approximates the L^2 inner product acting on the Laplacian function,

$$\langle \Delta u, \Delta v \rangle_{L^2} = \int_{\Omega} (\Delta u(\mathbf{x})) (\Delta v(\mathbf{x})) \mathrm{d}V$$

This can be done by finding the volume average of the required Laplacians in each element

$$\mu_k = \frac{\int_{E_k} \Delta u(\mathbf{x}) \mathrm{d}V}{\int_{E_k} 1 \mathrm{d}V}, \qquad \qquad \nu_k = \frac{\int_{E_k} \Delta v(\mathbf{x}) \mathrm{d}V}{\int_{E_k} 1 \mathrm{d}V}, \qquad (A.4)$$

$$= (D^{-1}Ru)_k = (D^{-1}Rv)_k$$
 (A.5)

and integrating these quantities over the respective elements. This formulation reduces to

$$\langle u, v \rangle_{DR} = \langle u, v \rangle_D + \alpha \mu D \nu,$$

= $\langle u, v \rangle_D + \alpha u^T R^T D^{-1} R v,$
= $u^T (D + \alpha R^T D^{-1} R) v.$ (A.6)

Looking at the inner product shown in eq. (A.6) as the maximum element volume tends to zero we see that

$$\lim_{\max(D)\to 0} \langle u, v \rangle_R = \int_{\Omega} u(\mathbf{x}) v(\mathbf{x}) dV + \int_{\Omega} (\Delta u(\mathbf{x})) (\Delta v(\mathbf{x})) dV,$$
$$= \langle u, v \rangle_{L^2} + \langle \Delta u, \Delta v \rangle_{L^2}.$$
(A.7)

It is interesting to note that such a formulation could be performed with other matrix approximations to differential operators. One particularly interesting operator not explored here is the approximation of the gradient operator on an unstructured mesh which would produce an approximation to the H^1 inner product over the mesh. It is also interesting to note that this formulation can be related to the H^2 Sobolev Space inner product as the induced norm of the L^2 inner product on the Laplacian is equivalent to the H^2 semi-norm as shown in the regularisation section. However, the full implementation of the H^2 norm has not been examined here.

The final inner product mentioned above is derived from the objective functional formulation of the EIT reconstruction,

$$F = \|V(\sigma) - m\|^2 + \alpha \|R\sigma\|^2,$$
 (A.8)

where V is the forward operator taking the conductivity map σ to a voltage, m is the measured voltage, α is a regularisation hyperparameter and R is one of the differential operators described above. Taking the value of the cost functional F is a standard technique for verifying the solution to an inverse problem and is usually called calculating the residual. However, F is unlikely to be zero for the true solution so taking the angle defined by the inner product

$$\langle u, v \rangle = \langle V(u), V(v) \rangle + \alpha u^T R^T R v$$
 (A.9)

allows a comparison of the reconstruction with the true solution under the modelling conditions used to reconstruction the image.

This formulation can be adjusted either to take into account the absolute values of conductivity given by the pseudo-absolute reconstruction algorithm or to simply take the difference measurements. This can be done by either performing a full forward solve or by using a Jacobian matrix to perform a linearised solve on the difference image.

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