Volume Estimation from Three-Dimensional Hyperpolarized ^{129}Xe Magnetic Resonance Images

by

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Abstract

Optical pumping and spin exchange methods can enhance the nuclear spin polarization of ^{129}Xe by 4 to 5 orders of magnitude to facilitate magnetic resonance (MR) imaging. This hyperpolarized ^{129}Xe can be delivered to both *in vitro* and *in vivo* gas spaces (i.e., lungs).

This thesis presents an approach to volume estimation from three-dimensional hyperpolarized images using the Carleton Magnetic Resonance Facility (CMRF) system. Phantoms were designed to test the performance of the proposed MR volume estimator *in vitro*. Rat lungs were also imaged *in vitro* and *in vivo*. To test the sensitivity of the MR volume estimator, *stachybotrys chatarum* fungal spores, known to cause lung volume changes due to inflammation, were instilled into the lungs of six 300 g Wistar rats while three rats were used as controls.

For the phantom images with signal-to-noise ratio (SNR) values greater than 7.5, the MR volume estimator overestimated geometrically estimated volumes by $2\% \pm 6\%$ with a 68% confidence level. Monte Carlo simulated images and phantom data indicated that increases in resolution and SNR are expected to improve measurement accuracy.

For *in vitro* and *in vivo* rat lung images, the imaging resolutions used were insufficient to estimate absolute lung volumes, providing only an upper-limit for the estimation of lung volumes which did not account for the presence of tissue. The uncertainties for upper-limit lung volumes were on the order of 5% to 20% of the estimated values, and statistics were insufficient to resolve trends associated with the spore instillation experiments. Entubation and improvements in ^{129}Xe polarization and imaging methods will likely allow *in vivo* absolute rat lung volume studies from 3D hyperpolarized ^{129}Xe MR images in the future.

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List of Abbreviations

3D	Three dimensional/dimensions
3DVAGE	Three dimensional variable flip angle gradient echo
CFA	Constant flip angle
CMRF	Carleton Magnetic Resonance Facility
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DTPA	Diethylenetriaminepentaacetic acid
FEV	Full expiratory volume
FFT	Fast Fourier transform
FID	Free induction decay
FOV	Field of view
FRC	Functional residual capacity
FT	Fourier transform
FWHM	Full width at half maximum
HNG	Hyperpolarized noble gas
ML	Maximum likelihood
MR	Magnetic resonance
NMR	Nuclear magnetic resonance
PET	Positron emission tomography
PDF	Probability density function
PFT	Pulmonary function test
RF	Radio frequency
ROI	Region of interest

SIMS	Steacie Institute for Molecular Sciences
SNR	Signal-to-noise ratio
SPECT	Single photon emission computed tomography
T_1	Longitudinal relaxation time
T_2	Transverse relaxation time
TE	Echo time
TR	Repetition time
VFA	Variable flip angle

1 Introduction

1.1 Historical Background

1.1.1 Magnetic Resonance Imaging

Since the discovery of X-rays and their potential for medical diagnostic imaging by Roentgen in 1895, the understanding of human physiology and anatomy has improved significantly from the use of non- and mildly invasive imaging modalities. Modern imaging technologies now provide a variety of means to assess the anatomical and physiological status of patients at negligible or low risks to patients and clinicians alike. Among them, magnetic resonance (MR) imaging, a non-invasive and non-ionizing modality, is renowned for its soft tissue contrast, multi-planar cross-sectional views, and lack of known physiological side-effects.

Nuclear magnetic resonance (NMR) is a means for studying a group of nuclear spins polarized in a primary external magnetic field by inducing and detecting secondary magnetic fields orthogonal to the primary field. The discovery of NMR was announced by Bloch [1] and Purcell [2] in 1946. Thereafter, there was steady development of NMR spectroscopy in chemistry, biology and medicine, though it was not until 1973 that Lauterbur published the first MR image of two tubes of water using linear magnetic gradients [3]. The first human image of a live finger [4] was reported by Mansfield and Maudsley in 1976 and was followed by a hand [5] and a thorax [6] in 1977. 1978 yielded the first MR brain [7] and abdominal [8] images, and the first commercial NMR scanner. Superconducting full-body MR imaging systems are now available in many hospitals, and are capable of imaging practically any part of the human body. The use of MR

imaging by the medical community has enjoyed sustained expansion. Moreover, research and development continue to lead to new and improved applications.

While NMR can be effectively used to examine a variety of nuclei, the vast majority of clinical MR imaging is of ^1H nuclei (protons) attached to the water molecules that account for 60 to 80% of the human body mass [9]. Non-proton imaging suffers from low atomic density and sensitivity *in vivo*. In terms of natural abundance in the body and sensitivity, ^{23}Na and ^{31}P are the most common candidates for non-proton MR and are used for metabolic studies [10]. While numerous nuclei could be introduced *in vivo* for the purpose of non-proton MR imaging, most would require concentrations that lead to unacceptable toxic effects. Among the low toxicity nuclei available are the inert noble gases ^3He and ^{129}Xe .

1.1.2 Hyperpolarized Noble Gases

In 1950 Kastler described that the ground state of nuclear spins in a magnetic field could be populated by optical pumping using circularly polarized light [11]. Techniques for this hyperpolarization of noble gases via optical pumping and spin-exchange were developed throughout the 1980s by Happer's group [12][13][14], and in 1991, Pines reported NMR spectroscopy studies using hyperpolarized ^{129}Xe [15].

While chemically inert, the Xe atom's large electron cloud makes it susceptible to forming Van der Waals bonds with other molecules. When inhaled or injected into the blood stream in high enough doses Xe is a general anaesthetic. Knowing ^{129}Xe was a candidate for NMR experiments; in the early 1990s Albert *et al* were considering ^{129}Xe for a functional study of anaesthetics *in vivo*. The resonant frequencies and relaxation times of ^{129}Xe in biological systems were measured, oxygen (O_2) was characterized as a relaxation agent, and it was determined that the ^{129}Xe signal for conventional MR imaging was too weak by approximately three orders of magnitude. Albert *et al* adopted the ^{129}Xe optical pumping and spin-exchange technique, and in 1994 reported images of

excised mouse lungs obtained in a time of 600 ms with ^{129}Xe gas hyperpolarized by five orders of magnitude [16]. Methods similar to those described for ^{129}Xe were also developed for ^3He [17][18][19], resulting in the birth of hyperpolarized noble gas (HNG) MR imaging. HNG-MR is well suited to both structural and functional experiments, and in the medical physics community has provided a new means of examining gas spaces *in vivo*. This capability makes HNG-MR an attractive candidate for studies of the respiratory system, in particular those of the lung.

1.2 Examination of the Respiratory System

The lung is the primary subject of interest for most HNG-MR studies. Section 1.2.1 describes the basic structure and function of the human lung, and Section 1.2.2 provides a general description of the diseases that affect it. For more detailed information on lung structure and diseases the reader is referred to West [20] and [21] respectively. Current clinical tests and imaging modalities, including the application of HNG-MR are described in Section 1.2.3.

1.2.1 Structure and Function of the Human Lung

The principle function of the lung is to exchange gas, allowing O_2 to enter the blood stream and CO_2 to leave it. O_2 and CO_2 move between air and blood via simple diffusion, i.e., from an area of high to low partial pressure. Fick's law of diffusion states that the amount of gas that moves across a fluid membrane is proportional to the area of the membrane and inversely proportional to its thickness. The blood-gas barrier meets the criteria for optimal diffusion quite well, with thicknesses of about $0.3\text{ }\mu\text{m}$, and surface areas on the order of $50\text{ to }100\text{ m}^2$. The lung achieves these dimensions in the confines of the thoracic cavity with a total volume of about 3 L by consisting of approximately 300

million air sacs wrapped in blood vessels, known as alveoli, each about 0.3 mm in diameter, and the bronchial tree. The tissue that makes up the alveolar sacs is known as the lung parenchyma.

Figure 1.1 Practical idealization of the human airways, adapted from [20]. Z indicates the branching generation.

The bronchial tree serves to deliver gas to the alveoli. An idealized representation of the human airways with 23 branching generations is shown in Figure 1.1. The tree begins with the trachea which bifurcates* into the right and left main bronchi, which in turn bifurcates into the lobar, then segmental bronchi. This branching continues for approximately 16 generations down to the terminal bronchioles. All the bronchi make up the conducting airways and are often referred to as the anatomic dead space as they do not participate in gas exchange. The anatomic dead space accounts for approximately 150 mL of the total lung volume. The terminal bronchioles are connected to the respiratory bronchioles, where occasional alveoli begin to line the bronchiole walls. The branching pattern continues in the respiratory bronchioles for a total of 23 generations.

* Bifurcation is a branching criterion that is energetically favourable for fluid transport, whereby the diameters of the parent and daughter vessels d_0 , d_1 and d_2 respectively, are related by $d_0^x = d_1^x + d_2^x$, and x is the bifurcation exponent. [22]

Elements of the final generation are known as alveolar ducts, and are completely lined with alveoli. The distance from a terminal bronchiole to the most distal alveolus is only a few mm, and is known as the acinus.

Figure 1.2 Illustration of various lung volume definitions and their estimation using spirometry [20]

Various definitions of lung volume are illustrated in Figure 1.2. The volume of the lung is regulated by the diaphragm and intercostal muscles. During inspiration, the volume of the thoracic cavity is increased and air is drawn through the airways by the pressure gradient. Beyond the terminal bronchioles, the cross-sectional area of the lung is large enough that the forward velocity of the gas becomes small and diffusion becomes the dominant mechanism of gas transport. The rate of diffusion of gas molecules within the respiratory bronchioles is rapid with respect to the distance to alveoli, such that differences in concentration within the acinus are abolished within a second. The maximum inflation of the lung is referred to as the total lung capacity. For most normal breathing the total lung capacity is not required and breaths are somewhat smaller. The change in volume of the lung for normal breathing is referred to as the tidal volume.

The lung is elastic and returns passively to its preinspiratory volume during normal breathing. Pressures required to distend and move gas through the lung are on the order of 200 to 300 Pa. The relationship between the pressure and volume of the lung during respiration traces out a hysteresis curve, illustrated in Figure 1.3, the slope of which is the lung compliance. The compliance of the human lung is about 2 mL/Pa.

In a deflated state, the structure of the lung may be considered a collection of 300 million bubbles with relatively little supporting tissue. In order to prevent surface tension effects from collapsing the alveoli, cells within the parenchyma secrete surfactant which dramatically lowers the surface tension of the alveolar lining layer. In addition, the lung is never completely deflated and maintains a gas volume known as the functional residual capacity (FRC) during normal breathing. With forced expiration it is possible to deflate the lung further, though not empty, leaving a residual volume of gas. The vital capacity is the difference between the total lung capacity and the residual volume.

Figure 1.3 Illustration of the pressure-volume relationship of an excised animal lung [20]

1.2.2 Diseases Affecting the Lung

Like any biological structure, the lung is susceptible to a variety of diseases. These diseases are classified by their general effect on the lung into obstructive, restrictive, vascular and environmental diseases.

Obstructive diseases prevent gas from reaching the vasculature in the alveolar walls. This may be due to airway obstruction via foreign particles or mucus as in bronchitis, narrowing of the airways such as in asthma, or by the destruction of the alveolar walls as in emphysema. While asthma and material obstruction are clearly identifiable, other diseases resulting in emphysema, chronic bronchitis and other chronic phenomena are often grouped using the term “chronic obstructive pulmonary disease” (COPD).

Restrictive diseases are those in which the normal expansion of the lung is limited. This may be due to changes in the parenchyma as in pulmonary fibrosis, whereby the lung tissue becomes more rigid, diseases in the pleura, compromising the seal between the lung and the pleural membrane or increasing the thickness of the pleura, diseases of the chest wall, either altering its shape or preventing its movement, or neuromuscular diseases whereby control of the intercostal muscles and/or diaphragm is lost.

Vascular diseases are those that affect the blood flow to and from the lung. They may result in fluid buildup in the lung as in pulmonary edema, blood flow reduction due to pulmonary embolism, or increases in the pulmonary artery pressure, known as hypertension.

Environmental diseases are those due to inhalation of foreign materials including atmospheric pollutants and aerosols. Sedimentation of foreign particulate matter in the lung may have a variety of obstructive and restrictive effects. In addition, certain foreign particulate matter, such as asbestos, cigarette smoke and coal, may elicit carcinogenic or inflammatory responses. In this work *Stachybotrys chartarum* spores, a common fungus known to cause inflammation when inhaled, were instilled into living rat lungs to provide as a lung disease model *in vivo*.

1.2.3 Non-Imaging Tests

The most common pulmonary function tests (PFT's) are relatively low-cost tests that provide one-dimensional measurements describing properties of the entire lung. These include pressure, volume and gas exchange measurements. Combinations of these measurements also yield useful parameters such as compliance, resistance and flow. Pressure measurements are achieved by attaching various pressure gauges and manometers to the mouth and the air columns of interest, and will not be discussed in detail.

1.2.3.1 Lung Volume Tests

The most basic volume measurement is the forced expiratory volume (FEV). This procedure involves forceful exhalation into a column of water or an air tight bag from full inspiration. Other static lung volume measurements may be found using spirometry (see Figure 1.2), helium dilution, and plethysmography.

Spirometry requires the patient to breathe from a sealed gas reservoir. The displacement of the gas in the reservoir is measured, and can be used to estimate the tidal volume and the vital capacity, though it cannot provide estimates of the FRC or residual volume. Helium dilution is a modification of spirometry, whereby Boyle's law is used in conjunction with helium in the gas reservoir. Helium is virtually insoluble in the blood, and hence only occupies the gas space in the lung. If the amount of helium in the reservoir is known and no helium is lost to the blood, after a number of breaths the concentration of helium in the system will reach equilibrium between the reservoir and the lung volume. Subsequent measurement of the partial pressure of helium in the reservoir provides an estimate of the total lung capacity, and the FRC can be derived.

Plethysmography may also be used to estimate the total volume of gas in the lung. Here, the subject is placed in an air-tight box and breathes from one end of a manometer. The pressure drops across the manometer and in the box are measured, providing an estimate for the volume of gas in the lung via Boyle's law.

Note that as plethysmography does not communicate with the mouth, it measures total lung capacity, including unventilated volumes behind obstructed airways, while spirometry and helium dilution only measure ventilated lung capacity.

1.2.3.2 Gas Exchange

As the primary function of the lung is gas exchange, measurements of the diffusion of oxygen into the blood are also useful. This is conventionally done by drawing blood from the radial artery, and measuring the partial pressure of oxygen and carbon dioxide, P_{O_2} and P_{CO_2} respectively, using polarographic electrodes. Measures of the blood pH are derived from P_{CO_2} measurements. Blood oxygenation may also be measured non-invasively via infrared spectroscopy of an optically thin appendage such as a finger.

Another measurement of gas exchange is the diffusing capacity. As carbon monoxide (CO) binds readily to hemoglobin, the most popular method of measuring the diffusing capacity is to administer a single breath of 0.3% CO and 10% He, have the patient hold their breath for 10 seconds and exhale. The gas is collected and analyzed. The partial pressure of He indicates the dilution of the inspired gas with the alveolar gas, yielding the initial alveolar P_{CO} . Assuming that CO is lost from the alveolar gas in proportion to the P_{CO} during breath holding, the diffusing capacity is calculated as the volume of CO taken up per minute per unit pressure of the alveolar P_{CO} .

1.2.4 Lung Imaging

While non-imaging measurements are useful in identifying some diseases, they do not provide location-specific information about lung structure, function or disease, which is particularly important for therapeutic intervention, and will often be complemented by imaging studies. The current tests: X-ray, radionuclide, ultrasound, and non-HNG-MR, and the relatively new technology that is HNG-MR are discussed in this section.

1.2.4.1 X-ray

X-rays are attenuated by dense tissues in the body. As the lung is predominantly filled with air, it appears underexposed in X-ray images. A conventional X-ray projection image of the thorax yields information about the overall geometry of the lung in two dimensions. Exposure times are usually sub-second depending on the strength of the X-ray source and the amount of tissue being imaged. The position of the diaphragm may be noted, and density changes and fibrous tissue in the lung may be identified. Information about the lung is obscured by superimposition of dense tissues and bone on the image.

Computed tomography (CT) X-ray imaging allows X-rays to map the density of the body in two or three dimensions, eliminating superimposition, and has much improved soft-tissue contrast. As CT images require multiple projections, CT acquisition times are greater than those of conventional X-ray projection imaging. Current helical systems are capable of imaging the entire lung within a 12 s breath-hold [23], eliminating most respiratory motion artefacts, though not fast enough to eliminate cardiac motion. Ultra-fast CT imagers using electron accelerators and tungsten targets are capable of more rapid scanning, and the addition of temporal gating of the exposure arranged to synchronously reject cardiac and respiratory rhythms can eliminate most motion artefacts. CT is well suited to identifying fibrosis, emphysema and cancers as it is sensitive to changes in tissue density [23]. CT may also be used to estimate static lung

volumes [24] and compliance [25]. It is however, of limited use in lung obstruction studies, as it cannot distinguish ventilated regions from unventilated regions of the lung.

To increase CT sensitivity to blood flow and respiration, radio-dense contrast agents may be used. For example, dual energy CT above and below the K-edge of inhaled Xe gas can be used to create subtraction images of the Xe distribution within the lung [26][27]. This procedure is best performed with highly monochromatic X-ray sources, such as synchrotron radiation, making the widespread use of such modalities improbable.

The limitation of X-ray studies is that the high energy photons used provide an ionizing radiation dose. Though scan times are decreasing and resolution is increasing, any gains in signal-to-noise beyond increasing detector efficiencies require correspondingly higher exposures that lead to increased estimates of risk to the subject. However, with appropriate dose regulation CT images have excellent signal-to-noise, and are used to provide complementary spatial information to many functional imaging tests.

1.2.4.2 Radionuclide Imaging

Radionuclide imaging requires either the injection or inhalation of radiopharmaceuticals to provide functional information. Similar to X-ray technology, projection images can be obtained using gamma-cameras and multiple projections can be combined to provide three-dimensional data, otherwise known as single-photon emission computed tomography (SPECT).

Ventilation images may be acquired via inhalation of ^{133}Xe , as well as ^{127}Xe , $^{81\text{m}}\text{Kr}$, $^{99\text{m}}\text{Tc}$ -labeled diethylenetriaminepentaacetic acid (DTPA) [23][28], and “Technegas” – small crystals of $^{99\text{m}}\text{Tc}$ cocooned in graphite and suspended in argon [29]. $^{99\text{m}}\text{Tc}$ -labeled blood proteins may be injected intravenously to image pulmonary perfusion (i.e., the blood distribution within the lung). Combination ventilation-perfusion scans are useful to evaluate the damage caused by pulmonary emboli. ^{67}Ga in combination with SPECT may be used to evaluate the extent of disease in patients with either lung carcinoma or

lymphoma. ^{111}In -labeled leukocytes may also be used to detect pulmonary bacterial infections [23].

Positron emission tomography (PET) provides three-dimensional images via coincidence counting of $\sim 180^\circ$ 0.511 MeV gamma rays emitted during positron annihilation. Positron-emitting isotopes are usually generated in a cyclotron and may include ^{11}C , ^{13}N , ^{15}O , ^{18}F and ^{19}Ne . ^{15}O for example, may be attached to H_2O , and CO for regional perfusion and water permeability studies. Similar to Xe for CT, ^{13}N may be bonded to N_2 for PET ventilation studies. ^{11}C and ^{18}F are often bonded to amino acids or amines for metabolic studies [23].

Like X-rays, radionuclide imaging is limited by dose and toxic effects. In order to avoid high doses only trace amounts of the radiopharmaceuticals are administered, and as a result radionuclide studies, while localized, are subject to counting noise – giving the appearance of blurrier images than those produced by CT and MR.

1.2.4.3 Ultrasound

Ultrasound does not penetrate normal lung due to the presence of air, making it a poor diagnostic tool for the lung. If a fluid or solid mass is present in the lung, ultrasound may be used in conjunction with other imaging methods. Endoscopic ultrasound may be used to monitor or diagnose some lung cancers as an alternative to some biopsies and surgical procedures [30].

1.2.4.4 Non-HNG MR

Though well-suited for most soft tissue imaging, conventional MR imaging of hydrogen (^1H -MR) in the body must overcome three main difficulties in imaging the lung [31]:

1. The inflated lung has a much lower tissue density of (~ 0.2 g/mL), and hence water density, than any other organ in the body. As such, in comparison to other organs with densities on the order of 1 g/cm^3 (i.e., water), there are fewer nuclei that contribute to the MR signal.
2. Susceptibility variations at air-tissue interfaces increase the decay rate of the transverse magnetization (T_2 and T_2^*), causing a broadening of the NMR linewidth, requiring increased bandwidth, and resulting in increased image noise and artefacts.
3. Respiratory and cardiac motions occur over time frames much shorter than typical MR scan times, causing motion blurring and a variety of other artefacts.

Even with these limitations, structural ^1H -MR of the lung is possible using breath-holds or respiratory gating and fast imaging sequences [31]. The temporal and spatial resolution of ^1H -MR of the lung is marginally worse than that of CT, though there are no known risks associated with the MR procedure for eligible patients. Such imaging procedures may be sensitive to a variety of diseased states resulting in increased tissue density such as tumours [32] or fibrosis, inflammation, and fluid in the lung [25]. Contrast-agent enhanced ^1H -MR studies are also possible. Gadolinium bonded to DTPA (Gd-DTPA) is a widely used ^1H -MR contrast agent used in perfusion imaging as well as pulmonary arteriography. Gd-DTPA can also be used as an aerosol in ventilation studies [33]. In addition to structural ^1H -MR of the lung, sulphur hexafluoride (SF_6) may also be imaged *in vivo* to provide ventilation images similar to HNG-MR [34]. SF_6 is limited however by low density and thermal polarizations, and therefore requires gated imaging and signal averaging, increasing acquisition times.

1.2.4.5 HNG-MR

While HNG-MR imaging has yet to see widespread clinical use, this modality yields a unique combination of results: the temporal and spatial resolution of CT may be matched while providing functional information similar to radionuclide imaging, with the virtually negligible risks associated with conventional MR.

HNG-MR may be performed using either ^3He or ^{129}Xe . The gyromagnetic ratio of ^3He is about 2.7 times larger than that of ^{129}Xe , giving it a fundamentally larger MR signal [35]. Hyperpolarization methods for both nuclei have been developed, with common ^3He polarizations of 30-50% and ^{129}Xe polarizations of 5-20% at litre volumes suited to human respiratory study [36]. The polarization relaxation rates of ^3He are smaller than those of ^{129}Xe , and the paramagnetic properties of O_2 in the lung increase the relaxation rates of both nuclei approximately equally. He diffuses more rapidly than Xe [38][39], though it is virtually insoluble in the blood, and therefore remains in the gas space of the lung. The aforementioned bonding properties of Xe enable small amounts of the total Xe in the lung to diffuse into the blood stream [40]. Bonded ^{129}Xe atoms resonate at a different frequency than gaseous ^{129}Xe , allowing the possibility of NMR spectroscopy work [41][42].

With a low natural abundance of $1.3 \times 10^{-4} \%$ [43], ^3He is obtained from the nuclear industry as a daughter of tritium (^3H) beta-decay at a cost of ~\$100-\$140/L [44]. Xe is present in the atmosphere at 0.086 ppm with a ^{129}Xe natural abundance of 26.4 %, and is collected as a by-product of the liquid air industry. The cost of Xe is ~\$20/L and 80% isotopically enriched ^{129}Xe may be purchased for ~\$700/L [35]. While there are some polarization gains from using isotopically enriched ^{129}Xe [45], the increase in cost per litre of enriched ^{129}Xe is proportionally larger than the increase in polarization.

In general, the larger dipole moment and higher presently achievable polarization make ^3He a better candidate for structural and ventilation imaging of the lung than ^{129}Xe , though recent and continuing improvements in ^{129}Xe polarizers have been narrowing the

gap in performance between the two modalities [37]. In addition, ^{129}Xe and ^3He are procedurally similar enough after polarization that findings in ^{129}Xe research at lower SNR may later be applied to ^3He studies and vice-versa. The principle reason for this laboratory to choose ^{129}Xe is to research potential spectroscopic applications.

Breath-hold and respiratory motion gated imaging of inhaled HNG yield morphologic information about the airways and the alveolar spaces [46][47][48]. Inhaled gas expands into all of the ventilated air spaces in a subject, and provides a means for diagnostic information with respect to obstructive diseases such as asthma [49][50], COPD [51][52], and cystic fibrosis [53]. As HNGs are non-radioactive and inert, 100% concentrations of ^3He and ^{129}Xe may be administered (subject to the anaesthetic constraints imposed on Xe) [35], providing superior statistics to radionuclide imaging. Similar to spirometry, such imaging procedures commute with the mouth and do not provide means of estimating the FRC, though in principle multiple-breath procedures could be implemented to detect residual volumes.

Gas flow imaging is also possible [54]. With appropriately designed fast imaging sequences, a bolus of HNG may be tracked through the lung permitting investigation of respiration with sub-second temporal resolution. Gas diffusion mapping may be performed with the appropriate use of magnetic gradients [51][55]. As the presence of oxygen causes the more rapid relaxation of the polarization, *in vivo* P_{O_2} measurements may be performed by investigating regional differences in signal decay [56].

While costs of high-field superconducting MR systems are quite high, in HNG imaging the magnet is not required to polarize the nuclei. Hence HNG-MR may be performed in less expensive resistive magnets without dramatic losses in signal-to-noise [57][58][59], offering new research opportunities at low field intensities.

Lastly, spectroscopy of Xe may reveal a variety of lung function tests by measuring the rates at which Xe diffuses into the blood [60].

1.3 Thesis Overview

With the spatial resolutions and polarizations attainable at the Carleton Magnetic Resonance Facility (CMRF), and the dependence of the MR signal on the density of nuclei being imaged, it is hypothesized that quantitative estimation of both gross and regional ventilated lung volumes is achievable using HNG-MR imaging.

In this thesis an algorithm to estimate absolute and relative volumes from three-dimensional hyperpolarized ^{129}Xe MR images is developed and tested using an experimental methodology suitable to the CMRF. Images from a variety of *in vitro* and *in vivo* experiments were collected and analyzed, with the ultimate goal of specifying signal-to-noise and resolution requirements for clinically relevant regional volume estimation of a ventilated lung.

Chapter 2 presents a theoretical description of magnetic resonance imaging, noble gas hyperpolarization procedures, and image-based volumetry. Chapter 3 details the experimental equipment and procedures and the analytical methods used. Data are presented and analyzed in Chapter 4 in order of the increasing geometrical complexity of the subject volumes. In Chapter 5 methods for increasing the precision of the volume estimation procedure and refining experimental methods are discussed and the thesis is summarized.

Appendix B presents the relative merits of a variety of estimators for MR image signal intensity in the context of estimating partial volume, and justification for the choice of the Maximum Likelihood estimator used.

2 Theory

This chapter contains the theoretical framework required to apply MR imaging techniques to the estimation of volume of complex geometrical gas spaces. The NMR signal is discussed in Section 2.1, the basics of MR imaging are discussed in Section 2.2, the laser polarization of ^{129}Xe in Section 2.3, and the principles of volume estimation from images are discussed in Section 2.4.

2.1 The Nuclear Magnetic Resonance Signal

The signal for nuclear magnetic resonance arises from the polarization and precession of a system of nuclear magnetic dipole moments placed in an external magnetic field. This section describes the NMR signal both classically and quantum mechanically as well as the fundamental methods of manipulating it.

2.1.1 Nuclear Magnetic Dipole Moment

A nucleus of atomic mass number A is composed of Z protons and N neutrons, such that $A = Z + N$. Both protons and neutrons exhibit intrinsic angular momentum known as spin, and the total angular momentum of the nucleus or nuclear spin, J , is defined as the vector sum of the intrinsic and orbital angular momentum of the nucleons.

The nucleons also carry electric charge (proton) or are composed of electrically charged particles (the neutron via the quark model). The combination of charge and

angular momentum provides the classical view of the nucleus as a bundle of circulating charge distributions and gives rise to the nuclear magnetic dipole moment, defined as

$$\mu = \gamma J, \quad 2.1$$

where γ is the gyromagnetic ratio of the nucleus being considered. The gyromagnetic ratios for a number of nuclei are given in Table 2.1.

Table 2.1 Gyromagnetic ratios of ^1H , ^3He and ^{129}Xe

Nucleus	Gyromagnetic Ratio [MHz/T]	
^1H	42.576	[61]
^3He	32.434	[62]
^{129}Xe	11.776	[61]

2.1.1.1 The Dipole Moment in a Magnetic Field

According to the uncertainty principle, the magnitude and direction of J and μ cannot be established. However, if an axis is defined by applying an external magnetic field with a flux density $B_0 = B_0 \hat{z}$, the z component of μ may be quantized. The Hamiltonian operator for a magnetic dipole in an external field is given both classically and quantum mechanically as

$$\begin{aligned} H &= -\mu \cdot B_0 \\ H &= -\gamma J \cdot B_0 \end{aligned} \quad 2.2$$

In the case that $B_0 = B_0 \hat{z}$,

$$H = -\gamma B_0 J_z. \quad 2.3$$

The allowed energy states of the Hamiltonian are

$$E = -\gamma \hbar B_0 m_I \quad m_I = -I, -I+1, \dots, I, \quad 2.4$$

where I is the nuclear spin quantum number and $\hbar = h/2\pi$ is Planck's constant, giving a degeneracy of $(2I+1)$, commonly known as Zeeman splitting.

For spin- $1/2$ nuclei, two states are possible with energies of $E = \pm \frac{1}{2} \gamma \hbar B_0$. These states are usually viewed as the dipole moment being aligned ($\uparrow$) and anti-aligned ($\downarrow$)

with the magnetic field with an energy difference $\Delta E = \gamma \hbar B_0$. If I is greater than $\frac{1}{2}$, nuclei have magnetic quadrupole moments that result in additional energy splitting and line-broadening effects. Most nuclei used for MR work are spin- $\frac{1}{2}$ and ^1H – a single proton forming the nucleus, and ^{129}Xe – having one unpaired neutron, are spin- $\frac{1}{2}$ nuclides [63].

In addition to the energy splitting, the dipole moment experiences a torque τ when placed in the magnetic field, defined by the Larmor equation:

$$\tau = \frac{d\mathbf{J}}{dt} = \boldsymbol{\mu} \times \mathbf{B}_0. \quad 2.5$$

Multiplying through by the gyromagnetic ratio:

$$\frac{d\boldsymbol{\mu}}{dt} = \gamma \boldsymbol{\mu} \times \mathbf{B}_0. \quad 2.6$$

Thus $\boldsymbol{\mu}$ undergoes precession about $\mathbf{B}_0$ with an angular frequency of $\omega_0 = \gamma B_0$, known as the Larmor frequency. This frequency is the resonant frequency to which the term “nuclear magnetic resonance” refers, and can also be expressed in terms of the energy difference between the $\uparrow$ and $\downarrow$ states:

$$\nu_0 = \frac{\omega_0}{2\pi} = \frac{\Delta E}{h} = \frac{\gamma}{2\pi} B_0 \quad 2.7$$

For nuclei such as ^1H and ^{129}Xe placed in a flux density on the order of 1 to 10 T, the Larmor frequency is on the order of MHz, enabling the use of radio-frequency (RF) coils and electronics to alter the spin-states of nuclei via the exchange of photons.

2.1.2 Bulk Magnetization

Of the two degenerate energy states of a nucleus in an external magnetic field, that which is aligned with the magnetic field is of lower energy and therefore favoured. For temperatures (T) greater than 0 K there is sufficient energy for some nuclei to occupy the higher energy state. If an ensemble of N nuclei is composed of $n_{\uparrow}$ nuclei aligned and $n_{\downarrow}$ anti-aligned to the magnetic field with large enough temperatures to prevent Fermion behaviour, the population may be described by the Boltzmann distribution:

$$\frac{n_{\downarrow}}{n_{\uparrow}} = e^{-\frac{\Delta E}{k_B T}} \quad 2.8$$

$$\frac{n_{\downarrow}}{n_{\uparrow}} = e^{-\frac{\hbar \omega_0}{k_B T}}$$

where k_B is the Boltzmann constant.

The polarization P is defined as the fraction of the excess aligned spins to the total number of nuclei:

$$P = \frac{n_{\uparrow} - n_{\downarrow}}{n_{\uparrow} + n_{\downarrow}} \quad 2.9$$

Substituting equation 2.8 into equation 2.9 and simplifying, the thermal equilibrium polarization P_{eq} is:

$$P_{eq} = \frac{1 - e^{-\frac{\hbar \omega_0}{k_B T}}}{1 + e^{-\frac{\hbar \omega_0}{k_B T}}} \quad 2.10$$

The bulk magnetization, hereafter referred to as the “magnetization” or M , is defined as the volume density of magnetic dipole moments, i.e., $M = \sum \mu$ per unit volume. Since the spin-states are polarized, there is a net magnetization along the z -axis. There is no *a priori* phase coherence of the precessing moments however, thus the vector sum of the components of the magnetization in the plane orthogonal to $\hat{z}$ is zero. The equilibrium magnetization is therefore parallel to B_0 .

The magnitude of M is directly proportional to the polarization

$$M = \frac{N}{2} \gamma \hbar P, \quad 2.11$$

and at thermal equilibrium M_{eq} can be calculated for a sample of N spin- $\frac{1}{2}$ nuclei with the approximation that $\gamma \hbar B_0 / k_B T$ is much less than 1:

$$M_{eq} \approx \frac{N \gamma^2 \hbar^2}{4 k_B T} B_0. \quad 2.12$$

By substituting $M = \sum \mu$ into equation 2.6, it can be shown that similar to the dipole moment of an individual nucleus, the bulk magnetization experiences a torque in the presence of a magnetic field.

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}_0 \quad 2.13$$

If $\mathbf{M}$ is not parallel to $\mathbf{B}_0$, the torque results in the precession of $\mathbf{M}$ about $\mathbf{B}_0$ at the Larmor frequency. In a static magnetic field at thermal equilibrium $\mathbf{M}_{eq}$ is parallel to $\mathbf{B}_0$ and the precession of $\mathbf{M}$ is not observed. Figure 2.1 illustrates the bulk magnetization of a system of spins under thermal equilibrium.

Figure 2.1 Illustration of thermal equilibrium of the bulk magnetization. There are more nuclei aligned ($n_{\uparrow}$) to the static field $\mathbf{B}_0$ than anti-aligned ($n_{\downarrow}$), thus the bulk magnetization $\mathbf{M}$ is aligned with $\mathbf{B}_0$. Note the net magnetization in the transverse (xy) plane sums to zero.

2.1.2.1 The Effect of an RF Pulse

In order to measure the magnetization, the system must be altered to have a component of $\mathbf{M}$ orthogonal to the z -axis. This is achieved by applying a secondary magnetic field $\mathbf{B}_1(t)$ orthogonal to both $\mathbf{B}_0$ and $\mathbf{M}$ in the xy plane, rotating at an angular frequency ω :

$$\mathbf{B}_1(t) = B_1 [\cos(\omega t) \hat{x} + \sin(\omega t) \hat{y}] \quad 2.14$$

The magnetic field experienced by the magnetization becomes the vector sum of the static and the rotating fields:

$$\mathbf{B}_{tot}(t) = \mathbf{B}_0 + \mathbf{B}_1(t) \quad 2.15$$

and equation 2.13 becomes:

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}_{tot}(t). \quad 2.16$$

Figure 2.2 The effect of a RF $\mathbf{B}_1$ pulse with frequency $\omega = \omega_0$ on the magnetization ($\mathbf{M}$) in (a) lab and (b) rotating frames of reference.

To avoid the mathematical complexities of a rotating magnetic field in the lab frame, it is convenient to work in a frame of reference rotating about the z -axis at a frequency ω . In this frame of reference, using the appropriate transformations

$$\mathbf{B}'_0 = \left(B_0 - \frac{\omega}{\gamma} \right) \hat{z} \quad 2.17$$

and

$$\mathbf{B}'_1 = B_1 \hat{x}'. \quad 2.18$$

Thus

$$\mathbf{B}'_{tot} = \left(B_0 - \frac{\omega}{\gamma} \right) \hat{z} + B_1 \hat{x}'. \quad 2.19$$

When $\omega = \omega_0$ the pulse is considered “on resonance” as in Figure 2.2 (b), and will be considered for simplicity. On resonance, the total magnetic field is seen to be entirely along $\mathbf{B}'_1$, causing the precession of the magnetization about the x' -axis for the duration

of the RF pulse, with an angular frequency of $\omega_1 = \gamma B_1$. For a given RF pulse of strength $B_1(t)$ and duration τ the magnetization will tip towards the y' -axis in the transverse plane by an angle:

$$\begin{aligned}\alpha &= \int_0^{\tau} \omega_1 dt \\ \alpha &= \int_0^{\tau} \gamma B_1(t) dt\end{aligned}\tag{2.20}$$

The angle by which an RF pulse rotates the magnetization from the direction of the static field is henceforth referred to as the “flip angle”. As shown by equation 2.20, flip angles can be varied by altering the duration and strength of an RF pulse.

Following the termination of the B_1 excitation field, the magnetization continues its precession about B_0 and is now described by its longitudinal (parallel to B_0) and transverse (orthogonal to B_0) components M_z^+ and M_{xy}^+ :

$$\begin{aligned}M_z^+ &= M_z^- \cos(\alpha) \\ M_{xy}^+ &= M_z^- \sin(\alpha)\end{aligned}\tag{2.21}$$

where M_z^- is the magnetization prior to the RF pulse.

From a quantum mechanics perspective, the RF pulse delivers energy defined by the resonant frequency to the energy difference between the $\uparrow$ and $\downarrow$ states. The nuclei absorb this energy and are excited to the higher energy state ($\downarrow$). The resulting population shift alters the polarization, and accounts for the longitudinal component. The transverse component arises from the phase coherence of the individual dipole moment precessions.

2.1.2.2 Signal Acquisition

Raw MR data is acquired by placing a receiving coil near a sample of spins excited by an RF pulse and using Faraday’s law of induction to detect the rotating transverse component of the magnetization. The signal is usually measured using synchronous detection to resolve the in-phase and quadrature components. The signal is then sampled,

scaled arbitrarily to facilitate digital storage, and stored as complex numbers. While it can be measured using a dedicated coil, the signal can also be detected by the same RF coil used to generate the B_1 field. The magnetization precession causes a change in flux (Φ) in the coil, inducing an electromotive force (ε):

$$\varepsilon = -\frac{\partial \Phi}{\partial t} = -\iiint_r \frac{\partial}{\partial t} [B_1(r) \cdot M(r, t)] dr. \quad 2.22$$

B_1 is the flux density at position $r = (x, y, z)$ per unit current in the receiver via the principle of reciprocity, and is indicative of the sensitivity or “filling factor” of the coil. The resulting time dependent voltage is the basic recorded NMR signal. Table 2.2 gives the units for the parameters in equation 2.22. Due to the arbitrary scaling for storage and variable receiver coil sensitivities, typically only relative MR signals are compared.

Table 2.2 Units for the EMF induced by magnetization in a coil

B_1	M	Φ	ε
$\frac{T}{A} = \frac{Wb}{m^2 A}$	$\frac{A m^2}{m^3}$	$\frac{Wb}{m^2 A} \cdot \frac{A m^2}{m^3} \cdot m^3 = Wb$	$\frac{Wb}{s} = V$

2.1.2.3 Relaxation

Whether altered by an RF pulse or polarized by some other means, the magnetization evolves to its thermal equilibrium state along the z -axis by relaxation mechanisms.

Relaxation is due to couplings between nuclear spins and both nuclear and electronic magnetic dipole moments, effectively causing fluctuations of the magnetic field in the vicinity of a nucleus. Couplings are weak for a monatomic gas such as ^{129}Xe , except during collisions with other atoms where magnetic dipole-dipole interactions occur, and in the presence of paramagnetic molecules (such as O_2) where the electronic magnetic dipole moments couple to the nuclear magnetic dipole moments.

The process by which the magnetization returns to thermal equilibrium is described by three phenomenological time constants:

- T_1 , the longitudinal or spin-lattice relaxation time
- T_2 , the transverse or spin-spin relaxation time
- T_2^* , the effective transverse relaxation time.

2.1.2.3.1 Longitudinal Relaxation – T_1

When a coupling occurs with a component of the dipole field in the transverse plane at the resonant frequency, an energy transition may be induced, affecting the longitudinal magnetization. As the nuclei transfer energy to each other and surrounding molecules (the “lattice”) the polarization relaxes to thermal equilibrium. The longitudinal component of the magnetization is characterized by:

$$\frac{dM_z}{dt} = -\frac{M_z - M_{eq}}{T_1}. \quad 2.23$$

The solution to equation 2.23 is:

$$M_z(t) = M_{eq} + (M_{z0} - M_{eq})e^{-\frac{t}{T_1}} \quad 2.24$$

where M_{z0} is the longitudinal magnetization at $t = 0$.

Figure 2.3 shows typical instances of T_1 relaxation. In Figure 2.3 (a) following a perfect 90° pulse M_{z0} is zero, and hence the longitudinal relaxation process increases $M_z(t)$ to M_{eq} . For a laser polarized sample illustrated in Figure 2.3 (b), M_{z0} is much greater than M_{eq} , thus $M_z(t)$ decays to the smaller equilibrium value.

Figure 2.3 T_1 relaxation towards equilibrium for (a) thermally polarized nuclei following a 90° pulse, (b) hyperpolarized nuclei after leaving a polarizer.

2.1.2.3.2 Transverse Relaxation – T_2 , T_2^*

The transverse component of the magnetization also decays, as there is no transverse component under thermal equilibrium. This decay is attributed to the loss of coherence of the spin precession due to the slightly different flux density induced on a nucleus by its neighbours. While indirect energy exchange via the lattice may play a role in transverse relaxation, additional processes directly affecting the coherence are also responsible. Subject to these additional relaxation processes, T_2 is always less than or equal to T_1 .

The transverse magnetization is characterized by:

$$\frac{dM_{xy}}{dt} = -\frac{M_{xy}}{T_2}, \quad 2.25$$

with the solution:

$$M_{xy}(t) = M_{xy0} e^{-\frac{t}{T_2}} \quad 2.26$$

where M_{xy0} is the transverse magnetization at $t = 0$.

Static magnetic field inhomogeneities also contribute to transverse relaxation, causing an apparent relaxation time T_2^* which is shorter than T_2 . The T_2^* relaxation can be expressed as in equations 2.25 and 2.26, replacing T_2 with T_2^* . The decay of the transverse magnetization following an RF pulse according to T_2^* is therefore the expected form of the basic MR signal, shown in Figure 2.4 (a) and is called a “free induction decay” (FID). A Fourier transform of the exponentially decaying FID gives the frequency spectrum, showing a peak with a Lorentzian line shape at the resonant frequency of the nuclei as shown in Figure 2.4 (b). The full-width at half-maximum (FWHM) of the Lorentzian is described by:

$$FWHM = \frac{2}{\pi T_2^*}. \quad 2.27$$

Figure 2.4 An illustration of the free induction decay of the transverse magnetization for a resonant frequency of 5 Hz. (a) The magnitude of the magnetization affected by a $T_2 = 3$ s decay, the magnitude as a result $T_2^* = 1$ s decay, and the magnitude of the y-component of the transverse magnetization as a function of time. (b) The frequency spectrum of the $T_2^* = 1$ s decay.

2.1.2.4 Bloch Equations

Combining the relaxation processes (equations 2.24 and 2.26) with the Larmor equation (equation 2.16) yields the phenomenological Bloch equation:

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}_{tot} - \frac{M_x \hat{x} + M_y \hat{y}}{T_2} - \frac{(M_z - M_{eq}) \hat{z}}{T_1} \quad 2.28$$

Equation 2.28 describes the evolution of the bulk magnetization, $\mathbf{M} = M_x \hat{x} + M_y \hat{y} + M_z \hat{z}$, in the presence of a magnetic field $\mathbf{B}_{tot}$. Note that γ , T_1 , T_2 and M_{eq} are constants, while the other terms are time dependent.

2.2 Nuclear Magnetic Resonance Imaging

Nuclear magnetic resonance imaging consists of exciting the bulk magnetization of a sample into the transverse plane and encoding the magnetization prior to and during data acquisition to localize the spin density distribution in one, two or three dimensions. This section will detail the practical aspects of bulk magnetization manipulation required to gather spatial information from a given sample.

2.2.1 Frequency Content of an RF pulse

In the preceding discussion, the RF pulse was characterized as a time dependent B_1 field in the transverse plane oscillating at the Larmor frequency. The concept of a pulse implies that the B_1 field is present for a finite amount of time, carrying a spectrum of frequencies centered about the carrier frequency and related to the temporal distribution of the B_1 field by the Fourier transform. The terms “hard” and “soft” are often used to describe the frequency distribution of an RF pulse.

A “hard” or “non-selective” pulse excites all of the spins of a given nuclide within the RF coil and is usually used to perform NMR spectroscopy. The ideal hard pulse would be a time-space Dirac delta function as in Figure 2.5 (a) with a uniform frequency distribution (Figure 2.5 (c)), however short pulses with high amplitudes serve as a practical approximation. A hard pulse is usually formed in time space by a square-wave envelope function like that shown Figure 2.5 (b), and is characterized in frequency space by an approximately flat spectrum in the vicinity of the carrier frequency (Figure 2.5 (d)).

A “soft” or “shaped” pulse has a smoother envelope function than a hard pulse, often in the form of $\text{sinc}(t)$ as shown in Figure 2.6 (a), and excites a much narrower band of frequencies than a hard pulse. The sinc envelope is chosen because its frequency spectrum is a rectangular pulse (Figure 2.6 (c)). True sinc functions span an infinite range, hence practical sinc pulses are truncated after some number of zero crossings (usually 3 or 5 lobes – Figure 2.6 (b)), resulting in non-ideal frequency distributions (Figure 2.6 (d)). Such non-ideal distributions are appropriate for spatially selective excitation of spins and are often used in imaging.

Figure 2.5 Temporal (a) and spectral (c) representations of an ideal hard pulse (i.e., a delta function), and temporal (b) and spectral (d) representations of a practical hard pulse.

Figure 2.6 Temporal (a) and spectral (c) representations of a sinc pulse, and temporal (b) and spectral (d) representations of a three-lobe truncated sinc pulse.

2.2.2 Spin Echoes

The additional loss of coherence of the transverse magnetization due to static field inhomogeneities results in T_2^* relaxation. Individual nuclei experience slightly increased or decreased local magnetic fields and therefore oscillate at higher or lower frequencies and accumulate phase-shifts with respect to the bulk average. When field inhomogeneities are not time dependent, the phase accumulation is reversible via the appropriate application of a 180° pulse. This process is illustrated in Figure 2.7.

At a time t following an excitation pulse, the phase accumulation in the rotating frame may be described by:

$$\frac{d\phi}{dt} = \gamma B. \quad 2.29$$

where B describes the local field seen by a given nucleus. The solution is thus:

$$\phi(t) = \phi_0 + \gamma B t \quad 2.30$$

where ϕ_0 is the phase at $t = 0$.

If a 180° pulse is applied at a time $TE/2$, where TE stands for echo-time, all the phases in the transverse plane are effectively mirrored through the longitudinal axis, while the local field remains constant. Assuming all nuclei have a phase of 0 at $t = 0$, then at a time $TE/2$ the phase accumulated and the phase immediately following the pulse will be:

$$\begin{aligned}\phi(TE/2)^- &= \gamma B TE/2 \\ \phi(t > (TE/2)^+) &= \pi + \gamma B(t - TE)\end{aligned}\tag{2.31}$$

At a time TE , the spins re-align creating a new signal called a spin echo. Multiple echoes can be obtained by applying additional 180° pulses, though each echo will have e^{-TE/T_2} the signal of its predecessor due to T_2 relaxation. Spin echoes provide a mechanism for estimating T_2 . Moreover, they are useful in imaging sequences to prolong the duration of the transverse magnetization.

Figure 2.7 Spin Echo

- (a) Two subsequent 180° RF pulses yield two spin echoes, with the amplitude of the transverse magnetization diminished by T_2 relaxation processes.
- (b) The loss of spin coherence and subsequent spin re-focusing following a 180° RF pulse at $TE/2$ in the rotating frame of reference for one spin echo.

2.2.3 The effect of a Magnetic Gradient

MRI systems are equipped with a set of well characterized gradient coils that allow approximately linear magnetic gradients to be applied in any direction within the bore of the magnet. The Larmor frequency of a given nucleus is governed by the gyromagnetic ratio and the local magnetic field as described in equation 2.7. If a linear gradient magnetic field $G(z) = (G_z z)\hat{z}$ is applied it perturbs the local magnetic field according to $B(z) = (B_0 + G_z z)\hat{z}$, and the frequency distribution of the spin precession becomes spatially varying for the duration of the gradient:

$$\omega(z) = \omega_0 + \gamma G_z z \quad 2.32$$

2.2.4 Slice Selection

If a linear magnetic gradient and a soft RF pulse are applied simultaneously, the gradient linearly alters the frequencies of the spins in one dimension, and only the spins oscillating at frequencies contained in the RF pulse are excited to the transverse plane. This operation is known as slice selection, as those spins at higher and lower frequencies than the RF pulse contains are not excited and hence unaffected by any subsequent operations on the transverse magnetization. The spatial profile of the slice is the frequency spectrum of the RF pulse with the gradient strength and bandwidth Δf defining the width of the slice Δz :

$$\Delta z = \frac{2\pi \Delta f}{\gamma G_z} \quad 2.33$$

2.2.5 Frequency Encoding

To facilitate frequency encoding, a flux gradient is applied to a sample volume with variation in the x-direction by convention: $G(x) = (G_x x)\hat{x}$. A time series of estimates of the flux in the receiver coil are generated with an analogue to digital converter. The frequencies present in the spectrum of the resulting time series correspond to different positions within the sample volume. The spectral energy density of the signal is proportional to the number of excited nuclei in the specified range of frequencies.

2.2.6 Phase Encoding

When a gradient is applied to the transverse magnetization for a duration τ , the spins in the excited plane resonate at different frequencies and develop a phase relationship that is a function of the gradient direction, $\hat{y}$ for example. When the gradient inducing coil is de-energized, the spins return to their original frequency ($\omega(y) \rightarrow \omega_0$), however the accumulated phase distribution is preserved:

$$\Delta\phi(y) = \gamma G_y y \tau \quad 2.34$$

Subsequent sampling with a frequency encoding gradient results in a signal that is a superposition of both spatial frequency and spatial phase information. Locking in on a specific range of phase allows for the detection of a narrow band of voxels in the Fourier transform of the spin distribution being measured.

Figure 2.8 Fourier space or k-space of an object. By convention, k_x is the frequency-encode direction, k_y is the first phase encode direction, and k_z is the slice-select or second phase-encode direction.

2.2.7 Gradient Echoes

Each time a gradient is applied the transverse magnetization loses coherence and develops a spatially varying phase distribution depending on the gradient strength (G), direction and duration (τ):

$$\phi_G(\mathbf{r}, \tau) = \gamma \int_0^{\tau} \mathbf{G}(t) \cdot \mathbf{r} dt. \quad 2.35$$

In the case of the phase-encode gradients this altered phase distribution or “de-phasing” is desirable. However, for slice-selection and frequency encoding, de-phasing must be compensated for by applying gradients opposite in magnitude following pulses and prior to sampling – “focusing” the spins so that they are in phase at the appropriate time in the data acquisition procedure.

Prior to frequency encoding, a gradient is applied with an area $-\frac{1}{2} G_x \tau_{fe}$, where G_x and τ_{fe} are the frequency encode gradient strength and duration respectively. When the data acquisition begins, the transverse magnetization is already de-phased by an amount $\phi_G(x) = -\frac{1}{2} \gamma G_x x \tau_{fe}$. Halfway through the acquisition process the phases are aligned such

that $\phi_G(x)=0$, and continue to de-phase to $\phi_G(x)=\frac{1}{2}\gamma G_x x \tau_{fe}$ at the end of the acquisition. This focusing of the spins is referred to as a gradient echo.

While spin echoes correct for static field inhomogeneities resulting in signal amplitudes governed by T_2 decay, gradient echoes only account for inhomogeneities in the gradient field and the inherent de-phasing caused by the gradient applications. Therefore gradient echoes do not compensate for static field inhomogeneities and the amplitude of the resulting coherence is governed by T_2^* decay.

2.2.8 3D Imaging

RF pulses, magnetic gradients, digital sampling and the Fourier transform are the basic tools required to image a spatial distribution of nuclear spins. The permutations and combinations of these are subject to the principles of superposition, are practically unlimited, and account for the diverse applications of NMR technologies. In the following sections two combinations are shown that yield 3D images. The first method, tomographic imaging, describes how one develops a 3D image from a set of 2D slices. The second method, 3D Fourier transform (FT) imaging, results in a true 3D image related to the data set by a 3D fast Fourier transform (FFT).

2.2.8.1 Tomographic Imaging

Figure 2.9 shows the pulse timing sequence for a tomographic imaging sequence, known as Spin-Warp imaging. The horizontal direction in the diagram corresponds to time, and the RF pulse, x , y and z gradients, and data acquisition channels are shown with arbitrary vertical units. Figure 2.8 is a point representation of k -space – the spatial frequency spectrum of the recorded signal, which corresponds to the spatial coordinates of the image. The sequence in Figure 2.9 is repeated $N_{PE} \times N_{SL}$ times (number of phase-encodes and slices respectively). For each slice the sequence is repeated N_{PE} times in

intervals of TR , with each repetition recording another line along the frequency-encode direction. By convention, the x -direction is the frequency-encode dimension, the y -direction the phase-encode direction, and the z -direction the slice-select direction. While each slice takes $N_{PE}TR$ seconds to complete, data from one slice may be acquired while waiting for T_1 relaxation to equilibrate the magnetization in the other slices in order to reduce imaging time.

In this 2D spin-echo sequence, a slice-select pulse and gradient are used to specify the width of an excited slab in the z -direction. This is followed by a phase-encode gradient accompanied by a compensation gradient in the x -direction. At time $TE/2$ a 180° soft pulse is applied accompanied by a slice-select gradient to preserve the magnetization in other slices and stimulate a spin-echo. At time TE , the frequency-encode gradient is applied and the signal is sampled, centered on the spin echo. After the sequence is repeated for each phase-encode step, there is sufficient information to fully reconstruct a slice of the image via a 2D Fourier transform. A different slice-select gradient is then applied and this procedure is repeated for each slice.

The slices are stored, and later combined by stacking the Fourier transformed slices in the z -dimension.

Figure 2.9 Spin-warp imaging timing sequence

2.2.8.2 3D FT Imaging

Figure 2.10 shows the pulse timing sequence for a 3D FT gradient echo sequence. First an RF pulse is applied paired with a slice select gradient. This slice selection is not for a narrow slice like in the spin-warp imaging described above, but rather serves to excite all the spins in the desired field of view of the sample. Subsequently a phase re-focusing gradient is applied, amplitude-modulated to phase-encode as a function of z . Simultaneously a phase-encode gradient is applied in the y -direction along with the compensating gradient for the frequency-encode in the x -direction, causing a gradient echo centered at TE . Note that the specific timing of the gradients is irrelevant with the exception of the slice select gradient, and applying the gradients concurrently can reduce the imaging time. The sequence is repeated for every combination of phase encodes, usually holding the z phase-encode step constant while each y phase-encode step is applied. Each acquisition is stored in its appropriate position in 3D k -space. The image is then reconstructed using a 3D FFT.

Figure 2.10 Variable flip angle (VFA) gradient-echo imaging timing sequence

2.2.9 Notes on ^{129}Xe Imaging

The preceding theory is applicable to all MR imaging, however imaging hyperpolarized ^{129}Xe requires some special considerations.

The T_1 of ^1H containing compounds in the body is in the range of 0.5 s - 3 s and TR values are typically half to three times as long as T_1 to allow the exponential “re-growth” of the magnetization. As a result, ^1H -MRI scans may take many minutes or even hours to acquire with the majority of the time spent waiting for relaxation processes to restore the thermal polarization after RF pulses. If images are noisy, signal averaging may be used resulting in even longer scans.

Unlike ^1H , after leaving an optical cell the ^{129}Xe polarization undergoes T_1 decay towards thermal equilibrium and cannot be re-polarized in the imaging environment (unless one is imaging the optical cell itself). Therefore in order to have adequate signal-to-noise, imaging sequences must occur in time intervals that are small with respect to T_1 , and minimizing the imaging time is beneficial. Moreover, Xe imaging is a one-shot procedure. Signal averaging may also be employed provided that the geometries can be aligned with sufficient precision.

2.2.10 Magnitude Image Noise

Changes of magnetic flux through the receiver coil are detected in quadrature, sampled, and converted to digital estimates that are stored as complex numbers. The acquired data are contaminated by noise that is due to a number of sources: thermal noise, receiver noise, interference from external RF sources, etc. The noise in both the quadrature channels is typically well described by a Gaussian (normal) probability density function (PDF). In the case that MR data are acquired on a uniform Cartesian grid in k -space, following Fourier reconstruction, the real and imaginary data remain degraded by Gaussian noise [64].

While all the image information is contained within the complex data, in order to derive spin-density information, the magnitude of the signal must be estimated.

2.2.10.1 The Rice Distribution

Once data are reconstructed, the magnitude may be computed voxel-by-voxel as:

$$M_i = \sqrt{R_i^2 + I_i^2} \quad 2.36$$

where M_i denotes the i^{th} data point in the magnitude image with real component R_i and imaginary component I_i . As the square-root operation is nonlinear, the PDF of the magnitude data is no longer expected to be Gaussian. If the original Gaussian noise is stationary and uncorrelated, it can be shown (see Appendix B.2) that the magnitude PDF may be well described by the Rice distribution:

$$p_{Rice}(M|A, \sigma) = \frac{M}{\sigma^2} e^{\left(-\frac{A^2 + M^2}{2\sigma^2}\right)} I_0\left(\frac{AM}{\sigma^2}\right) U(M), \quad 2.37$$

where A is the true signal, I_0 is the zero-order modified Bessel function:

$$I_0(z) = \frac{1}{2\pi} \int_0^{2\pi} e^{z \cos \varphi} d\varphi \quad 2.38$$

and $U(M)$ is the unit step Heaviside function:

$$U(M) = \begin{cases} 0 & M < 0 \\ 1 & M \geq 0 \end{cases}, \quad 2.39$$

indicating that the PDF is only valid for non-negative values of M .

The signal to noise ratio (SNR) of a given voxel is defined as:

$$SNR = \frac{A}{\sigma}. \quad 2.40$$

Figure 2.11 shows the form of the Rice distribution at selected SNR values. It is asymmetric, skewed to the left, and always positive. As the SNR increases, the Rice PDF approaches a Gaussian distribution.

Producing an un-biased estimator with a small variance for the magnitude in an MR image at low SNR is non-trivial. Estimation theory indicates that the Maximum-

likelihood (ML) approach is a general way to design asymptotically unbiased estimators with a minimum variance. ML estimation theory has been applied to the Rician distribution and can be found in detail elsewhere [64][65][66], but the relevant results to single ^{129}Xe images are given in Appendix B. Two estimators are used throughout this thesis: $\hat{\sigma}_{ML}$, the ML estimator for σ , and $\hat{A}_{ML}$, the ML estimator for A . Note that the “^” symbol is used in estimation theory to label a parameter as an estimator as opposed to a unit vector.

Figure 2.11 – The Rice distribution for four different signal-to-noise ratios (SNR).

2.2.10.2 Estimating Background

Every ^{129}Xe image is expected to contain some number of voxels where negligible signal exists in order to fit the object of interest within the given field of view and avoid artefacts. From a region of interest (ROI) containing N background voxels with zero signal and magnitudes M_i , the maximum likelihood estimator for σ is:

$$\hat{\sigma}_{ML} = \sqrt{\frac{1}{2N} \sum_{i=1}^N M_i^2}, \quad 2.41$$

with variance:

$$\text{var}(\hat{\sigma}_{ML}) \approx \frac{\sigma^2}{4N} \quad 2.42$$

It may be noted that the expectation value of $\hat{\sigma}_{ML}$ is approximately:

$$E[\hat{\sigma}_{ML}] \approx \sigma \left(1 - \frac{1}{8N}\right), \quad 2.43$$

which means that because of the square root operation, $\hat{\sigma}_{ML}$ is biased. While a bias correction may be applied, this would increase the variance of the estimator.

2.2.10.3 Estimating Magnitude

Assuming that σ^2 is known or has been estimated using equation 2.41, for a group of N voxels with true signal A , and magnitudes M_i , the ML estimator for A , $\hat{A}_{ML}$, may be found by solving:

$$\hat{A}_{ML} = \frac{1}{N} \sum_{i=1}^N M_i \frac{I_1\left(\frac{\hat{A}_{ML} M_i}{\sigma^2}\right)}{I_0\left(\frac{\hat{A}_{ML} M_i}{\sigma^2}\right)} \quad 2.44$$

Equation 2.44 cannot be solved explicitly for $\hat{A}_{ML}$. Therefore $\hat{A}_{ML}$ must be computed numerically.

2.3 Laser Polarization of Noble Gases

Since the bulk magnetization is proportional to the number of nuclei (equation 2.11), ^1H in the form of liquid H_2O has a considerably higher volume density and signal compared to the inert and gaseous ^{129}Xe at room temperature. In order to perform practical imaging experiments on ^{129}Xe gas, its polarization may be increased by several orders of magnitude to achieve “hyperpolarization”. There are several ways to achieve hyperpolarization, however this Section will describe only the spin exchange approach employed at the CMRF. This method uses optical pumping of rubidium (Rb) vapour in

the presence of nitrogen (N_2), helium (He) and Xe in a pressurized gas cell placed within a magnetic field. While a detailed discussion of this process can be found elsewhere [14][67][68], the basic procedure is summarized below.

2.3.1 Optical Pumping of Rubidium

The purpose of optical pumping is to add angular momentum to a system of Rb nuclei by altering the electron spin polarization of the Rb 5^2S orbital in a magnetic field, the ground state being $5^2S_{1/2}$. This process is illustrated in Figure 2.12. Right circularly polarized light resonant with the transition between the $5^2S_{1/2}$ ground state and the $5^2P_{1/2}$ excited state at 794.8 nm is used. The photon carries one unit of angular momentum ($m = 1$). When interactions occur angular momentum is conserved and the $\Delta m = +1$ selection rule is obeyed, allowing only the D_1 ($5^2S_{1/2} \rightarrow 5^2P_{1/2}$) transition.

Once excited to the $5^2P_{1/2}$ excited state, collisions with noble-gas atoms (He and Xe) equalize the populations of the $5^2P_{1/2}$ and $5^2P_{-1/2}$ states. Subsequent collisions of the Rb with N_2 quench the electrons to the $5^2S_{1/2}$ and $5^2S_{-1/2}$ states with nearly equal probability and absorb the fluorescent photons. Without the N_2 un-polarized fluorescence photons would induce transitions from the $5^2S_{1/2}$ state, defeating the optical pumping of the nuclei.

Since the Rb atoms have $-1/2$ units of electron-spin angular momentum before absorbing the laser photons, and an average of 0 units of electron-spin angular momentum after being quenched from the excited state, on average each photon deposits $1/2$ a unit of spin angular momentum, the remainder being lost to translational motion. As the $5^2S_{1/2}$ electrons are subsequently re-excited by the laser, resulting in the rapid and almost total polarization of the $5^2S_{1/2}$ state, defined as $\frac{\Gamma}{2}$.

Figure 2.12 Optical pumping of Rb electrons with left-circularly polarized light. Adapted from [68].

2.3.2 Spin Exchange

In order to polarize ^{129}Xe , spin exchange occurs between the optically pumped Rb electrons and the ^{129}Xe nuclei via hyperfine coupling [14]:

As shown in Figure 2.13, two types of collisions allow the polarization transfer to occur: a binary collision between a polarized Rb atom and an un-polarized ^{129}Xe atom, and the formation of a van der Waals complex of the two atoms for a mean time τ . In the case of ^{129}Xe , the contribution of van der Waals molecules to the spin exchange greatly exceeds that of binary collisions, and is further enhanced in the presence of N_2 where three-body collisions increase the probability of van der Waals complex formation. The probability of forming a van der Waals complex also depends on the relative velocities of the ^{129}Xe and Rb ($\bar{v}$) and the ^{129}Xe spin-exchange cross-section (σ_{Xe}) [15].

Figure 2.13 Spin exchange between ^{129}Xe and optically pumped rubidium. (a) The formation and break-up of an alkali-metal/noble-gas van der Waals molecule. (b) Binary collision between an alkali-metal atom and a noble gas atom. Adapted from [68].

2.3.3 Relaxation

Following spin exchange, a system of ^{129}Xe nuclei will be spin-polarized to the state aligned to the static magnetic field in excess of thermal equilibrium. Collisions of the ^{129}Xe with other atoms (N_2 , Rb, buffer He, and other ^{129}Xe atoms) and the walls of the pumping cell will cause magnetic interactions that induce spin relaxation. This relaxation is described by the longitudinal relaxation time constant T_1 , and is a function of the gas concentrations, cell wall material and geometry.

2.3.4 Achievable Xe Polarization

A balance between the spin-exchange and relaxation mechanisms sets the achievable ^{129}Xe polarization within a given cell. The pumping rate at which ^{129}Xe nuclei become

polarized is related to the number of polarized rubidium atoms at the spin-exchange probability:

$$\frac{1}{T_{\text{pump}}} = \frac{\Gamma}{2} [\text{Rb}] \bar{v} \sigma_{\text{Xe}} \quad 2.46$$

where $[\text{Rb}]$ is the rubidium concentration, and is independent of the number of polarized Xe nuclei. The relaxation rate is proportional to the number of polarized atoms and inversely proportional to T_1 . Thus the polarization rate is:

$$\frac{dP}{dt} = \frac{1}{T_{\text{pump}}} - \frac{P}{T_1} \quad 2.47$$

with the solution:

$$P = \frac{T_1}{T_{\text{pump}}} (1 - e^{-t/T_1}) \quad 2.48$$

assuming an initial thermal polarization of zero, and where t is the time spent in the pumping cell. The maximum achievable ^{129}Xe polarization is the limit as t approaches infinity [69], with typical values between 5% and 70% depending on cell configuration.

$$P(t \rightarrow \infty) = \frac{T_1}{T_{\text{pump}}} \quad 2.49$$

2.4 Volume from ^{129}Xe MR Images

This section describes the assumptions and approximations required to estimate volume from an MR image.

2.4.1 Volume from ^{129}Xe -MR Signal Magnitude

Using the equations 2.7, 2.10, 2.11, 2.21, 2.22, 2.24, 2.26 and 2.28, the MR signal per unit volume may be derived. Through a process known as “shimming” the $\mathbf{B}_{\text{tot}}$ field can be made homogeneous along the z -axis (i.e., $\mathbf{B}_{\text{tot}} = B_0 \hat{z}$). Following an RF pulse with a

flip angle α on an initial magnetization $M_0\hat{z}$, with M_0 defined by equation 2.11, equation 2.22 may be re-written for an elemental volume $d\mathbf{r} = dxdydz$:

$$\frac{d\varepsilon}{d\mathbf{r}} = -\frac{\partial}{\partial t} \left[\mathbf{B}_1(\mathbf{r}) \cdot \left(\begin{aligned} &M_0(\mathbf{r},t)\sin(\alpha)e^{-\frac{t}{T_2}} [\cos(\omega_0 t)\hat{x} + \sin(\omega_0 t)\hat{y}] + \dots \\ &\left(M_{eq} + (M_0(\mathbf{r},t) - M_{eq})\cos(\alpha)e^{-\frac{t}{T_1}} \right) \hat{z} \end{aligned} \right) \right] \quad 2.50$$

Taking the partial derivative with respect to time:

$$\frac{d\varepsilon}{d\mathbf{r}} = \mathbf{B}_1(\mathbf{r}) \cdot \left(\begin{aligned} &\omega_0 M_0(\mathbf{r},t)\sin(\alpha)e^{-\frac{t}{T_2}} [\sin(\omega_0 t)\hat{x} - \cos(\omega_0 t)\hat{y}] - \dots \\ &\frac{M_0(\mathbf{r},t)\sin(\alpha)e^{-\frac{t}{T_2}} [\cos(\omega_0 t)\hat{x} + \sin(\omega_0 t)\hat{y}]}{T_2^*} + \dots \\ &\frac{(M_0(\mathbf{r},t) - M_{eq})\cos(\alpha)e^{-\frac{t}{T_1}} \hat{z}}{T_1} \end{aligned} \right) \quad 2.51$$

$B_0 = 1.89$ T for the magnet at the CMRF, making the Larmor frequency of ^{129}Xe 22.2 MHz. Typically T_2^* values are on the order of milliseconds to seconds, while T_1 values for ^{129}Xe range from seconds to hours. Therefore:

$$\omega_0 \gg \frac{1}{T_2^*} > \frac{1}{T_1} \quad 2.52$$

and:

$$\frac{d\varepsilon}{d\mathbf{r}} \approx \mathbf{B}_1(\mathbf{r}) \cdot \omega_0 M_0(\mathbf{r},t)\sin(\alpha)e^{-\frac{t}{T_2}} [\sin(\omega_0 t)\hat{x} - \cos(\omega_0 t)\hat{y}] \quad 2.53$$

If one makes the assumption that the receiving coil is designed to be uniformly sensitive across the three dimensional field of view (FOV) of the object imaged (i.e., $\mathbf{B}_1 = B_1\mathbf{r}$),

then switching to the on-resonance rotating frame of reference:

$$\frac{d\varepsilon}{d\mathbf{r}} \approx -B_1\omega_0 M_0(\mathbf{r},t)\sin(\alpha)e^{-\frac{t}{T_2}} \hat{y}' \quad 2.53$$

A miscalculation of the resonant frequency of the rotating frame of reference will result in phase accumulation of the signal. Quadrature detection is employed such that these changes in phase are measured. The magnitude of the signal may then be computed. Substituting equations 2.7 and 2.11 into equation 2.53:

$$\left| \frac{d\varepsilon}{dr} \right| \approx \frac{1}{2} \gamma^2 \hbar B_0 B_1 N(\mathbf{r}, t) P(\mathbf{r}, t) \sin(\alpha) e^{-\frac{t}{T_2^*}} \quad 2.54$$

For the signal magnitude to be directly proportional to the number of nuclei in a voxel, on the time scales of a voxel acquisition equation 2.54 must have the form:

$$\left| \frac{d\varepsilon}{dr} \right| \approx \frac{1}{2} \gamma^2 \hbar B_0 B_1 N(\mathbf{r}) P \sin(\alpha) \quad 2.55$$

Ideally the polarization $P(\mathbf{r}, t)$ is a constant for all nuclei and therefore independent of $\mathbf{r}$ and t . This is achieved assuming the polarization has a negligible effect on the diffusion of the gas, and that the gas has sufficient time to homogenize via diffusion and mixing prior to imaging.

The time dependence of equation 2.55 is governed primarily by the approximations made in equation 2.52 and the T_2^* decay in equation 2.54. Therefore T_1 and T_2^* must be large with respect to the acquisition time of a given voxel. Furthermore, T_2^* must be large with respect to the frequency-encoded acquisition times, as the signal magnitude following a spin or gradient echo will be governed by T_2^* decay. Both T_1 and T_2^* effects can be accounted for in pulse sequencing and data analysis if they are observable.

The time dependence of $N(\mathbf{r}, t)$ indicates that atomic motion limits the ultimate resolution of MR imaging. The self-diffusion coefficient of Xe is 0.061 cm²/s in air [39]. In the lung, the diffusion coefficient is limited by the presence of tissue (for example, in a guinea pig lung, the diffusion coefficient has been estimated as 0.021 cm²/s [70]). Acquisition times for voxels must therefore be short with respect to the distances travelled by Xe atoms. In this thesis, the longest acquisition time per voxel* was approximately 0.08 ms, and the smallest voxel dimension† used was 0.01 cm². Using the diffusion coefficient in air, a Xe atom is expected to diffuse 5×10⁻⁶ cm² in 0.08 ms – three-orders of magnitude less than the smallest voxel dimension used. Therefore the time dependence of $N(\mathbf{r}, t)$ is expected to be negligible.

* From a 64×32×32 scan in 10 cm × 10 cm × 10 cm FOV with a TE of 5 ms.

† From a 256×32×32 image in a 10 cm × 10 cm × 10 cm FOV with a TE of 7 ms.

Provided the signal does have the form of equation 2.55, the signal will be proportional to volume if $N(\mathbf{r})$ has a uniform density (i.e., pressure is constant) and is constrained by the boundaries of the structure being imaged. For rigid phantoms, these conditions may be satisfied, and for lungs *in vivo* may be approximated by a breath-hold. It was mentioned in the Chapter 1 that Xe is soluble in the blood, thus facilitating NMR spectroscopy *in vivo*. If pulse sequences are designed such that dissolved ^{129}Xe frequencies are not excited, only the gas-phase of ^{129}Xe will be imaged.

2.4.2 Partial Volume

If the assumptions presented in the preceding section hold, then the MR-signal magnitude is proportional to volume. Approximating Xe as an ideal gas*, the atomic density of ^{129}Xe at 300 K and atmospheric pressure is approximately 6.5×10^{21} atoms/L. The ^{129}Xe -MR imaging voxel sizes used in this thesis are on the order of 4 μL to 60 μL . The average diameter of a human alveolus is 0.3 mm [20] with a volume of 14 nL. Thus the expected voxel dimensions are three orders of magnitude larger than the alveolar dimensions, and each alveolus contains about 10^{14} atoms. While the lung is adequately sampled by the atomic resolution of ^{129}Xe , it is under-sampled by the MR-imaging procedure, as illustrated in Figure 2.14. ^{129}Xe -MR image voxel magnitudes therefore represent the volume of the imaged geometry contained within the voxel boundaries, and may vary from “zero” – where no polarized ^{129}Xe nuclei are present†, to “full” – where no tissue is present, and the entire volume of the voxel is homogeneously filled with Xe gas.

* An ideal gas obeys the ideal gas law: $PV=nRT$

† Technically, the thermal polarization of ^{129}Xe in zero-signal regions is expected to produce signals greater than zero. However, the 0.023 ppm abundance of ^{129}Xe in air is negligible, thus the principle source of thermal ^{129}Xe is residual gas from previous experiments. Furthermore, even in a 100% ^{129}Xe environment, thermal polarizations are about five orders of magnitude smaller than those of hyperpolarized gas. Since the highest image SNRs presented in this thesis is ~ 50 , it is predicted that a thermal SNR of $\sim 10^{-4}$ would not be detectable.

For an image consisting of N voxels, each with the “true” magnitude A_i (this is the “perfect” estimator of magnitude from Section 2.2.10), in a 3D FOV, the volume of the imaged structure is therefore:

$$vol = \frac{FOV}{N \cdot A_{full}} \sum_{i=1}^N A_i \quad 2.56$$

where A_{full} is the magnitude of a completely filled voxel.

Figure 2.14 Under-sampling of a complex geometry. (a) A computer-generated image rendered in greyscale at 1200×800 pixels, (b) the same image under-sampled to 9×6 pixels.

2.4.3 Challenges in Volume Estimation

If equation 2.56 held for real MR data, volume estimation would be trivial provided pulse sequences could be made to enforce all the assumptions presented in Section 2.4.1. As indicated in Section 2.2.10 however, due to the influence of Rice distributed noise, no perfect estimator for the MR-signal magnitude exists. It can be seen in Appendix B, that even for the ML estimator, zero-signal magnitudes are positively biased, thus implementing equation 2.56 would result in over-estimation of volume as typically more than 90% of the voxels in an imaged FOV represent the zero-signal distribution.

Therefore, in order to produce a practical volume estimator, the following criteria must be addressed:

1. The polarization of ^{129}Xe must be sufficiently high to produce a detectable signal from volumes large enough to sample the largest full-volume in the imaged structure.
2. The MR pulse sequence must be sufficiently rapid to image the structure before relaxation processes diminish the ^{129}Xe signal.
3. The MR pulse sequence must be designed such that signal magnitude from a homogeneous distribution of gas is in turn homogeneous and free from artefacts and distortion.
4. The bias due to noise on MR signal magnitudes must be reduced as much as possible, or eliminated.
5. A criterion must be formed to reject zero-signal voxels, such that they do not contribute to the sum in equation 2.56.

3 Materials and Methods

This chapter describes the current methods and procedures used at the CMRF to image ^{129}Xe and estimate volume from the corresponding images. The Xe polarizer is discussed in Section 3.1, the specific MR methods and pulse sequences used in Section 3.2, post-imaging procedures and the volume estimation algorithm are discussed in Section 3.3, and subject volumes in the form of phantoms and *in vivo* experimental setups are discussed in Section 3.4. A schematic of the ^{129}Xe MR imaging system and *in vivo* setup may be found in Figure 3.8 and Figure 3.9 respectively. Components are described by functional names and numbers (i.e., the console₍₂₂₎). Model numbers and specific vendor information is given in Appendix A.

3.1 Laser Polarization of ^{129}Xe

The CMRF ^{129}Xe polarizer used for this work followed the design described by Moudrakovski *et al.* [71]. The polarization cell_(8,9) consisted of two main chambers: the Rb cell₍₈₎ – where Rb was stored and vaporized, and the optical pumping cell₍₉₎ – where laser light was focused and spin-exchange processes occurred. The polarization cell_(8,9) was made of glass coated with SurfaSil[®]₍₂₃₎ and was pressurized to 550 kPa using a 1% natural abundance Xe (26.4% ^{129}Xe), 10% N₂, and ballast He gas mixture₍₁₎ flowing at 0.32 ± 0.03 L/min. Prior to polarization, gases were passed through a water vapour trap₍₂₎ and an oxygen trap₍₅₎ to reduce T_1 losses due to collisions with paramagnetic molecules and prevent Rb oxidation. Flow was monitored with a gas flow meter₍₃₎ and controlled by a needle valve_(v-8). Rb was vaporized by elevating and maintaining the temperature of

the Rb chamber₍₈₎ using resistive heating wire₍₇₎ and a thermocouple-driven temperature controller₍₆₎.

^{129}Xe was polarized using a 60 W 795 nm diode array laser_(10,11). The optical cell₍₉₎ was placed approximately 80 cm off the axis of a 30 cm bore, 1.89 T superconducting magnet₍₁₈₎ in the fringe field of approximately 300 Gauss. The laser beam was transmitted by a fiber-optic cable₍₁₁₎ to a 795 nm quarter-wave polarizer and lens set₍₁₀₎ and directed parallel to the magnet bore (i.e., the z -axis in Figure 3.8) onto the optical cell₍₉₎. After polarization, the gas mixture was passed through a glass wool Rb trap₍₁₃₎. Rb was removed from the administered gas mixture as it would continue spin exchange, depolarizing the ^{129}Xe , and is toxic and therefore undesirable in the lab and *in vivo* work.

Following the Rb trap₍₁₃₎, gas was passed through a cryogenic gas trap₍₁₄₎ immersed in liquid nitrogen₍₁₅₎ at 77 K. With a melting point of 161.3 K, Xe froze out of the gas mixture in the trap₍₁₄₎, while the N_2 gas and He passed through it without changing states. Valves V-9, V-10, V-11, V-12 and V-13 were used to regulate the flow of the gas mixture through the trap₍₁₄₎. Xe was frozen out of the flow in time intervals ranging from 1 to 30 minutes. For *in vitro* experiments, both the trap₍₁₄₎ and phantoms₍₁₇₎ were evacuated of gas using a water tap-based vacuum system (i.e., the Venturi effect) connected to a three-way valve_(V-13). The frozen Xe₍₁₆₎ was then thawed by immersing the trap₍₁₄₎ in warm tap water. For *in vitro* experiments V-13 was left open between the trap₍₁₄₎ and the phantoms₍₁₇₎ during the thawing procedure to allow the expansion of Xe into the phantom volume.

For *in vivo* experiments, evacuation was not performed to avoid collapsing the lungs, and gas was thawed with V-13 switched to a ventilator₍₂₄₎. A pressure sensor₍₂₅₎ connected to an oscilloscope₍₂₆₎ was attached to animals to monitor thoracic expansion due to breathing. When the oscilloscope trace indicated the *in vivo* lungs were in their most deflated state, V-13 was closed to the ventilator₍₂₄₎, opened to the trap₍₁₄₎, and gas was administered as a bolus to the animals₍₁₇₎.

Save for the polarization estimation experiments described in section 3.1.1, all images were acquired by administering gas following the above freeze-thaw procedures. The administered gas was ideally 100% Xe, with impurities due to residual He and N₂ not evacuated from the Xe trap₍₁₄₎ and tubing for *in vivo* experiments.

3.1.1 Experimental Determination of the Polarization

¹²⁹Xe polarization was estimated by comparing the MR signals obtained from the hyperpolarized ¹²⁹Xe flow with the signals obtained from a thermal cell₍₂₇₎ with partial pressures of 505 kPa and 152 kPa of ¹²⁹Xe and O₂ respectively, following a 90° hard pulse. A pressure of 101.3 kPa was assumed for the flowing gas mixture. A 1 cm solenoidal coil₍₂₈₎ was used for both measurements, and the Xe flow was made to conform to the geometry of the thermal cell such that the volume and RF coil filling factors were the same for each measurement. 64 pulses were applied to the thermal sample₍₂₇₎, one every 4 s, allowing for T₁ re-growth of the thermal signal, and averaged. Pulses were applied to the polarized gas every 7.5 s to ensure the gas flow replaced the previous gas in the coil, and every 8 acquisitions were averaged. The theoretical polarization of the thermal gas was calculated via equation 2.10 as 1.78×10⁻⁶.

The hyperpolarized ¹²⁹Xe polarization was calculated as:

$$P_{hp} = P_{therm} \left(\frac{S_{hp}}{S_{therm|V}} \right) \frac{[^{129}\text{Xe}_{therm}]}{[^{129}\text{Xe}_{hp}]} \quad 3.1$$

Where S_{hp} and S_{therm} are the relative signals from the hyperpolarized and thermal samples respectively, and $[^{129}\text{Xe}_{hp}]$ and $[^{129}\text{Xe}_{therm}]$ are the partial pressures of ¹²⁹Xe in each respective sample. A sample calculation using equation 3.1 indicates a polarization of 12%:

$$P_{hp} = 1.78 \times 10^{-6} \left(\frac{2.8 \times 10^6}{7.7 \times 10^4} \right) \left(\frac{505 \text{ kPa}}{101 \text{ kPa} \cdot 1\%_{\text{Xe}} \cdot 26.4\%_{^{129}\text{Xe}}} \right)$$

$$P_{hp} = 12\%$$

Note that this calculation of polarization does not account for losses incurred in the freeze-thaw Xe trapping process, which have been estimated in other experiments at the CMRF to be on the order of 20-50%.

3.1.2 Optimization of the Polarization

As mentioned in Section 2.2.4, the polarization achieved is the result of the optical pumping rates, the relaxation rates, and polarization times of ^{129}Xe nuclei within a given cell₍₉₎. While ^{129}Xe polarizations on the order of 50 to 70% are achievable at low pressures [72], such procedures do not currently produce sufficient amounts of polarized gas to fill a volume for imaging experiments. Over the lifetime of the cells, Rb oxidizes in the cells_(8,9) due to O_2 contamination and acts as a relaxation agent, decreasing the maximum achievable polarization. Operating polarizations for the described setup ranged from 4% to 20% polarization of the ^{129}Xe , dependant on the temperature of the cell₍₈₎ and the amount of Rb_2O present. Higher polarizations were obtained on cells_(8,9) within their first few weeks of use.

For each run of experiments, the laser alignment was checked and the flow rate was set to between 0.30 and 0.35 L/min via the needle valve_(V-8). The temperature controller₍₆₎ was activated and allowed approximately 20 minutes to vaporize Rb to an equilibrium vapour pressure. The temperature was then adjusted in increments of 5 °C to optimize the polarization as a function of temperature. An increase in temperature results in a higher Rb vapour pressure and an increased optical pumping efficiency, however it also increases the number of volatile particles in the cell and their mean velocity. As a result, the number of collisions and the probability of depolarizing ^{129}Xe is increased, decreasing T_1 in the cell. Typical optimal temperatures were in the range of 120 °C to 220 °C.

The absorption of the laser light by the Rb was monitored via a fiber-optic spectrometer₍₁₂₎, where the line shape as shown in Figure 3.1 provided a secondary

qualitative indicator for optimal laser and temperature setup. Figure 3.2 shows a typical plot of polarization as a function of time as the cell is initialized and adjusted with respect to temperature.

Figure 3.1 Absorption of laser light by Rb vapour at 180 °C, 190 °C and 200 °C in an optical cell₍₉₎ using the fiber-optic spectrometer₍₁₂₎. The Gaussian distribution illustrates the form of the original laser line shape. As the Rb vapour pressure increases with temperature, the absorption efficiency increases.

Figure 3.2 Changes in ^{129}Xe polarization as a function of time and temperature following initialization of the temperature controller₍₆₎ set to 170 °C. Temperatures indicate those set on the temperature controller, not necessarily those in the cell. A maximum polarization is reached 18 minutes following initialization as the Rb vapour pressure passes through an optimum value. At higher temperatures, while the optical pumping efficiency is greater (see Figure 3.1), the increased temperature causes more collisions, increasing relaxation rates and lowering the polarization.

3.2 NMR Methods and Pulse Sequences

All MR experiments were performed on a SMIS MR5000 console₍₂₂₎ using a 1.89 T Magnex magnet and gradient set₍₁₈₎ and a 12 cm (inner diameter) quadrature bird cage coil₍₁₉₎ that was tuned to 22.175 MHz, the resonant frequency of ^{129}Xe at 1.89 T.

3.2.1 ^{129}Xe Flip Angle Calibration and T_1 Measurement

For a given sample and receiver coil arrangement, the power settings required to specify a flip angle were constant. Flip angles were estimated from power settings and measured to ensure appropriate use of the magnetization during pulse sequences. Each gas volume placed within the magnet was also expected to have a different T_1 due to interactions of the polarized gas with the walls of the structures. T_1 is a necessary parameter in many pulse sequence optimizations, and therefore was determined to either correct for or justify approximations used.

T_1 and flip angles were estimated simultaneously on Xe samples. Phantoms were sealed with boluses of hyperpolarized ^{129}Xe and placed near the isocenter* of the magnet₍₁₈₎. The pulse sequence in Figure 3.3 (a) was used, consisting of a series of constant flip angles α , separated by a repetition time TR [73]. Each pulse diminished the longitudinal magnetization by a factor of $\cos\alpha$, while between pulses the magnetization was diminished by a factor of e^{TR/T_1} . The signal measured (S_n) after the n^{th} RF pulse was:

$$S_n = M_n^- \sin \alpha, \quad 3.2$$

where M_n^- is the longitudinal magnetization immediately prior to the pulse.

The signal of the n^{th} pulse may also be written as a function of time:

$$S_n(t) = M_0 \sin \alpha (\cos \alpha)^n e^{-t/T_1}, \quad n = \text{floor}(t/TR), \quad 3.3$$

* The isocenter lies approximately in the middle of the magnet bore. It is the point where field homogeneity and coil sensitivity are maximized, and is ideally where all MR experiments are performed.

where the function *floor* rounds down its argument to the nearest integer.

The integral of the gas-phase Lorentzian in the FFT of the FID was used to estimate the signal magnitude and plotted as a function of time. The resulting curve was fitted to equation 3.3 to find M_0 , α and T_1 . The fit was found to be extremely sensitive to initial conditions for α however, and was therefore reduced to a two parameter fit on M_0 and T_1 . The pulse sequence was then repeated by changing α by a multiplicative factor λ and generating α/λ vs. T_1 curves for each data set. The intercept of the two or more curves was then used to estimate α and T_1 for that object. Once the power settings for a desired flip angle were known; only one sequence was run and T_1 was fit to the selected α .

An alternative method for T_1 estimation and flip angle calibration is described in [39], whereby instead of estimating both parameters from long TR sequences (i.e., $TR \approx T_1$), flip angle calibrations are estimated from a similar short TR sequence (i.e., $TR \ll T_1$), which is then used as an input parameter for α in a long TR sequence.

Figure 3.3 (a) T_1 estimation pulse timing sequence and (b) resulting MR spectra for a series of 15° pulses on a bolus of hyperpolarized ^{129}Xe .

3.2.2 Variable Flip Angle 3D Gradient Echo Sequence

All 3D imaging sequences used for this work were variants of the 3DFT gradient echo sequence shown in Figure 2.10. Equation 3.3 indicates that for a series of constant flip angles (CFA) the measured signal diminishes after each pulse. It can be shown that the flip angle that provides the highest SNR for a sequence of constant flip angles is the Ernst angle θ_E [74]:

$$\cos \theta_E = e^{-\frac{TR}{T_1}} \quad 3.4$$

However, a CFA sequence results in an inhomogeneous signal mapping of a ^{129}Xe image as polarization is not restored, and produces regional signal distortions with varying SNR, which is undesirable for a magnitude-based approach to volume estimation. If a sequence of variable flip angles (VFA) is applied, equation 3.3 can be re-written to express the signal of the $(n+1)^{\text{th}}$ pulse:

$$(S_{n+1})_{VFA} = M_i \sin \alpha_{n+1} \left(\prod_{j=0}^n \cos(\alpha_j) \right) e^{-\frac{t}{T_1}}. \quad 3.5$$

By forcing the measured signals in equation 3.5 to be equal for a train of N pulses, i.e., $S_1 = S_2 = \dots = S_N$ and $(N = N_{PEz} \times N_{PEy})$, and $\alpha_N = 90^\circ$ to employ all the remaining magnetization on the final pulse, the flip angle of the n^{th} pulse is [75]:

$$\alpha_n = \tan^{-1} \left(e^{-\frac{(N-n)TR}{T_1}} \prod_{j=n+1}^{N-1} \cos(\alpha_j) \right) \quad 3.6$$

$$\alpha_n \approx \tan^{-1} \left(\frac{e^{-\frac{(N-n)TR}{T_1}}}{\sqrt{N-n}} \right)$$

It is typical in ^{129}Xe imaging however that T_1 is on the order of $10^4 TR$, in which case

$$\alpha_n \approx \tan^{-1} \left(\frac{1}{\sqrt{N-n}} \right) \quad 3.7$$

becomes a reasonable approximation requiring little *a priori* information. This approximation was used.

3DFT VFA gradient echo (3DVFAGE) sequences were run at a variety of resolutions with the constraint that the number of phase encodes in the z and y directions were the same. Table 3.1 indicates the resolutions, echo and repetition times used. VFA sequence angles were calculated according to equation 3.7 for 16×16 and 32×32 phase-encode steps, and stored as two look-up tables that were used to specify flip angles as pulse sequences were run.

Table 3.1 Echo and repetition times for the VFA 3D FT gradient echo sequences used.

Resolution	$64 \times 16 \times 16$	$128 \times 16 \times 16$	$64 \times 32 \times 32$	$128 \times 32 \times 32$	$256 \times 32 \times 32$
TE [ms]	4	5	4	5	7
TR [ms]	16	16	16	16	20

3.3 Volume Estimation Procedure

This section describes the algorithm used to estimate volumes from simulated and measured MR images. The algorithm is presented in 8 steps below, and illustrated in Figures 3.4 and 3.5 at the end of this section.

1. Images were constructed from the raw data

MR data were stored in the computer as a three-dimensional array of complex numbers in time-space. The Matlab₍₂₉₎ “fftn” function, a three-dimensional FFT, was used to convert time-space data to frequency space – corresponding to a three-dimensional Cartesian mapping of the MR spectrum. To facilitate the later drawing of regions of interest (ROIs) by a human operator*, images with 128 frequency-encode samples or fewer were zero-filled to a final matrix size of $128 \times 128 \times 128$.

* Zero-filling does not alter average voxel magnitudes and hence has little effect on the derived volume (see Figures 4.15 (b) and 4.17 (b)), however it gives the operator the impression of increased resolution and cubic voxels, making structures easier to identify.

Images with 256 frequency-encode samples were zero-filled to a $256 \times 128 \times 128$ matrix. Magnitude-scaled images M were then estimated voxel-by-voxel:

$$M_i = \sqrt{R_i^2 + I_i^2}, \quad 2.36$$

where R_i and I_i are the real and imaginary components of the i^{th} voxel.

Zero-filling was not performed on simulated data sets as they were constructed directly in Cartesian space and did not require operator input to define ROIs.

2. The noise parameter σ was estimated

Images were then viewed in planes with edges corresponding to the frequency-encode dimension and one phase-encode dimension. ROIs were drawn by the operator on contiguous slices in the FOV to encompass voxels describing the zero-signal distribution, known *a priori* to be empty by geometrical arguments, and the corresponding voxel magnitudes were stored as a vector. The ROIs were defined such that they encompassed a similar range as the dimensions of the imaged object in the frequency-encode dimension, as there was a tendency for a systematic background signal variation in the frequency-encode dimension leading to larger signal magnitudes near the edges of the image. For a vector $\vec{m}$ containing the magnitudes of N_m voxels, the maximum likelihood background noise parameter $\hat{\sigma}_{ML}$ was calculated:

$$\hat{\sigma}_{ML} = \sqrt{\frac{1}{2N_m} \sum_{i=1}^{N_m} m_i^2} \quad 2.41$$

with a variance of

$$\text{var}(\hat{\sigma}_{ML}) = \frac{\hat{\sigma}_{ML}^2}{4N_m}. \quad 3.8$$

On simulated data sets the indices of all voxels in the image prior to noise addition with signal values of zero were stored. Following noise addition to the images, the vector $\vec{m}$ was created using all the stored indices to minimize uncertainties in $\hat{\sigma}_{ML}$ estimation, and no operator-selected ROIs were required.

3. Images were cropped to reduce the number of background voxels

Due to the imaging constraints required to place all of an object within the FOV at an acceptable SNR, it was typical that a large number of voxels in images consisted of background noise signal. To reduce the sensitivity of the volume estimation procedure to such voxels, images were cropped in three-dimensions to a FOV with boundaries much closer to the gas distribution signal.

On simulated data sets, two cropping procedures were automatically performed. In the first case, the indices of all voxels with non-zero signal in the image prior to noise addition were stored. This allowed “perfect” segmentation of the image, whereby only voxels with true signal content were used in subsequent steps. In the second case, projections of the image prior to noise addition along each dimension were taken. Along each projection non-zero indices were stored to define a rectangular box that contained all voxels with signal and as few background voxels as possible, dependent on the geometry of the object being imaged. This second approach was designed to simulate the operator cropping criteria, and allowed prediction of optimal thresholds.

4. “Full” voxel signals were estimated

Similar to step 2, ROIs were drawn by the operator in regions of the gas signal assumed not to contain partial volume effects using *a priori* geometrical knowledge, and the corresponding N_f voxel magnitudes were stored in a vector $\vec{f}$. The maximum likelihood estimator for the sample $\hat{A}_{MLfull}$ was calculated by numerically solving:

$$\hat{A}_{MLfull} - \frac{1}{N_f} \sum_{i=1}^{N_f} f_i \frac{I_1 \left(\frac{\hat{A}_{MLfull} f_i}{\hat{\sigma}_{ML}^2} \right)}{I_0 \left(\frac{\hat{A}_{MLfull} f_i}{\hat{\sigma}_{ML}^2} \right)} = 0 \quad 2.44$$

using the Matlab₍₂₉₎ “fsolve” function. As no convenient expression for the variance of $\hat{A}_{MLfull}$ was known, the standard deviation of $\tilde{f}, \hat{\sigma}_{full}$, was estimated to check the homogeneity of magnitude values in the ROIs using the Matlab “std” function. The SNR of the image was then calculated as:

$$SNR = \frac{\hat{A}_{MLfull}}{\hat{\sigma}_{ML}}, \quad 3.9$$

with the corresponding uncertainty

$$\hat{\sigma}_{SNR} = \sqrt{\left(\frac{\hat{A}_{MLfull}}{\hat{\sigma}_{ML}^2} \sqrt{\text{var}(\hat{\sigma}_{ML})} \right)^2 + \left(\frac{\hat{\sigma}_{full}}{\hat{\sigma}_{ML}} \right)^2}. \quad 3.10$$

For simulated data, full voxel indices were stored prior to noise addition to allow optimal estimation of full voxel magnitudes, such that no operator-specified ROIs were required.

5. Voxels were binned according to signal magnitude

Voxel magnitudes in cropped images were then counted in n_{bins} bins centered linearly on values between zero and the maximum voxel magnitude in the image producing two vectors: $\vec{F}$ and $\vec{M}_F$, denoting the number of voxels and magnitudes respectively for each bin. $\vec{F}$ vs. $\vec{M}_F$ was then plotted to produce a histogram of voxel magnitudes.

This step was not performed on simulated images.

6. Re-evaluate signal magnitudes using the Maximum Likelihood estimator

To reduce the bias between bin magnitude values, $\bar{A}_F$ was computed by solving the maximum likelihood estimator equation for the magnitude bin values $\bar{M}_F$:

$$A_{Fi} - M_{Fi} \frac{I_1 \left(\frac{A_{Fi} M_{Fi}}{\hat{\sigma}_{ML}^2} \right)}{I_0 \left(\frac{A_{Fi} M_{Fi}}{\hat{\sigma}_{ML}^2} \right)} = 0. \quad 3.11$$

As simulated images were not zero-filled, there were fewer voxels to compute. Each voxel in the cropped simulated image was independently estimated using equation 3.11. In principle voxel-by-voxel maximum-likelihood estimation can be done for the zero-filled MR data, though the loss in precision due to binning is small with respect to the uncertainties observed, and reduces computation time.

7. Lower signal magnitude thresholds were chosen

To further reduce the effects of zero-signal voxels on volume estimation a low-magnitude cut-off threshold A_T was chosen, such that voxels in the cropped image with magnitudes below the threshold were not considered in volume estimation. The threshold was chosen by alternating between slice and projection representations of the image as well as the histogram, and choosing the value that rejected as many background voxels as possible without rejecting voxels clearly containing signal. On phantoms with known volumes this threshold was both operator-chosen to assess the user-guided accuracy of the algorithm, and subsequently computer-optimized to solve for the known volume to facilitate the investigation of threshold-selection trends.

8. Estimate volume by magnitude-weighted voxel counting

Volume was then computed as:

$$vol = \frac{FOV}{N_{FE} \cdot N_{PE}^2} \frac{1}{\hat{A}_{MLfull}} \sum_{i=1}^{n_{bins}} \begin{cases} 0 & A_{Fi} \leq A_T \\ A_{Fi} F_i & A_{Fi} > A_T \end{cases} \quad 3.12$$

where N_{FE} and N_{PE} are the zero-filled dimensions of the image (i.e., usually 128), and FOV is the volume of the imaged space (i.e., 6 cm $\times$ 6 cm $\times$ 6 cm for the image presented in Figures 3.4 and 3.5).

Figure 3.4 Illustration of steps 1-4 of the the volume estimation algorithm using a 64 $\times$ 32 $\times$ 32 image of a syringe partially filled with spherical beads in a 6 cm $\times$ 6 cm $\times$ 6 cm FOV. Gravity is in the negative y-direction. Steps 5-8 are on the following page.

(8) $vol = 10.6 mL$

Figure 3.5 Illustration of steps 5-8 of the the volume estimation algorithm using a $64 \times 32 \times 32$ image of a syringe partially filled with spherical beads in a $6\text{ cm} \times 6\text{ cm} \times 6\text{ cm}$ FOV. Steps 1-4 are on the preceding page.

3.4 *In vitro* Experiments

A set of phantoms with well known gas-volume properties were constructed to investigate the performance of the MR volume estimation procedure. Individual phantom designs are described in this section, accompanied by the experimental procedures performed. Illustrations of the phantoms are shown in Figure 3.6 at the end of this Section.

3.4.1 Empty Syringe Phantoms

20 mL and 60 mL plastic syringes₍₃₀₎ were converted to the empty syringe phantoms like the one illustrated in Figure 3.6 (a). 16 gauge catheters₍₃₁₎ were attached to the nozzles of the syringes via silicone tubing to create an air-tight seal with the syringes₍₃₀₎ and the Xe trap₍₁₄₎. Holes were drilled along the syringe plungers at approximately 2 mL and 5 mL intervals for the 20 mL and 60 mL phantom respectively, so that the plungers could be pinned (using pieces of a 5 mL plastic syringe₍₃₀₎) during phantom evacuation procedures without the volume of the phantoms changing. Volume was estimated geometrically from the graduations on the syringes, and confirmed by checking the calibration of the syringe scales via measuring the mass of displaced water on a mass scale₍₃₃₎.

The purpose of the empty syringe phantoms was to provide images with few partial volume effects to evaluate gas distribution homogeneity as well as provide simple-geometry volume measurements to test the basic applicability of the volume estimation algorithm. Plunger positions, trapping times and image resolutions were varied to alter volume, pressure, the relative number of partially filled voxels and the SNR.

3.4.1.1 Simulations

In order to evaluate the volume-estimation algorithm described in Section 3.3 subject to the assumptions made, the interior of the empty syringe phantom described in Section 3.4.1 was modeled as a cylinder subtended by additive and subtractive cones as illustrated in Figure 3.6 (b). The geometry was generated as a binary image at a resolution of $1024 \times 1024 \times 1024$ and down-sampled to the MR imaging resolutions achieved with the 3DVFAGE sequence. The Matlab “rand” pseudo-random number generator was used to shift the high-resolution image with respect to the down-sampling dimensions to simulate the random placement of a phantom near the FOV. The true volume of the image was calculated as the sum of the voxel values in the image multiplied by the volume of the field of view and divided by the number of voxels in the original binary image. The indices for zero-signal, full-signal voxels, and non-zero voxels were stored to automate volume estimation following noise addition.

Rice distributed noise was then added to the image, I_0 , to produce I_N :

$$I_{Ni} = \sqrt{(I_{0i} \cdot \sin(2\pi U_i) SNR + N_{1i})^2 + (I_{0i} \cdot \cos(2\pi U_i) SNR + N_{2i})^2} \quad 3.13$$

where U is a uniform random matrix generated using the Matlab₍₂₉₎ “rand” function, N_1 and N_2 are Gaussian distributed matrices with mean 0 and standard deviation 1, generated using the Matlab₍₂₉₎ “randn” function, and i denotes the i^{th} element of each matrix.

3.4.2 Bead Phantoms

The bead phantom was constructed to test the volume estimation procedure on images with large numbers of partially filled voxels. Precision ground cellulose acetate balls₍₃₂₎ with a diameter of 5 mm were counted and placed within a 60 mL plastic syringe₍₃₀₎. The geometrical volume of the phantom was calculated using the graduated scale of the

syringe₍₃₀₎ and subtracting the volume of the beads₍₃₀₎ placed within the phantom. The plunger position was pinned similarly to the static volume phantom, and images were collected for a variety of plunger positions with varying numbers of beads₍₃₀₎ within the phantom.

In Figure 3.6 (c), the phantom is shown with a void above the settled beads to ensure “full” voxels would be present in the resulting images. The alternative configuration without such a void was used to test the performance of the algorithm in the absence of well defined “full” voxels, but with a known volume, as well as identify resolution requirements for small geometries.

3.4.3 Excised and Desiccated Rat Lung

Following the procedure outlined in Blumler *et al* [76] lungs were excised from a sacrificed rat, fixed in an inflated state, desiccated and sealed with epoxy. The fixed lungs then had a constant, though unknown, volume. An upper limit of the volume was later derived by measuring the displaced volume of the phantom in water: 13.30 ± 0.01 mL. It can be seen in Figure 3.6 (d) however, that a substantial amount of the phantom volume is the epoxy sealant. The phantom was then weighed to be 7.659 ± 0.002 g. It was estimated that 2 ± 1 g of the phantom mass was composed of lung tissue, and that the density of the epoxy sealant was 1 g/mL. An upper limit volume estimate was therefore derived as 7.6 ± 1.0 mL, whereby lung tissue was assumed to have a negligible effect on the lung volume.

Following evacuation procedures the lungs were filled with hyperpolarized ^{129}Xe gas and imaged. In vitro lung images were used to observe the signal magnitude distribution of lung images as well as test the effect of changing resolutions and polarizations on the lung image quality without the complexity of *in vivo* procedures. Furthermore, comparisons between MR upper-limit volumes and the geometrically determined upper limit volume were made.

Figure 3.6 *In vitro* subject volumes: (a) an illustration of the empty syringe phantom, (b) the simulated empty syringe phantom geometry – plunger position, plunger depth and diameter could be arbitrarily defined, (c) an illustration of the bead phantom, and (d) optical images of the desiccated lung phantom.

3.5 *In vivo* Experiments

A set of *in vivo* experiments were performed to assess the possibilities of detecting volume changes associated with lung inflammation in rats instilled with *Stachybotrys chartarum* fungal spores. Six 300 g Wistar rats were anesthetised using a zylazene/ketamine mixture [77] and instilled with 110 spores/g wt animal via intra-tracheal instillation at St. Mary's University, Nova Scotia, and flown to the CMRF. MR data were collected from the spore-instilled rats 48-60 hours after instillation. 3 control rats, with no instilled spores were also imaged for comparison.

The CMRF *in vivo* experimental setup is illustrated in Figure 3.9. At the CMRF, rats were anesthetized using isoflurane₍₃₄₎. Tracheotomies were performed, and rats were mechanically ventilated₍₂₄₎. Breathing was monitored using a pressure sensor₍₂₅₎ secured to the rats' thorax. When not in the magnet₍₁₈₎, rat heart rates and PO₂ levels were monitored using an infrared spectrometer₍₃₆₎. A pressure release valve_(V-14), set to 10 kPa above the ambient pressure, was placed between the rats and V-13. Rats were then placed in the magnet₍₁₈₎ bore on a customized platform₍₃₅₎ with their lungs positioned near the isocenter of the magnet₍₁₈₎. Hyperpolarized ¹²⁹Xe was collected in the Xe trap₍₁₄₎ and thawed. When the lungs were in their most deflated position V-13 was switched to the hyperpolarized ¹²⁹Xe flow and V-12 was opened to administer a bolus of gas. The 3DVFAGE sequence was then run while the rat lungs were held in an inflated position by the pressure of the Xe. Following the imaging sequence, rats were switched back to the ventilator₍₂₄₎. A range of 1 to 7 images were acquired per rat.

Following the imaging procedure the rats were sacrificed. Their lungs were excised and fixed with formalin₍₃₈₎, and returned to St. Mary's University for sectioning and histological estimation of spore inflammation. The volume of formalin₍₃₈₎ required to fill the lungs was also recorded as an estimate of lung volume. Upon arrival at St. Mary's the grade of inflammation was determined in a single lobe from each lung as shown in Figure 3.7:

Figure 3.7 *Stachybotrys chartarum* -instilled rat lung inflammation histology. Images courtesy of Thomas Rand at St. Mary's University, Nova Scotia. (a) No inflammation, (b) Grade 1, (c) Grade 2, (d) Grade 3, and (e) Grades 4 and 5, with grades defined as following:

Grade 0: No inflammation

Grade 1: Low inflammation; modestly thickened alveolar walls at sites of spore impaction with concurrent reduction of alveolar space equal to or less than 10% with 10 fields of view at 250× magnifications.

Grade 2: Inflammation; focal granulomas surrounding impacted spores with concurrent reduction of alveolar space from 10 to 25% within 10 fields of view at 250× magnifications.

Grade 3: Inflammation; confluent granulomas surrounding impacted spores resulting in alveolar space reduction from 25 to 50% within 10 fields of view at 250× magnifications.

Grade 4: Inflammation; confluent granulomas surrounding impacted spores resulting in alveolar space reduction from 50 to 75% within 10 fields of view at 250× magnifications.

Grade 5: Inflammation; confluent granulomas surrounding impacted spores resulting in alveolar space reduction greater than 75% within 10 fields of view at 250× magnifications

Figure 3.8 Schematic of the ¹²⁹Xe polarization and imaging apparatus.

4 Results, Analysis and Discussion

This chapter reports the experimental data acquired using the methods and procedures outlined in the preceding chapter, and the analysis thereof. Section 4.1 contains MR data and simulated data from the empty syringe phantom configurations. Section 4.2 describes the results from bead phantom configurations. Section 4.3 reports data from the desiccated lung phantom, and Section 4.4 reports the in vivo results of both the animal from which the desiccated lung phantom was excised and the *stachybotrys chatarum* spore-instilled rats.

4.1 Empty Syringe

A total of 46 images of the empty syringe phantom suitable for analysis were acquired in a FOV of $10\text{ cm} \times 10\text{ cm} \times 10\text{ cm}$. Resolutions ranged from $64 \times 16 \times 16$ to $256 \times 32 \times 32$, volumes ranged from 3 mL to 40 mL, and full-voxel SNR values ranged from 2.4 to 52. The empty syringe phantom provided a cylindrical geometry that was simple to simulate compared with other phantoms, and thus simulated images were compared to MR data to test the assumptions that were made in the volume estimation algorithm. The T_1 for the empty syringe phantom is estimated in Section 4.1.1. In Section 4.1.2 the assumption of Rice-distributed data is tested for both full and empty signal distributions. In Section 4.1.3 representative images and signal distributions of the phantoms are shown along with simulated images. The selection of optimal low-signal rejecting thresholds is discussed in Section 4.1.4, and the performance of the volume estimation algorithm on

empty syringe phantom data is evaluated in Section 4.1.5. All figures are located at the end of this section.

4.1.1 T_1 Estimation

T_1 and flip angle scaling parameters were estimated using the procedure outlined in Section 3.2.1 for the empty syringe phantom set to 12 mL. Gas was trapped for 300 ± 10 s and the phantom and trap were evacuated of residual gas to approximately 5 kPa. Xe was then thawed into the phantom and sealed by closing V-12 to the phantom. Sequences of 32 RF pulses separated by a repetition time of 30 s were used with flip angle settings of 5° , 10° and 15° . The resulting time series of spectra were integrated and plotted as a function of time. Equation 3.3 was fit to the data for M_0 and T_1 with input values of TR and α . Figure 4.1 shows the three resulting series.

The average and standard deviation of all points on the boundaries of the intersection of the three series were taken to give $T_1 = 939 \pm 11$ s and a flip angle calibration value of $106.9\% \pm 1.1\%$ (uncertainties are one standard deviation). The expected angular and magnitude variations due to the approximate VFA sequence given in equations 3.7 and 3.5 respectively for $T_1 = 939 \pm 11$ s are shown in Table 4.1.

Table 4.1 Average angular and absolute signal deviation from uniform magnitude mapping as a function of the number of pulses and repetition time, for the approximate VFA sequence for $T_1 = 939 \pm 11$ s.

Number of pulses	TR [ms]	Average angular deviation [%]	Average absolute signal deviation [%]
16×16	16	0.109 ± 0.002	0.109 ± 0.002
32×32	16	0.438 ± 0.005	0.436 ± 0.005
32×32	20	0.548 ± 0.007	0.545 ± 0.007

Discussion

While the T_1 of the 12 mL configuration of the empty syringe phantom was estimated as 939 ± 11 s, it is unknown for other configurations of the phantom and is assumed similar. The slopes of the series in Figure 4.1 show that T_1 estimation using the sequence described by equation 3.3 becomes increasingly less sensitive to flip angle variation for small flip angles. Accordingly, other estimates of T_1 were derived using 5° and 10° flip angles, and power settings were reduced to 93.5% of the those used previously to appropriately calibrate flip angles with an uncertainty of 1.4%. With an uncertainty of 1.4% on flip angle calibrations and the limitations of MR operating console, it is expected that the average 0.11% to 0.55% fluctuation in the flip angles cannot be resolved by the system, making the sequence used a reasonable approximation not requiring correction. Furthermore, image spatial signal distributions were not observably inhomogeneous in the phase-encode directions, suggesting that the prescribed VFA sequence was appropriate.

4.1.2 Confirmation of Rice Statistics

The design of the volume estimation procedure specified in Section 3.3 includes features to account for the nonlinearities of Rice-distributed data at low SNR, using maximum likelihood estimators based on the Rice PDF (equation 2.37, re-written below).

$$p_{Rice}(M|A, \sigma) = \frac{M}{\sigma^2} e^{\left(-\frac{A^2+M^2}{2\sigma^2}\right)} I_0\left(\frac{AM}{\sigma^2}\right) U(x) \quad 2.37$$

This assumption was tested on $256 \times 32 \times 32$ and $64 \times 16 \times 16$ images of the empty syringe phantom set to 9 mL with SNRs of about 7 and 26 respectively. The images were not zero-filled such that only true voxel frequencies were measured.

Figure 4.2 shows the average integrated signal along both phase-encode dimensions (i.e., a projection along y and z) of the images. For the $256 \times 32 \times 32$ image (Figure 4.2 (a))

it can be seen that background magnitude has a symmetric profile that increases at the edge of the FOV and is homogeneous in the region of the object imaged. The cropping criteria for both the zero-signal and full-signal distributions of the $256 \times 32 \times 32$ image are shown in Figure 4.3. Note that higher intensity regions near the edge of the image in the frequency encode dimension (up on the page in Figure 4.3) are avoided to ensure the background distribution reflects that in the region of the object.

4.1.2.1 Zero-signal Distribution

Under the condition of zero-signal, the Rice PDF can be simplified to the Raleigh distribution and is dependent only on σ :

$$p_{Rice}(M|0, \sigma) = \frac{M}{\sigma^2} e^{\left(-\frac{M^2}{2\sigma^2}\right)} U(M) \quad 4.1$$

The magnitudes of the N voxels in the zero-signal distributions of the two images were mapped to bins with width w to give $\bar{M}$ magnitudes containing $\bar{F}$ voxels. A cutoff was made above a SNR of 4, corresponding in each case to 99.9% of the data. The noise distribution parameter was then estimated as:

$$\hat{\sigma}_{ML} = \sqrt{\frac{1}{2 \cdot N} \sum_{i=1}^N F_i M_i^2} \pm \sqrt{\frac{\hat{\sigma}_{ML}^2}{4 \cdot N}} \quad 4.2$$

to give $\hat{\sigma}_{ML256} = 0.6647 \pm 0.0011$, and $\hat{\sigma}_{ML64} = 0.841 \pm 0.006$. Note that MR magnitude units are arbitrary and that these values only apply to the respective images. The vector $\vec{fit}$ was calculated for each histogram, based on the discrete integral form of equation

4.1:

$$fit_i = N \left[U(M_i + w/2) \left(1 - \exp\left(-\frac{(M_i + w/2)^2}{2 \cdot \hat{\sigma}_{ML}^2}\right) \right) - U(M_i - w/2) \left(1 - \exp\left(-\frac{(M_i - w/2)^2}{2 \cdot \hat{\sigma}_{ML}^2}\right) \right) \right] \quad 4.3$$

Figure 4.4 shows the histograms of the data and the resulting fits. A χ^2 (chi-squared) test was performed. The parameter X^2 was derived for the distribution as:

$$X^2 = \sum_{i=1}^N \frac{(F_i - fit_i)^2}{fit_i}, \quad 4.4$$

with the results:

$$\begin{aligned} X_{256}^2 &= 265.73 & dof_{256} &= 325 & CL_{256} &= 99.3\% \\ X_{64}^2 &= 18.71 & dof_{64} &= 29 & CL_{64} &= 92.8\% \end{aligned}$$

Where dof the number of degrees of freedom (i.e., bins in the fit), and CL is the confidence level derived from a χ^2 distribution.

Discussion

Confidence levels greater than 90% for 99.9% of the data in the selected ROIs suggest that modeling zero-signal voxels as Rice-distributed data in homogeneous regions of the background signal is appropriate. With the large number of background voxels in the images and the selected ROIs (i.e., 5000-90000 voxels for the images shown here), uncertainties of $\hat{\sigma}_{ML}$ are found on the order of 0.1% to 0.7%. $\hat{\sigma}_{ML}$ can therefore be estimated from the voxels in similarly chosen ROIs with sufficient precision to be used in further calculations without significant contribution to the error as SNRs are typically less than 30 – producing 3% or greater fluctuations in full-signal values. As all images were acquired using a similar pulse sequence and experimental setup, the validity of estimating $\hat{\sigma}_{ML}$ from the background distribution was extended to the rest of the images.

As thresholds will later be applied to reduce the effects of background voxels in cropped images, also note the shape of the zero-signal Rice distribution. There is a 0.2% probability of background voxels exceeding $M/\sigma = 3.5$, a 0.03% probability above $M/\sigma = 4$, and 0.004% above $M/\sigma = 4.5$.

4.1.2.2 Full-signal Distribution

For the two images, the magnitudes of $N_{256} = 960$ and $N_{64} = 98$ voxels in the selected full-signal ROI were mapped to 20 bins and 16 bins respectively. The values of $\hat{\sigma}_{ML256}$

and $\hat{\sigma}_{ML64}$ found in the previous section was used, and a single parameter fit was performed for $\hat{A}_{ML}$ by solving:

$$\hat{A}_{ML} = \frac{1}{N} \sum_{i=1}^N F_i M_i \frac{I_1\left(\frac{\hat{A}_{ML} M_i}{\hat{\sigma}_{ML}^2}\right)}{I_0\left(\frac{\hat{A}_{ML} M_i}{\hat{\sigma}_{ML}^2}\right)} \quad 2.44$$

numerically with the Excel₍₄₁₎ “Goal Seek” function, giving $\hat{A}_{ML256} = 4.719$, and $\hat{A}_{ML64} = 22.28$. As there is no deterministic equation for the integral of the Rice PDF, the histogram based approximation was used to construct the resulting $\overline{fit}$:

$$fit_i = wN \frac{M_i}{\hat{\sigma}_{ML}^2} \exp\left(-\frac{\hat{A}_{ML}^2 + M_i^2}{2\hat{\sigma}_{ML}^2}\right) I_0\left(\frac{\hat{A}_{ML} M_i}{\hat{\sigma}_{ML}^2}\right). \quad 4.5$$

χ^2 tests were then performed by applying equation 4.4:

$$\begin{aligned} X_{256R}^2 &= 33.8 & dof_{256R} &= 19 & CL_{256R} &= 1.9\% \\ X_{64R}^2 &= 5.4 \times 10^{11} & dof_{64R} &= 15 & CL_{64R} &= 0\% \end{aligned}$$

It is clear that the 1-parameter Rician fits failed. A 2-parameter Gaussian fit was applied to the data using the mean and standard deviation of the data to parameterize the fit, giving:

$$\begin{aligned} A_{G256} &= 4.828 & A_{G64} &= 22.28 \\ \sigma_{G256} &= 0.716 & \sigma_{G64} &= 2.30 \end{aligned}$$

and the resulting χ^2 tests:

$$\begin{aligned} X_{256G}^2 &= 13.0 & dof_{256G} &= 18 & CL_{256G} &= 79\% \\ X_{64G}^2 &= 9.1 & dof_{64G} &= 14 & CL_{64G} &= 83\% \end{aligned}$$

Figure 4.5 (a) and (b) show both fits for the $256 \times 32 \times 32$ and $64 \times 16 \times 16$ images respectively. Note that the plots have been normalized with respect to $\hat{\sigma}_{ML}$.

Discussion

Considering Figure 4.5, the source of discrepancy for the Rician fits is not the signal parameter $\hat{A}_{ML}$ obtained, but rather that the variance in magnitude of the data for both cases is significantly larger than the $\hat{\sigma}_{ML}$ parameters derived in Section 4.1.2.1. While in both cases the Gaussian fit performs better, it should be noted that this is fitted with an extra degree of freedom, and that at above a SNR of 7, a 2 parameter Rician fit yields nearly identical results. The relatively poor fit for full-signal voxels when compared with the good fit for zero-signal voxels suggests that the selected full-signal regions are not homogenous – particularly in the case of the $64 \times 16 \times 16$ image. This may be attributed to:

- incorrect voxel selection by the operator
- the gas distribution having varying density within the volume (i.e., pressure gradients not eliminated by diffusion in the imaging time scales, sedimentation)
- systematic artefacts due to the MR procedures and hardware used.
- Regional T_1/T_2 differences, the latter dependent on static field homogeneity for a gradient echo sequence

If one assumes that there is no significant distribution of “hyper-filled” voxels (i.e., those voxels that have signal magnitudes significantly greater than those selected in the full voxel distribution), the incorrect selection of full-signal voxels would involve the selection of partially-filled voxels, and would result in systematic overestimation of voxel intensities. If deviation from the predicted distribution is due to inhomogeneity of the signal, then the appropriate sampling across the true full-signal voxel distribution will average the inhomogeneities in the volume and reduce the sensitivity of the algorithm to systematic or geometric variability.

4.1.3 Images

Three images representative of the range of resolution, SNR and volume, and the corresponding cropped-image signal distributions of the empty syringe phantoms, are presented in Figure 4.6, Figure 4.7, and Figure 4.8.

Discussion

Figure 4.6 shows data from the 20 mL phantom set at 3.0 ± 0.1 mL and imaged at $64 \times 16 \times 16$, resulting in a full-signal SNR of 40 ± 5 . This represents the case whereby there are few voxels describing the object, but SNR is relatively high. As volumes shrink with respect to voxel size, the ability to specify a full voxel diminishes and there are insufficient statistics to adequately model the object with a single image. (c) shows that there is a wide range of partially filled voxel magnitudes in the image. The continuous range of partial-signal magnitudes extends into the zero-signal voxel distribution. Therefore when thresholds are applied to reject zero-signal voxels, they will also be rejecting partial-signal voxels.

Figure 4.7 shows data from the 20 mL phantom set at 9.0 ± 0.1 mL and imaged at $64 \times 32 \times 32$, resulting in a full-signal SNR of 10.8 ± 1.5 . The full-signal distribution is seen to agree well with the simulated result. Note in (c) that there is a higher frequency of background voxels than the simulations predict. This is due to operator-defined cropping that is more conservative towards rejecting voxels than the idealized simulations (i.e., the operator defined FOV is larger than simulated ones). As the voxel dimensions are small with respect to the volume being imaged, a large proportion of the signal distribution corresponds to full-signal voxels. While the continuous distribution of partial-signal voxels defining the boundaries is still present, it contains relatively less of the total signal in the image than in Figure 4.6.

Figure 4.8 shows data from the 60 mL phantom set to 32 ± 1 mL and imaged at $64 \times 32 \times 32$, resulting in a SNR of 2.9 ± 1.2 . In (a) ii) and iv) the catheter is visible as a hyper-intense horizontal line. The projection of the catheter is also visible as a bright spot in the middle of the phantom in (a) i). In (a) iii) a small DC artefact is visible. The artefact does not lie within the imaged object however, and was cropped out of the image prior to binning the signal distribution. Figure 4.8 (c) shows the signal distribution of the image. Above an SNR of about 6, the higher intensity voxels are expected to correspond to the catheter distribution, and may be rejected via an upper threshold. At low SNR the full and zero-signal distributions become merged. As there are reasonable statistics to describe both the full and zero-signal distributions due to the volume of the object, it is expected that a threshold can be picked to on-average balance “false-full” voxels with the “false-empty” voxels rejected, resulting in a reasonable estimate of volume. In this simulation a fixed SNR of 3 was used as opposed to a SNR per image randomly generated using Gaussian statistics about the estimated SNR, as it provided visibly better agreement with the imaged distribution.

4.1.4 Threshold Optimization

Thresholds were applied to images to eliminate the signal contributions of low-signal voxels to volume estimation. During the analysis of images with known volumes thresholds were optimized such that the known volume was reproduced to an average precision of $0.07\% \pm 0.21\%$. Simulations were run to compare these ideal MR thresholds for each individual data set to the expected distribution resulting from ideal images degraded by Rice-distributed noise.

4.1.4.1 Simulations

The frequency distribution of zero-signal voxels in all images is expected to be the zero-signal Rice distribution. However estimator bias and the frequency of low-signal voxels subject to the geometry of the object being imaged, and the ability to reject background voxels with cropping or segmentation also have an effect on the ideal threshold values. In simulated images of the empty syringe phantom, volume, resolution and the SNR were varied; the results are shown in Figure 4.9.

Discussion

It can be seen in both Figure 4.9 (a) and (b), that the optimal threshold has a strong dependence on both the SNR and resolution. At low SNRs, the distributions of full and empty voxels are expected to merge, requiring that thresholds accept more false-positive zero-signal voxels to account for the false-negative voxels rejected at the lower end of the distribution. As the SNR increases the dependence is seen to approach a plateau with an average threshold SNR of about 2.3, rejecting 93% of the zero-signal voxels. Increased resolution has the effect of increasing the number of full-signal voxels with respect to the number of partial-signal voxels describing the surface of the object, improving statistics and hence parameter estimation.

4.1.4.2 MR Data

Figure 4.10 shows the optimal thresholds derived from the MR data, with separate series for each resolution, and the expected optimal thresholds from simulated images. A linear fit of all the MR thresholds with respect to SNR has the form:

$$T_{opt} = (0.31 \pm 0.02)SNR + (1.1 \pm 0.4)$$

with the goodness-of-fit parameter $R^2=0.87$. Figure 4.11 shows the distribution of operator-selected thresholds with respect to the optimal thresholds for each image and all resolutions. The mean of the distribution is 95% with a standard deviation of 25%.

Discussion

It can be seen in Figure 4.10 that the predicted thresholds from simulations do not adequately describe the optimal thresholds for the MR images. This disagreement indicates that the MR imaging procedure introduces systematic artefacts that violate the perfect linear mapping of signal used in the simulations.

However, while the optimized thresholds disagree with simulated results, it is encouraging that they exist. This indicates that precise estimates of the imaged volume may be found with empirically derived thresholds until simulations are made that yield improved estimates for expected threshold values. Figure 4.11 indicates that an operator with minimal *a priori* knowledge of appropriate thresholds criteria can set values distributed about the optimal thresholds with an average and standard deviation of 95% and 25% respectively. If the outlier at 190% is ignored the mean and standard deviation are 93% and 21% respectively. The operator-defined thresholds presented are not influenced by optimal threshold values as procedurally they were chosen prior to optimal threshold estimation. If the linear fit in Figure 4.10 proves to adequately describe optimal threshold selection criteria for other phantom geometries, this may yield a superior threshold selection criterion, not requiring operator input.

4.1.5 Accuracy of MR Volume Estimation

This Section reports the performance of the algorithm for estimating the set volumes of the empty syringe phantom. Section 4.1.5.1 presents simulated results to demonstrate the fundamental limits of the ML estimator technique with “perfect” image segmentation

(i.e., no zero-signal voxels in the image are analyzed, thus no thresholds are applied). Section 4.1.5.2 presents the volumes derived from the MR data.

4.1.5.1 Predicted Performance of the ML Estimator

The maximum-likelihood estimator for the Rice distribution is biased. As the distribution of voxel magnitudes is expected to contain a continuum of SNRs ranging from zero to the full-signal SNR the bias is dependent on the geometry, the resolution, and the SNR. Groups of 80 simulated images were generated. Prior to noise addition, the images were segmented to reject all zero-signal voxels.

Figure 4.12 (a) shows the dependence for 3 volumes imaged at $64 \times 16 \times 16$. The smallest volume, 4.8 mL, has the highest dependence on SNR, as there are relatively more partial-signal voxels and fewer statistics on full-signal voxels than for the 14 mL and 30 mL volumes. In all cases, the maximum-likelihood estimator slightly over-estimates volume.

Figure 4.12 (b) shows the dependence of simulated images at different resolutions for varying volumes while SNR is held constant. The volume estimation accuracy is seen to improve with increasing resolution at each SNR, and accuracy is again seen to increase for larger volumes.

Discussion

As the size of the volume under investigation, resolution and the SNR increase, it is expected that bias introduced by Rice-distributed data will be reduced. The algorithm should slightly over-estimate volumes on real data as the ML estimator cannot eliminate the positive bias introduced by the Rice distribution on low-signal voxels, however low-signal rejection via applied thresholds may arbitrarily reduce this bias. Note that increasing the volume and SNR requires higher Xe polarizations, improved instrument

sensitivity, and larger polarized gas volumes. Increasing the resolution requires longer scan times, and will result in decreased SNR for a given bolus of gas.

4.1.5.2 Algorithm Performance on MR data

Figure 4.13 shows the dependence of the MR-estimated volumes on SNR, resolution and phantom geometry. Figure 4.14 shows the distribution of MR-estimated volumes irrespective of resolution and SNR, with a mean of 102.0% and a standard deviation of 5.7%.

Discussion

As seen in Figure 4.13 (a), there is no obvious correlation between SNR and improved accuracy for the MR-estimated volumes. In Figure 4.13 (b) the relative accuracy of volume estimation improves with increasing geometrical volume, though there are too few images at the larger volumes to enable statistical analysis of the variance. The improved performance for larger volumes is expected, as the statistics of and confidence in full-voxel selection is increased by having relatively more data to sample.

The mean accuracy of $102\% \pm 6\%$ describes the expected performance for the volume estimation algorithm on the empty syringe phantom, irrespective of resolution, geometry and the SNR. With larger volumes, higher resolutions, and higher SNRs, it is expected that the accuracy will improve and the variance will diminish.

Figure 4.1 Estimated T_1 as a function of inputted flip angle for power settings for 5, 10 and 15 degrees. The final estimated T_1 and flip angle with their respective errors are indicated by the cross in the middle of the plot.

(a) 256x32x32

(b) 64x16x16

Figure 4.2 Integrated magnitude over phase encode dimensions to show magnitude variation due to the object and background variations in frequency encode dimension for 256x32x32 and 64x16x16 images of the empty syringe phantom with SNRs of 7 and 27 respectively.

Figure 4.3 Illustration of image projections and cropping criteria to test Rice statistics.

Figure 4.4 Voxel magnitude distribution of and 1-parameter Maximum Likelihood fits of the zero-signal Rice distribution to selected regions in the background of 256×32×32 and 64×16×16 images of the empty syringe phantom. The 256×32×32 distribution represents 92160 voxels, and the 64×16×16 distribution represents 5040 voxels.

Figure 4.5 Voxel magnitude distribution, 1-parameter Maximum Likelihood fit of a non-zero-signal Rice distribution, and a 2-parameter Gaussian fit to selected “full-signal” regions of (a) 256×32×32 and (b) 64×16×16 images of the empty syringe phantom.

Figure 4.6 Image (a), simulated image (b), and signal distribution (c) of the empty syringe phantom with a volume of 3.0 ± 0.1 mL imaged at $64 \times 16 \times 16$ with a SNR of 40 ± 5 .

For images, the frequency encode dimension is up on the page. i) and ii) are projections along the first and second phase encode dimensions respectively. iii) and iv) are selected slices along the first and second phase encode dimensions respectively.

The simulated series in the signal distribution corresponds to the average distribution of 400 randomly placed simulated images in the FOV at the specified resolution, with a SNR described by a Gaussian distribution with a mean = 39.51 and $\sigma = 4.58$. The simulated plunger position was similarly described by a Gaussian distribution to vary the defined volume to 3.0 ± 0.1 mL. Simulated distributions with imperfect segmentation and with perfect zero-signal background rejection are shown.

Figure 4.7 Image (a), simulated image (b), and signal distribution (c) of the empty syringe phantom with a volume of 9.0 ± 0.1 mL imaged at $64 \times 32 \times 32$ with a SNR of 10.8 ± 1.5 .

For images, the frequency encode dimension is up on the page. i) and ii) are projections along the first and second phase encode dimensions respectively. iii) and iv) are selected slices along the first and second phase encode dimensions respectively.

The simulated series in the signal distribution corresponds to the average distribution of 400 randomly placed simulated images in the FOV at the specified resolution, with a SNR described by a Gaussian distribution with a mean = 10.76 and $\sigma = 1.43$. The simulated plunger position was similarly described by a Gaussian distribution to vary the defined volume to 9.0 ± 0.1 mL. Simulated distributions with imperfect segmentation and with perfect zero-signal background rejection are shown.

Figure 4.8 Image (a), simulated image (b), and signal distribution (c) of the empty syringe phantom with a volume of 32 ± 1 mL imaged at $64 \times 32 \times 32$ with a SNR of 2.9 ± 1.2 .

For images, the frequency encode dimension is up on the page. i) and ii) are projections along the first and second phase encode dimensions respectively. iii) and iv) are selected slices along the first and second phase encode dimensions respectively.

The simulated series in the signal distribution corresponds to the average distribution of 400 randomly placed simulated images in the FOV at the specified resolution with a SNR of 2.9 and volume of 32 mL. Simulated distributions with imperfect segmentation and with perfect zero-signal background rejection are shown.

(a) Resolution and geometry

(b) All images 64x16x16

Figure 4.9 Dependence of optimal threshold SNRs of simulated images of empty syringe phantoms for varying (a) volume and (b) full-signal SNR. Each point corresponds to the mean of the optimal thresholds from 80 simulated images. Error bars are the standard deviation of the mean.

Figure 4.10 Optimal threshold values for 44 MR images and simulated optimal threshold results at a variety of resolutions for empty syringe phantom configurations. MR data error bars are 1-sigma confidence intervals. Simulation error bars are 5-sigma confidence intervals. A linear fit for all resolutions is shown with $R^2 = 0.86$.

Figure 4.11 Distribution of operator selected thresholds with respect to optimal image thresholds for empty syringe phantom data. The mean and standard deviation of the distribution are 95% and 25% respectively. Excluding the bin at 190%, the mean and standard deviation are 93% and 21% respectively.

(a) SNR dependence, 64x16x16

(b) Geometrical dependence

Figure 4.12 Maximum likelihood estimator bias on perfectly segmented simulated volumes. The dependence on full-signal SNR (a), and on volume geometry (b) for empty syringe phantom configurations are shown. Each point corresponds to the mean and the 1-sigma error on the mean for 80 simulated images.

(a) SNR dependence

(b) Geometrical dependence

Figure 4.13 Accuracy of MR estimated volumes with respect to (a) full-signal SNR and (b) geometrically measured volumes for empty syringe phantom data. Each point corresponds to a single MR image evaluated with an operator-selected threshold. All error bars represent 1-sigma confidence intervals. Horizontal error bars in (b) are not presented as they are small with respect to the scale of the plot.

Figure 4.14 Distribution of MR estimated volumes with respect to geometrical volumes for empty syringe phantom data. The mean and standard deviation of the distribution are 102.0% and 5.7% respectively

4.2 Bead Phantom

A total of 27 images of the bead phantom suitable for analysis were acquired. FOVs of $10\text{ cm} \times 10\text{ cm} \times 10\text{ cm}$, $6\text{ cm} \times 6\text{ cm} \times 6\text{ cm}$, and $5\text{ cm} \times 5\text{ cm} \times 5\text{ cm}$ were used with resolutions ranging from $64 \times 16 \times 16$ to $128 \times 32 \times 32$. Seven different configurations of the phantom were imaged with volumes ranging from 3.2 mL to 13.7 mL, and full-voxel SNR values ranged from 2.5 to 43. The phantoms were used to evaluate algorithm performance in the presence of large numbers of partial-signal voxels.

4.2.1 T_1 Estimation

A variety of configurations of the bead phantom were used. T_1 was estimated for the 10.6 mL configuration of the phantom using the procedure outlined in Section 3.2.1, with

the trapping times and settings described in section 4.1.1. Flip angles of $5.00^\circ \pm 0.07^\circ$ and $10^\circ \pm 0.14^\circ$ were used, and the average T_1 for the two data sets was estimated as 120 ± 9 s. The expected magnitude variations due to the approximate VFA sequence given in equation 3.7 for $T_1 = 120 \pm 9$ s are shown in Table 4.2.

Table 4.2 Average angular and absolute signal deviation from uniform magnitude mapping as a function of the number of pulses and repetition time, for the approximate VFA sequence for $T_1 = 120 \pm 9$ s.

Number of pulses	TR [ms]	Average angular deviation [%]	Average absolute signal deviation [%]
16×16	16	0.86 ± 0.07	0.8535 ± 0.07
32×32	16	3.5 ± 0.3	3.4 ± 0.3
32×32	20	4.476 ± 0.4	4.3 ± 0.4

Discussion

While the T_1 of the 10.6 mL configuration of the bead phantom was estimated as 120 ± 9 s, it is unknown for other configurations and assumed similar. The highest resolution scan performed on the bead phantoms was $128 \times 32 \times 32$ with a TR of 16 ms, and angular calibration is expected to be precise within 1.4%. Signal deviations due to non-ideal pulses could therefore be corrected for higher resolution scans, however corrections were not implemented for this study.

4.2.2 Images

Four images representative of phantom configurations, resolution and SNR, and their corresponding cropped-image signal distributions of the bead phantom configurations are presented in Figure 4.15, Figure 4.16, and Figure 4.17. Images and distributions have been zero-filled for better presentation.

Discussion

In Figure 4.15 a zero-filled image, non-zero filled distribution and zero-filled distribution of a 13.2 mL bead phantom are shown. One $64 \times 16 \times 16$ and one $64 \times 32 \times 32$ image of this phantom were analyzed. This phantom was filled almost completely with beads such that the placement of full-signal voxels within the image was unknown. It can be seen in Figure 4.15 (b) that there is no distinct distribution representing full voxels in the image, making full-signal voxel selection a difficult task. In both cases volume was underestimated by 40% to 50% as ROIs were placed around high intensity voxels likely several sigma above the average full-signal magnitude.

To facilitate analysis, future bead phantoms were partially filled with beads, increasing the amount of the total volume dependent on successful partial volume analysis, but providing a clear *a priori* distribution of full-signal voxels to sample. FOVs were also narrowed to produce smaller voxels to ensure more full-signal voxels were present.

Figure 4.16 shows $64 \times 16 \times 16$ and $64 \times 32 \times 32$ images of a 10.6 mL bead phantom configuration with an obvious full-voxel distribution in a $6 \text{ cm} \times 6 \text{ cm} \times 6 \text{ cm}$ FOV. The force of gravity is aligned with the vertical page dimension and the settling of beads in the bottom of the phantom is clearly visible. In (a) iii) and (b) iii) the outlines of individual beads are visible. In (c) the signal distributions of both images are shown. Both images were acquired on the same day with similar polarizations and Xe trapping times. The increase in resolution at the expense of SNR is seen as the approximately $2.6\times$ reduction of full-signal SNR of the $64 \times 32 \times 32$ image over the $64 \times 16 \times 16$ image.

Figure 4.17 shows a $64 \times 16 \times 16$ image of a 3.7 mL bead phantom configuration in a $6 \text{ cm} \times 6 \text{ cm} \times 6 \text{ cm}$ FOV. A 20 mL syringe was used as opposed to the 60 mL syringes in Figure 4.16. While the volume is smaller with respect to voxel dimensions than in Figure 4.16, there is still a visible distribution of full-signal voxels, making analysis possible.

4.2.3 Threshold Optimization

Thresholds were applied to images to eliminate the signal contributions of low-signal voxels to volume estimation. During the analysis of images with known volumes, operator-selected thresholds were chosen, and subsequently optimal thresholds were estimated such that the known volume was reproduced to an average precision of $0.04\% \pm 0.20\%$. The two images of the 13.2 mL phantom described in the previous section were excluded as threshold optimization was not possible.

Figure 4.18 shows the optimized thresholds as a function of resolution and full-signal SNR. The linear fit and simulation data for the empty syringe phantoms are shown for comparison. Figure 4.19 shows the distribution of operator-selected thresholds with respect to optimal thresholds, with a mean of 92% and a standard deviation of 28%, or 88% and 18% if the outlying data point at 200% is rejected.

Discussion

Inspection of Figure 4.18 suggests two approximately linear trends, though they do not appear correlated with resolution. There are insufficient data for each phantom configuration to resolve configuration-dependent trends. The linear fit and simulations from the empty syringe data are shown to indicate that neither trend agrees well with the bead phantom data. Therefore, each signal distribution imaged will have independent trends, if any, that must be considered, preventing the cross-comparison of subjects. As the simulations performed did not suitably describe the relatively simple geometry of the empty syringe phantom, efforts to describe more complicated geometries such as the bead phantom configurations were abandoned.

Similar to Figure 4.11, Figure 4.19 indicates that the operator-selected thresholds are on-average consistent with the optimal thresholds, though are biased towards being

smaller. Until simulations can better predict trends for specific geometries, it may be concluded that operator-selected thresholds can be used to estimate volume and require less *a priori* knowledge.

4.2.4 Algorithm Performance on MR Data

Using operator-selected thresholds, volume estimates were derived from the bead phantom data. Figure 4.20 shows the relative accuracy of MR-estimated volumes with respect to geometrically estimated volumes for varying (a) SNR and (b) volume (i.e., configuration). The two points with the relative accuracy below 80% correspond to the images described in Figure 4.15 and can likely be attributed to insufficient full signal voxel data. Figure 4.21 shows the average accuracy and variance as a function of SNR.

Discussion

Figure 4.20 (a) shows a general trend towards more accurate volume estimation with increasing SNR. It can also be seen that low SNR data tend to result in over-estimated volumes. In Figure 4.20 (b) no dependence of accuracy on the phantom configuration can be seen for a given resolution. Figure 4.21 indicates that above an SNR of 4.5, MR-estimates are consistent with geometrical estimates of volume to within 4%.

At SNRs greater than 35, volume estimates are seen to increase. As the number of points considered for each data point is decreasing (ultimately to 1 point being “averaged”) the statistical merit of the averaging procedure is diminished. Furthermore, all higher SNR scans were achieved at resolutions of $64 \times 16 \times 16$ with poorer statistics for full volume determination, and an increased likelihood of selecting partial volumes in the full-signal distributions – thereby increasing the estimated volume.

(a) $64 \times 16 \times 16$ image

(b) Signal distribution

Figure 4.15 (a) Zero-filled image and (b) signal distribution of a 13.2 mL bead phantom in a $10\text{cm} \times 10\text{cm} \times 10\text{cm}$ FOV.

(a) i) and ii) are projections along one phase encode dimension and the frequency encode dimension respectively. iii) and iv) are selected slices along the same dimensions as i) and ii) respectively. All projections and slices are aligned such that gravity is down on the page.

(b) The non-zero-filled distribution is in 32 bins, while the zero-filled distribution is of the same image with slightly different cropping criteria, zero-filled to $128 \times 128 \times 128$ prior to Fourier transformation and was binned in 128 bins and scaled vertically to overlay the non-zero-filled data.

(a) $64 \times 16 \times 16$ image

(b) $64 \times 32 \times 32$ image

(c) Signal distributions

Figure 4.16 Zero-filled images with resolutions of (a) $64 \times 16 \times 16$ and (b) $64 \times 32 \times 32$ with SNRs of 13 and 5 respectively, and (c) signal distributions of a 10.6 mL bead phantom in a $6 \text{ cm} \times 6 \text{ cm} \times 6 \text{ cm}$ FOV.

(a,b) i) and ii) are projections along one phase encode dimension and the frequency encode dimension respectively. iii) and iv) are selected slices along the same dimensions as i) and ii) respectively. All projections and slices are aligned such that gravity is down on the page.

(b) Zero-filled distributions for the images shown in (a) and (b) with similar cropping criteria. Frequencies have been re-scaled to better show the shape of the distributions relative to one another. The $64 \times 16 \times 16$ distribution represents 2584 non-zero-filled voxels, and the $64 \times 32 \times 32$ represents 9000 non-zero-filled voxels.

Figure 4.17 (a) Zero-filled image and (b) signal distribution of a 3.7 mL bead phantom in a 6 cm × 6 cm FOV.

(a) i) and ii) are projections along one phase encode dimension and the frequency encode dimension respectively. iii) and iv) are selected slices along the same dimensions as i) and ii) respectively. All projections and slices are aligned such that gravity is down on the page.

(b) The non-zero-filled distribution is in 32 bins, while the zero-filled distribution is of the same image with slightly different cropping criteria, zero-filled to 128×128×128 prior to Fourier transformation and was binned in 128 bins and scaled vertically to overlay the non-zero-filled data.

(a) SNR dependence

Figure 4.18 Optimal threshold values for 27 MR images of bead phantom configurations, simulated optimal threshold results for empty syringe phantom configurations, and the linear fit for empty syringe data shown in Figure 4.10. MR data error bars are 1-sigma confidence intervals. Simulation error bars are 5-sigma confidence intervals.

Figure 4.19 Distribution of operator estimated thresholds with respect to optimal thresholds for bead phantom data. The mean and standard deviation of the distribution are 93% and 28% respectively. Excluding the 200% bin, the mean and standard deviation are 88% and 18% respectively.

(a) SNR dependence

(b) Geometrical dependence

Figure 4.20 Accuracy of MR estimated volumes with respect to geometrically measured volumes for bead phantom data. Each point corresponds to a single MR image. All error bars represent 1-sigma confidence intervals.

Figure 4.21 Average MR-volume estimate relative to geometrical volume estimate as a function of the full-signal SNR for bead phantom data, excluding the 13.2 mL bead phantom configuration described in Figure 4.15. Averages represent all data points with SNRs equal to or greater than the SNR of the point shown. Error bars correspond to the uncertainty on the mean of the average (i.e., the standard deviation divided by the square-root of the number of points contributing to the average)

4.3 Desiccated Lung Phantom

Five images of the desiccated lung phantom suitable for analysis were acquired. All images were acquired with a FOV of $10\text{ cm} \times 10\text{ cm} \times 10\text{ cm}$. One image was acquired at a resolution of $256 \times 32 \times 32$, two images at $128 \times 32 \times 32$, and two images at $128 \times 16 \times 16$.

4.3.1 T_1 Estimation

T_1 was estimated for the desiccated lung phantom using the procedure outlined in Section 3.2.1, with the trapping times and settings described in section 4.1.1. Flip angles of $5.00^\circ \pm 0.07^\circ$ and $10^\circ \pm 0.14^\circ$ were used, and the average T_1 for the two data sets was estimated as 437 ± 6 s. The expected magnitude variations due to the approximate VFA sequence given in equation 3.7 for $T_1 = 437 \pm 6$ s are shown in Table 4.3.

Table 4.3 Average angular and absolute signal deviation from uniform magnitude mapping as a function of the number of pulses and repetition time, for the approximate VFA sequence for $T_1 = 437 \pm 6$ s.

Number of pulses	TR [ms]	Average angular deviation [%]	Average absolute signal deviation [%]
16×16	16	0.235 ± 0.004	0.234 ± 0.004
32×32	16	0.95 ± 0.02	0.94 ± 0.02
32×32	20	1.19 ± 0.02	1.17 ± 0.02

Discussion

With an uncertainty on flip angle calibration of 1.4%, a maximum average deviation of the signal by 1.17% from ideal is not expected to be observable. Therefore, no corrections were applied to the approximate VFA sequence.

4.3.2 Images

Two images of the desiccated lung phantom and their corresponding cropped-image signal distributions are presented in Figure 4.22 and Figure 4.23. The images and distributions have been zero-filled for improved presentation.

Discussion

In Figure 4.22 (a) a $128 \times 32 \times 32$ image is shown. In slices 1_z , 2_z , 3_z , 4_y and 5_y the trachea appears as the most intense voxels in the image. The trachea and upper airways are the largest structures in the lung known *a priori* to be completely filled with gas at the resolutions used. All other ventilated regions of the lung are expected to contain some amount of tissue. The diameter of the trachea is approximately 1.7 mm; the gauge of the catheter used. Voxel dimensions for a $128 \times 32 \times 32$ scan in a $10 \text{ cm} \times 10 \text{ cm} \times 10 \text{ cm}$ FOV are $0.78 \text{ mm} \times 3.1 \text{ mm} \times 3.1 \text{ mm}$. The voxels are therefore not small enough to fit within the trachea and provide a statistically meaningful estimate of the full-signal distribution. In slice 1_z , the cross-section of the trachea is shown and a ringing artefact occurs in the phase-encode dimension; indicative of under-sampling. As the under-sampling is in the phase-encode dimension, the $256 \times 32 \times 32$ image is similarly inadequate for resolving the structure of the trachea. In Figure 4.23 (a) a $128 \times 16 \times 16$ image is shown, and the trachea cannot be resolved.

In both images however, the parenchyma appears to have a homogeneous signal, interrupted by normal thoracic structures such as the heart (Figure 4.22 (a) slices 4_z , 5_z , 6_z , 3_y and 4_y). Therefore, “full” voxels may be sampled within the parenchyma, to provide an upper-limit of lung volume without attempting to correct for partial volume effects due to the tissue in the lung.

In Figure 4.22 (b) and Figure 4.23 (b), signal distributions of the desiccated lung are shown. The distributions bear a closest resemblance to Figure 4.6 (c) (the 3 mL empty syringe phantom imaged at $64 \times 16 \times 16$) whereby a homogeneous volume is under-sampled such that most voxels cross geometrical boundaries to varying degrees and no distinct full distribution can be seen.

4.3.3 Volume Estimation

Upper-limit volumes of the desiccated lung phantom were found by defining full-signal voxels in the lung parenchyma. Uncertainties were computed as:

$$\sigma_{vol} = vol \cdot \frac{\hat{A}_{fML}}{s_{fML}} \quad 4.6$$

where s_{fML} is the standard deviation of the full-signal distribution, representing the full-signal homogeneity, and is typically larger than $\hat{\sigma}_{ML}$. Table 4.4 shows the estimated volumes. The weighted mean MR-estimated upper-limit volume is 6.9 ± 0.9 mL.

Table 4.4 Estimated SNRs and upper-limit volumes for the desiccated lung phantom.

Image	Resolution	SNR	Upper-limit volume [mL]
1	256×32×32	8.7 ± 2.0	6.3 ± 1.5
2	128×32×32	7.0 ± 1.7	6.5 ± 1.6
3	128×32×32	13 ± 3	6.5 ± 1.5
4	128×16×16	13.6 ± 2.7	7.5 ± 1.5
5	128×16×16	18 ± 4	7.5 ± 1.5
Geometry	N/A	N/A	7.6 ± 1.0

Discussion

All the MR upper-limit volumes derived are less than and consistent with the geometrically determined upper-limit volume of 7.6 ± 1.0 mL. Uncertainties are on average 22% of the derived volumes however, indicating that confidence in the precision of the volume estimates is low. It may also be noted that the average volume for the 16×16 phase-encode images is elevated with respect to that of the 32×32 phase-encode images. It is expected that ROIs drawn in the 16×16 phase-encode images encompassed more low-signal voxels than those in the 32×32 phase-encode images with fewer partial-volume effects, resulting in a relatively lower full-signal description, and an elevated estimate of volume.

(a) Image

(b) Signal distribution

Figure 4.22 Zero-filled $128 \times 32 \times 32$ (a) image and (b) signal distribution of the desiccated lung phantom in a $10 \text{ cm} \times 10 \text{ cm} \times 10 \text{ cm}$ FOV. Projections and all slices along both phase-encode dimensions are shown. Projections have been three-dimensionally mapped to the surface of a box. The average SNR in the parenchyma is estimated as 7.0 ± 1.7 .

(a) Image

(b) Signal distribution

Figure 4.23 Zero-filled $128 \times 16 \times 16$ (a) image and (b) signal distribution of the desiccated lung phantom in a $10 \text{ cm} \times 10 \text{ cm} \times 10 \text{ cm}$ FOV. Projections and all slices along both phase-encode dimensions are shown. Projections have been three-dimensionally mapped to the surface of a box. The average SNR in the parenchyma is estimated as 18 ± 4 .

4.4 *In vivo*

All *in vivo* results are derived from $64 \times 16 \times 16$ images with FOVs of $10 \text{ cm} \times 10 \text{ cm} \times 10 \text{ cm}$. SNRs ranged from 4 to 18, with an average SNR of 9 ± 4 . At $64 \times 16 \times 16$ resolutions tracheal structures were not resolved, thus only upper-limit lung volumes were estimated.

4.4.1 T_1 Estimation

T_1 was not estimated for *in vivo* rat experiments. The presence of O_2 in *in vivo* rat lungs is expected to decrease T_1 substantially from *in vitro* conditions such as for the desiccated lung phantom. Previous estimates of *in vivo* T_1 's performed at the CMRF yielded a value of $6.5 \pm 0.6 \text{ s}$ [80], which would be expected to cause an average absolute signal deviation of 22% in a $64 \times 16 \times 16$ approximate VFA sequence with a TR of 16 ms. However, no corrections based on this estimate were applied to the VFA sequence. In general the SNR values from lung images were low in comparison with phantom data as a result of low Xe polarizations, and no distinct trend associated with incorrect VFA implementation was observed.

4.4.2 Desiccated lung

The rat from which the desiccated lung phantom was excised was also imaged five times *in vivo*. Projections of a $64 \times 16 \times 16$ *in vivo* image and the $256 \times 32 \times 32$ excised image along the y-phase encode are shown in Figure 4.24 (a) and (b) respectively. The upper-limit *in vivo* volume was estimated as $19.2 \pm 1.4 \text{ mL}$.

Discussion

The upper-limit estimated *in vivo* volume of 19.2 ± 1.4 mL is 2.78 ± 0.41 times greater than the excised upper-limit MR volume of 6.9 ± 0.9 mL. This is a surprising result, as the lungs were fixed in an inflated state, however the difference in inflation can clearly be seen in Figure 4.24. The discrepancy is therefore real.

The main force distending the lung for the *in vivo* imaging procedures was the pressure of the trapped Xe expanding into the lung. The Xe ventilation pressure was known to be greater than that of normal ventilated breathing, and could be seen on traces of chest movement to potentially double the chest expansion during inhalation. During the fixing procedure for the desiccated lung, gas was pulled through the lung to such that the lung was completely unfolded. The gas flow^{*} was limited *in vivo* to prevent over-expansion and potential destruction of the lung tissues. One may therefore conclude that the pressure used while fixing the lung was less than that of the average Xe bolus administered.

It may also be seen in Figure 4.24 (b) that the desiccated lung has dark spots when compared with the *in vivo* image. While the orientation of the images differs, these dark spots are not found in the *in vivo* image. This may be due to either the under-sampling of the *in vivo* image making such features un-noticeable or obstructive damage to the excised lung during its preparation. Such obstructive features will also reduce the estimated volume.

It is possible that such large inflations of the rat lungs *in vivo* are detrimental to the health of the animals. However, since rats were sacrificed after lung imaging studies due to the irreversible tracheotomies performed, any negative effects following imaging procedures could not be studied.

* As there is no membrane sealing the excised lung during the fixing procedure, gas passes through the lung in a steady state flow that may be controlled by adjusting the pressure drop across the lung.

4.4.3 *Stachybotrys chartarum* Model

The MR upper-limit volume estimates and formalin displacement estimates of lung volume for the *stachybotrys chartarum* spore-instilled rats are shown in Figure 4.25 as a function of inflammation grades determined by histological analysis. The data corresponds to 9 rats in total, with three control rats (grade 0), three grade 4 inflamed rats, and one of each grade 1, grade 2, and grade 3 inflamed rats.

Discussion

The data shown in Figure 4.25 show no convincing trends for either the MR or formalin-fill volume estimates. While the grade-0 inflamed rats have on average a 34% larger MR upper-limit volume than the grade-4 rats, the variances of both distributions make the estimated volumes consistent. As upper-limit MR volumes are presented that include tissue volumes and employ higher maximum pressures (13.3 kPa *in vivo* vs. 2.45 kPa excised), they are expected to exceed formalin-fill volume estimates which one assumes only fill the gas spaces of the lung in time periods measured.

The uncertainties on all MR volume estimates were on the order of 1 to 2 mL and were limited by the SNR and resolution of the acquired images. Furthermore, the statistical spread of the volumes from different rats, despite having similar masses, was on the order of 3 to 4 mL. With only 9 rats and variances on the order of 5% to 20% of derived volumes, the data ensemble does not support further statistical analysis. The required changes in volume from *stachybotrys chartarum*-induced inflammation would have to be on the order of 40% to be detectable.

If *stachybotrys chartarum*-induced inflammation occurs homogeneously on the scale of voxel dimensions throughout the entire lung, a diminished SNR would be observed in inflamed rats while upper-limit volume estimates would remain unchanged. However, gas polarization was not constant for each animal imaged and was not continually

monitored. Furthermore, a large variability in the amount of gas trapped for each image was observed, and is partially responsible for the variance of volume on subsequent images of the same animal. As such, a study of SNR with respect to the grade of inflammation is inappropriate with the current data and gas-handling capabilities.

In order to reduce the effects of biological variability between animals, ideally each rat would be imaged prior to and following spore instillation so that it could act as its own control reference. Unfortunately, the CMRF does not have adequate animal-handling expertise or facilities to entubate or store the animals for extended periods of time. This resulted in the performed tracheotomies, requiring the sacrifice of the animals following the imaging procedures, and preventing their survival for future investigation.

4.4.3.1 Lung Obstruction

One anecdotal result is worth commenting on in light of the previous discussion. Following the tracheotomy of one rat, two subsequent ^{129}Xe -MR images revealed that only one side of the lung was being inflated. The rat was removed from the magnet and it was observed that the catheter was pushed past the first division of the bronchial tree, obstructing the ventilation to half the lung. The catheter was then pulled back such that the entire lung was inflated with Xe, and was imaged. Figure 4.26 shows projections of the lung image in both states. Upper limit MR-estimated volumes were derived from the images. The average upper-limit volumes of the half-ventilated lung and the fully ventilated lung are 7.2 ± 1.1 mL and 11.8 ± 0.7 mL respectively, indicating a difference in volume of 4.6 ± 1.3 mL. In other words, there is a 3.5 sigma ($4.6/1.3$) difference between the two values, indicating with 99.8% confidence that the two estimates differ.

Discussion

As mentioned in the previous section, with uncertainties on the order of 5% to 20%, a change of the upper-limit volume on the order of 40% is required to be detected with confidence. Such is the case here with a 99.8% confidence in the difference of the two volume estimates. This accidental modification to the *in vivo* procedure illustrates the diagnostic potential of ^{129}Xe imaging for identifying obstructive diseases in the lung. It also illustrates the potential of the MR volume estimation procedure to provide a quantitative estimate that differentiates the two states of the lung.

Figure 4.24 (a) $64 \times 16 \times 16$ *in vivo* and (b) $256 \times 32 \times 32$ excised and desiccated lung image projections. The FOV is $10 \text{ cm} \times 10 \text{ cm} \times 10 \text{ cm}$ for both images.

Figure 4.25 Upper-limit MR estimated lung volumes and excised formalin-filled lung volumes for a group of 9 rats instilled with *Stachybotrys chartarum* spores. The grade-0 and grade-4 inflamed points each represent the mean volume estimated from 3 rats, while the other data points each represent data from one rat.

Figure 4.26 (a) Half-lung and (b) full-lung images due to catheter misalignment *in vivo*.

5 Conclusions and Future Work

This chapter presents suggestions for the future development of volume estimation from HNG-MR images and summarizes the findings of the work presented in the thesis. In Section 5.1 improvement in zero-signal rejection criteria is discussed in the context of segmentation and modeling of images. In Section 5.2 methods of increasing the SNR for imaging are discussed, and in Section 5.3 required resolutions are discussed, both being efforts to improve image quality. In Section 5.4 specific recommendations for the improvements and requirements for *in vivo* procedures are presented. Section 5.5 is a summary of the work in this thesis.

5.1 Segmentation and Modeling

In Sections 4.1.4 and 4.2.3, the use of operator-selected thresholds to reject positively-biased zero-signal voxels was examined. Low-signal cut-off thresholds were found necessary due to the relatively coarse cropping criteria used to isolate the object signal-distributions in the imaged FOV. Operator-selected rectangular cropping of the image was employed because it is time consuming and difficult for an operator to contour the outline of an object, particularly when the geometry is unknown. Simulations performed on geometries similar to that of the empty syringe phantom were not successful at predicting optimal thresholds. Empirical trends for empty syringe and bead phantom data were seen to vary with resolution, SNR and phantom geometry.

If the deviations of the MR images from simulated images could be identified systematically and modeled, simulations could be run to yield automated criteria for threshold selection. If more efficient and automated spatial segmentation of the imaged distribution from the background was used, threshold magnitudes could be minimized or eliminated. At the SNRs and resolutions attained in this study, edges are three dimensional and poorly defined, making computational segmentation of the images difficult, though worth further consideration.

5.2 SNR

Simulations and bead phantom results predicted that volume estimation accuracy would improve with higher SNR values, warranting future efforts to increase the image SNR.

The SNR may be increased by:

- increasing the concentration of the HNG in the administered gas mixture
- increasing the pressure of the administered gas mixture
- increasing the voxel size (i.e., decreasing the resolution) in the imaging sequence
- increasing the polarization of the HNG
- increasing the sensitivity of the imaging apparatus (i.e., the receiving coil)
- signal averaging
- increasing the signal per nucleus by switching to ^3He

In phantom studies, the SNR was increased by changing the Xe trapping time, thus trapping more Xe atoms, and administering the Xe at elevated pressures. Further, residual gases were evacuated from both the Xe trap and the phantom to increase the concentration of Xe in the phantom toward 100%.

For *in vivo* studies however, the susceptibility of lung tissues to damage sets the upper-limit for administered Xe pressures and the lower-limit for residual gas evacuation. The anaesthetic effects of Xe permit only single breath-hold studies *in vivo* using 100%

Xe gas, and must be followed by oxygen administration, though lower concentrations may be used for more repetitive and steady-state imaging. As the volume-estimation accuracy is also expected to improve with increased resolution, increasing voxel sizes is not desirable. Therefore the first three options above may be considered fixed for *in vivo* imaging.

Increasing polarization levels for HNG-MR experiments is a separate field of research. Development work continues to optimize polarization cell geometries, laser power and gas concentrations to produce higher and constant polarizations of larger volumes [37]. Similarly, the prevention of polarization losses incurred prior to imaging, such as in the cryogenic trapping procedure, is being studied at the CMRF.

Instrument sensitivity may be improved with more specific coil designs. In general, placing coils closer to the field of view increases the SNR. In addition, with the use of multi-coil systems images may be taken from several regions of the FOV simultaneously, decreasing imaging times. This reduction in imaging times through multi-coil systems may be ideally suited to HNG-MR given the large non-renewable magnetization available, as increased imaging times require both longer breath-holds and are more greatly affected by T_1 relaxation. Currently at the CMRF a single 12 cm coil is used, though most of the rats evaluated could fit into a 5 or 6 cm diameter coil if suitably designed. For further rat studies, it is recommended that a coil be constructed specifically for lung imaging to wrap around the thorax of an anesthetised rat. Human studies are not yet underway, but will require the construction of a ^{129}Xe chest coil.

In order to apply signal averaging there must be confidence that the subject matter is in the same position for each image. For anesthetised rats, this criterion may be met, as the rats are not frequently re-positioned in the magnet. However, significant variability exists in the gas-handling and administration procedures at the CMRF due to the quality of the valves and pressure regulators used. Furthermore, breath-hold imaging of rats inflated with a bolus of gas induces large transients in lung inflation, and is subject to continual motion blur with relaxation of the chest wall. A gated imaging procedure is

therefore recommended, whereby hyperpolarized ^{129}Xe is administered in precisely controlled boluses, concentrations and precisely measured polarizations by a ventilator, and images are acquired with timing specific to the motion of the chest wall. Furthermore, while improved gas handling may enable signal averaging, it is also expected to reduce variability in distension of the lungs for a set of images not signal-averaged, allowing for lower variances between individual images. Cardiac gating, to a similar but lesser degree would also be desirable.

For human procedures, general anaesthetic is not expected to be required or desirable. As such, human imaging will likely require coaching, voluntary inhalation and breath holds of the HNG. Signal averaging on human studies will be limited by the ability of a patient to inhale the same amount of gas repeatedly and image registration due to patient motion.

Switching to ^3He for HNG ventilation imaging will result in a signal gain per nucleus of ~ 2.75 due to the higher gyromagnetic ratio. This choice is particularly warranted for HNG ventilation studies, as higher polarizations are currently achieved for larger volumes of ^3He than ^{129}Xe , and He does not have the anaesthetic properties of Xe, enabling higher concentrations for *in vivo* studies.

5.3 Resolution

It was determined that resolution must be sufficiently high to estimate the magnitude of full-signal voxels in an image. For the *in vivo* studies, it was found that the $64 \times 16 \times 16$ resolution used was inadequate to define ROIs in the upper bronchial structures of the rat lung, known *a priori* to be full. If absolute lung volume is to be estimated for rat studies voxel sizes must be decreased. This can be performed by narrowing the FOV around the object and increasing the resolution by altering pulse sequences.

In a hypothetical case, if the FOV was reduced to 6 cm × 6 cm × 6 cm, in order to resolve the 1.6 mm diameter of the trachea in two dimensions, pixels would have to be smaller than 1.13 mm × 1.13 mm ($\sqrt{\frac{1}{2}1.6^2}$), equating to a two dimensional resolution of 53×53. To include some extra precision one rounds up to 64×64. As the current pulse sequence requires both phase-encode dimensions to be the same resolution, the final dimension (i.e., the frequency encode dimension) could be increased, say to 128, to improve statistics. However, a decrease in voxel size is always accompanied by a decrease in the SNR of the image, as fewer nuclei are contained within each voxel. This would result in a change of the image SNR over the current imaging sequence by:

$$\frac{SNR_{128 \cdot 64 \cdot 64}}{SNR_{64 \cdot 16 \cdot 16}} = \frac{64 \cdot 16 \cdot 16}{128 \cdot 64 \cdot 64} \frac{6^3}{10^3} = 6.8 \times 10^{-3}$$

using geometrical arguments alone. Anticipating a maximum increase in achievable polarizations by an order of magnitude, and a similar increase due to instrument sensitivity gains, the image SNR would be similar to those currently obtained *in vivo*, where uncertainties on the order of 20% were obtained.

The human trachea has a diameter of 1.5 cm to 2.5 cm [78], and is approximately 10 cm long. These dimensions are similar to the diameters of the empty syringe phantoms of 1.85 cm and 2.6 cm. As the voxel sizes used in this work were sufficient to gather full-signal distribution information from the phantoms, they are sufficiently small to gather such information from human lung images. However, while the phantoms have a volume on the order of 3 mL to 40 mL, the human lung has a volume of 3 L, and will require a correspondingly larger FOV and number of voxels. As smaller voxels are not required, the SNR for human lung images is expected to be similar to that of empty syringe phantom images, subject to T_1 relaxation, and increased through increasing the polarization and applying signal averaging.

However, the specific pulse sequence used for this study is not adequate to attain the required voxel sizes in times suited to breath-holds on rats or diseased patients. A reasonable estimate for the required FOV of the thorax to encompass the human lung is

estimated as $40\text{ cm} \times 30\text{ cm} \times 30\text{ cm}$. Maintaining the voxel size of a $64 \times 16 \times 16$ scan in a $10\text{ cm} \times 10\text{ cm} \times 10\text{ cm}$ FOV would require a $256 \times 48 \times 48$ image. Given the pulse sequence TR of 16 ms, while a 3DVFAGE sequence with 16×16 phase encodes would elapse 4.1 s, a similar 48×48 scan would elapse 37 s. Comfortable breath holds for healthy humans are on the order of 20 s, and are shorter for diseased patients. Furthermore, scan times of 37 seconds are expected to be comparable to the T_1 of HNG in the human lung. Therefore, future work into selecting and developing faster three-dimensional pulse sequences for the HNG imaging environment is also required. For example, fast spin echo (FSE), rapid acquisition with re-focussed echoes (RARE), or echo-planar imaging (EPI) may be good candidates for HNG studies [79].

5.4 *In vivo* Procedures

In the study of *stachybotrys chatarum*-instilled rats, uncertainties in MR-estimated upper-limit volumes were found to be about 5%, while uncertainties due to normal biological variability were on the order of 20%. While improvements in the MR-precision may be achieved by increasing SNR, resolution and gas handling ability (described in Section 5.2 with respect to signal averaging), in order to resolve trends associated with upper-limit volume-changes, biological variability must be reduced.

To isolate the effects of an introduced disease, it is recommended that tracheotomies be replaced by intubation procedures, whereby tracheal catheters are inserted through the mouth of an anesthetised rat. Following imaging procedures catheters may be removed from intubated rats and the rats may be revived as opposed to sacrificed. This would allow for rats to be imaged prior to and after the introduction of a diseased state. Moreover, they may be monitored for any detrimental effects of the ^{129}Xe imaging procedures. Changes in upper-limit volume or other MR parameters may then be monitored relative to initial states, thereby investigating only the change in the rat lung in the time-interval of the experiment.

For rat procedures, it was also noted that upper-limit volumes are not sensitive to homogeneous obstruction of lung ventilation. If a disease is expected to produce a uniform inflammatory response in the lung, it is recommended that polarization and gas concentrations be more precisely monitored and controlled, such that normalized signal-magnitudes may be compared between images to potentially correlate the image SNR and other signal-magnitude dependent parameters with diseased states.

In addition, the rats studied were anesthetised via inhaled isoflurane. The effects of isoflurane on ^{129}Xe T_1 relaxation are unknown, and therefore for ventilation studies it is also recommended that an injected anaesthesia be used to avoid such interaction.

5.5 Thesis Summary

It was hypothesized that ventilated volumes could be estimated from hyperpolarized ^{129}Xe -MR images based on signal-magnitudes with sufficient precision to be relevant to the diagnosis of obstructive lung diseases. A volume estimator was procedurally outlined, and three phantoms were constructed and imaged in a variety of configurations to test the limitations of the suggested approach. Two *in vivo* studies were performed on rats to identify possible uses and limitations of the proposed estimator.

For the empty syringe and bead phantom data, MR-estimated volumes were found to overestimate corresponding geometrically estimated volumes by $2\% \pm 6\%$ for all images with a SNR greater than 7.5. Simulations and bead phantom data indicated that increases in resolution and SNR are expected to improve measurement accuracy. Low signal cut-off thresholds were used to reduce the signal contribution of positively biased zero-signal voxels however optimal threshold values were not predicted by simulations. Thresholds were therefore operator-chosen, and were found to be on average $95\% \pm 25\%$ of optimal threshold values on empty syringe phantom data, and $88\% \pm 18\%$ on bead phantom data, leading to the 2% overestimation bias with respect to geometrical estimates.

For *in vitro* and *in vivo* images of rat lungs, the imaging resolutions used were insufficient to resolve full-signal voxel distributions. ROIs were sampled in ventilated regions of the parenchyma to estimate upper-limit lung volumes. In a study of rats instilled with *stachybotrys chartarum* spores changes in upper-limit lung volumes were not observed, potentially due to a lack of precision in the volume estimation procedure for the SNRs attained or due to insufficient statistics to resolve effects of the spores from normal biological variances. The uncertainties for upper-limit lung volumes were on the order of 10% to 20% of the estimated volumes due to variability of lung inflation and SNRs of subsequent images. Following the incorrect insertion of a tracheal catheter, the difference between a fully inflated lung and one lobe of the lung was found to be 4.6 ± 1.3 mL, demonstrating that the MR estimator with the current imaging limitations is capable of resolving changes in volume on the order of 40%.

Based on geometrical arguments it is predicted that with current polarization levels it is possible to image human lungs *in vivo* provided suitable volumes of hyperpolarized ^{129}Xe can be produced. The development of special purpose coils and pulse sequences would be expected to lead to estimates of absolute ventilated volumes with a precision of about 6%. Gains in image SNR and resolutions as a result of improved gas polarization methods and pulse-sequence design are expected to increase the precision of the estimator.

In conclusion, with improvement in ^{129}Xe polarizations, instrumentation and pulse sequence design, the precision of the volume estimator proposed in this thesis will also improve, yielding quantitative estimates of ventilated volumes useful in the diagnosis of obstructive diseases.

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Appendix A – Parts and Vendors

#	Functional Name	Model #/Description	Vendor	Location
V-1	gas regulator	regulates T-tank output pressure to 80 psi	Matheson gas products	Irving TX, USA
V-2..7	stem valves	B-4JN	Swagelok	Willoughby OH, USA
V-8	needle valve	B-4MG steel needle replaced with brass at SIMS, coated with Surfamil®	Swagelok SIMS	Willoughby OH, USA Ottawa, ON, Canada
V-9..12	Xe trap valves	3× Model 920 Rev A 1× Model 920 Rev A	Acro Associates	Concord CA, USA
V-13	3-way valve	B1000064 3-way stopcock	B. Braun Medical Inc.	Bethlehem PA, USA
V-14	Pressure release valve	418		
(1)	Xe gas cylinder	[1% Xe, 10% N ₂ , He]	Praxair	Mississauga ON, Canada
(2)	H ₂ O trap	Oxiclear DGP-250-R1	Labclear	Oakland, CA, USA
(3)	flow meter	GR-112-3-A-PV	Fathom Technologies	Round Rock TX, USA
(4)	pressure gauge			
(5)	O ₂ trap	Model 1000 Oxygen trap	Chromatography Research Supplies	Louisville KY, USA
(6) (7)	temperature controller, thermocouple and heating wire	Temperature controller system model: 689-0010	Barnant	Barrington IL, USA
(8) (9)	Rb cell Optical pumping cell	Polarization cell, design from [71]	SIMS	Ottawa, Canada
(10) (11)	795 nm polarizer fiber-optic cable to laser, laser	FAP LX Scientific CW 60 W 795 nm diode laser system	Coherent	Santa Clara, CA, USA
(12)	fiber-optic spectrometer	USB2E2000	Ocean Optics	Dunedin FL, USA
(13)	Rb trap	glass wool	SIMS	Ottawa, Canada
(14)	Xe trap	glass-blown cryogenic gas trap	SIMS	Ottawa, Canada

(15)	liquid nitrogen	melting point = 77 K	Praxair	Mississauga ON, Canada
(18)	1.89 T magnet and gradients	Magnet: 30 cm bore, 1.89 T superconducting Gradients: SGRAD MKIII 305/178/5	Magnex	Abington, England
(19)	transmit/receive coil	12 cm ID "birdcage" design, tuned to 22.175 MHz	Morris Instruments	Ottawa, Canada
(22)	console	SMIS MR5000	Surrey Medical Imaging Systems, now MRRS	Surrey, UK
(23)	SurfaSil®	SurfaSil® siliconizing fluid 42800	Pierce Chemical Laboratories	Rockford IL, USA
(24)	Ventilator	A.D.S. 1000 Veterinary Anesthesia Delivery System	Engler Engineering Corp.	Hialeah, FL, USA
(25)	thoracic expansion sensor	Pressure Monitor BP1-C	World Precision Instruments	Sarasota, FL, USA
(26)	oscilloscope	TDS 360 two-channel digital real time oscilloscope	Tektronix Inc.	Beaverton, OR, USA
(27)	thermal cell	~ 1 cm in diameter glass cell [¹²⁹ Xe]=505 kPa, [O ₂]=152 kPa	SIMS	Ottawa, Canada
(28)	1 cm coil	1 cm solenoidal NMR coil	CMRF	Ottawa, ON
(29)	Matlab	Matlab 6.5 Release 13 with signal processing, image processing and optimization toolboxes	MathWorks	Natick, MA, USA
(30)	syringe	1, 3, 20, and 60 mL latex free plastic syringes	Becton Dickinson & Co.	Franklin Lakes, NJ, USA
(31)	catheter	SURFLO® I.V. Catheter 16 gauge 1.7mm×2"	Terumo Medical Corporation	Somerset, NJ, USA
(32)	beads	5 mm in diameter cellulose acetate spheres	Preciball division, Saluc	Callenelle, Belgium
(33)	electronic mass balance	V1-1mg	Acculab	Newton, PA, USA
(34)	isofluorane vaporizer	T3150	Benson medical industries	Markham, Ontario, Canada
(35)	isofluorane	1-chloro-2,2,2-trifluoroethyl difluoromethyl ether	Bimedia-MTC Animal Health Inc.	Cambridge ON, Canada
(36)	rat bed	A customized platform for rat imaging that fits in (18) and (19)	CMRF	Ottawa, Canada
(37)	heart rate / PO ₂ monitor	8500V Pulse Oximeter	Nonin	Plymouth MN, USA

(38)	Formalin	10% neutral buffered	Sigma Diagnostics	St. Louis MO, USA
(39)	vacuum meter	VM 1500	Ebro	West Germany
(40)	Maple®	Maple® 8 Student Edition	Waterloo Maple Inc.	Waterloo, ON, Canada
(41)	Excel	Microsoft Excel 2002 10.2614.2625	Microsoft Corp.	Redmond WA, USA

Appendix B – Maximum Likelihood Estimators for the Rice Distribution

This appendix details the construction of the maximum likelihood (ML) estimators for the Rice distribution. The Rice distribution describes magnitude data constructed from two Gauss-distributed variables. In B.1, a general definition of the ML method is given. In B.2 the Rice distribution is derived. In B.3 the ML method is applied to the Rice distribution. For a more complete derivation for the generalized Rice distribution (i.e., a distribution constructed from more than two Gauss-distributed variables), the reader is referred to [64].

B.1 Parameter Estimation

B.1.1 The Maximum Likelihood Method

Let x be a variable distributed by a probability density function (PDF) determined by a single parameter λ : $p(x|\lambda)$. If N independent observations of x are recorded, the joint PDF of the observations, regarded as a function of the single parameter λ , is called the likelihood function of the sample, and is written:

$$L(x|\lambda) = \prod_{i=1}^N p(x_i|\lambda) \quad \text{B.1}$$

The Maximum Likelihood principle states that the estimator of λ , denoted by $\hat{\lambda}_{ML}$, will maximize $L(x|\lambda)$ within the admissible range of λ :

$$L(x|\hat{\lambda}_{ML}) \geq L(x|\lambda) \quad \text{B.2}$$

Working with large products is often inconvenient, and so, using the properties of the natural logarithm function, often the log-likelihood function is used:

$$\log L(x|\lambda) = \sum_{i=1}^N \log p(x_i|\lambda) \quad \text{B.3}$$

Similar to equation B.2, equation B.3 can also satisfy the ML criterion:

$$\log L(x|\hat{\lambda}_{ML}) \geq \log L(x|\lambda) \quad \text{B.4}$$

B.1.2 The Minimum Variance Bound

For an estimator S with a bias $B(\lambda)$ (i.e., $E[S] = \lambda + B(\lambda)$), it can be shown [81] that the lowest bound on the variance of the estimator is given by $\text{var}(S) \geq \text{MVB}(S)$, where:

$$\text{MVB}(S) = - \frac{\left\{1 + \frac{dB(\lambda)}{d\lambda}\right\}^2}{E\left(\frac{\partial^2 \log L(x|\lambda)}{\partial \lambda^2}\right)} \quad \text{B.5}$$

Equation B.5 is known as the Minimum Variance Bound (MVB) or the Cramér-Rao Lower Bound (CRLB).

In deriving estimates for the variance of ML estimators, it is typical to approximate using the MVB, as it can be shown that if there exists an unbiased estimator having the MVB as its variance, it is the ML estimator [64].

B.2 The Rice Distribution

The raw data from an MR imaging sequence are acquired from the in-phase and quadrature components of the signal and are both described by the Gaussian PDF [64]:

$$p_{\text{Gauss}}(x|\mu, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} \quad \text{B.6}$$

Where $p_{Gauss}(x|\mu, \sigma)$ is the probability of measuring x from a Gaussian distribution with mean, μ , and variance, σ^2 .

If the phase of the data is ϕ and the true magnitude is A , then the joint PDF for the real and imaginary data R and I respectively, is:

$$p(R, I | A, \phi, \sigma) = p_{Gauss}(R | A \cos \phi, \sigma) p_{Gauss}(I | A \sin \phi, \sigma) \quad B.7$$

$$p(R, I | A, \phi, \sigma) = \frac{1}{2\pi\sigma^2} e^{-\frac{(R-A\cos\phi)^2}{2\sigma^2}} e^{-\frac{(I-A\sin\phi)^2}{2\sigma^2}} \quad B.8$$

As the strength of the magnetization is proportional to the magnitude, it is preferable to estimate the magnitude, M , and phase, ϕ . To do so, equation B.8 may be transformed to polar coordinates:

$$R = M \cos \phi \quad B.9$$

$$I = M \sin \phi \quad B.10$$

$$p(M, \phi | A, \phi, \sigma) = \frac{1}{2\pi\sigma^2} e^{-\frac{(M \cos \phi - A \cos \phi)^2}{2\sigma^2}} e^{-\frac{(M \sin \phi - A \sin \phi)^2}{2\sigma^2}} \quad B.11$$

As we only seek the PDF describing M , we must integrate B.11 over the admissible range of ϕ to eliminate the dependence on phase:

$$p(M | A, \phi, \sigma) = \int_0^{2\pi} p(M, \phi | A, \phi, \sigma) d\phi \quad B.12$$

Substituting equation B.11 into equation B.12 and using trigonometric identities, one can derive:

$$p(M | A, \phi, \sigma) = \frac{1}{2\pi\sigma^2} e^{-\frac{M^2 + A^2}{2\sigma^2}} \int_0^{2\pi} e^{-\frac{MA}{\sigma^2} \cos(\theta - \phi)} d\phi \quad B.13$$

Since the integral is over a full cycle of the cosine function, it is equivalent to write:

$$p(M | A, \phi, \sigma) = \frac{1}{2\pi\sigma^2} e^{-\frac{M^2 + A^2}{2\sigma^2}} \int_0^{2\pi} e^{-\frac{MA}{\sigma^2} \cos(\phi)} d\phi \quad B.14$$

The integral over ϕ is of the same form as that of the 0th order modified Bessel function of the first kind:

$$I_0(z) = \frac{1}{2\pi} \int_0^{2\pi} e^{z \cos \phi} d\phi \quad 2.38$$

And so equation B.10 may be written in the form:

$$p_{Rice}(M|A, \sigma) = \frac{M}{\sigma^2} e^{\left(-\frac{A^2+M^2}{2\sigma^2}\right)} I_0\left(\frac{AM}{\sigma^2}\right) U(M) \quad 2.37$$

where $U(M)$ is the unit step Heaviside function:

$$U(M) = \begin{cases} 0 & M < 0 \\ 1 & M \geq 0 \end{cases}, \quad 2.39$$

indicating that equation 2.37 is valid only for non-negative values of M .

Prior to computing estimators for the Rice distribution, it is worthwhile to compute symbolically the first, second and fourth moments of the distribution (evaluated with Maple[®]₍₄₀₎):

$$\begin{aligned} E[M] &= \int_0^{\infty} M \cdot p_{Rice}(M|A, \sigma) dM \\ E[M] &= \sigma \sqrt{\frac{\pi}{2}} e^{-\frac{A^2}{4\sigma^2}} \left[\left(1 + \frac{A^2}{2\sigma^2}\right) I_0\left(\frac{A^2}{4\sigma^2}\right) + \frac{A^2}{2\sigma^2} I_1\left(\frac{A^2}{4\sigma^2}\right) \right] \end{aligned} \quad B.15$$

$$\begin{aligned} E[M^2] &= \int_0^{\infty} M^2 \cdot p_{Rice}(M|A, \sigma) dM \\ E[M^2] &= A^2 + 2\sigma^2 \end{aligned} \quad B.16$$

$$\begin{aligned} E[M^4] &= \int_0^{\infty} M^4 \cdot p_{Rice}(M|A, \sigma) dM \\ E[M^4] &= A^4 + 8A^2\sigma^2 + 8\sigma^4 \end{aligned} \quad B.17$$

B.3 Maximum Likelihood and Conventional Parameter Estimation for MR Data

B.3.1 Estimating the Noise Variance

In order to estimate the magnitude of a group of voxels, it is useful to first estimate the background noise variance σ^2 . If more than one image can be acquired under identical imaging geometries and SNR, there exists a more precise method of estimating the noise variance [64] than the one presented in this Section. However, duplicating a SNR with sufficient precision is typically impractical with hyperpolarized gases due to the need to re-polarize the gas and the variability in gas handling procedures, making the method inapplicable. The method presented here assumes that N background voxels may be selected with the *a priori* knowledge they are described by:

$$p_{\text{Rice}}(M|0, \sigma) = \frac{M}{\sigma^2} e^{\left(-\frac{M^2}{2\sigma^2}\right)} U(M) \quad \text{B.18}$$

To apply the maximum likelihood method, we now construct the joint PDF for all valid M_i :

$$L = \frac{1}{\sigma^{2N}} \prod_{i=1}^N M_i e^{\left(-\frac{M_i^2}{2\sigma^2}\right)} \quad \text{B.19}$$

where $L = L(\{M_i\}|0, \sigma)$. Converting to the log-likelihood function:

$$\log L = -2N \log(\sigma) - \frac{1}{2\sigma^2} \sum_i^N M_i^2 \quad \text{B.20}$$

To maximize equation B.20, we compute:

$$\frac{\partial \log L}{\partial \sigma} = -\frac{2N}{\sigma} + \frac{1}{\sigma^3} \sum_i^N M_i^2 \quad \text{B.21}$$

and

$$\frac{\partial^2 \log L}{\partial \sigma^2} = \frac{2N}{\sigma^2} - \frac{3}{\sigma^4} \sum_i^N M_i^2 \quad \text{B.22}$$

Setting equation B.21 to zero, and re-arranging yields:

$$\hat{\sigma}_{ML} = \sqrt{\frac{1}{2N} \sum_i^N M_i^2} \quad 2.41$$

Equation 2.41 is the maximum likelihood estimator and fulfills equation B.5, since:

$$\left. \frac{\partial^2 \log L}{\partial \sigma^2} \right|_{\sigma=\hat{\sigma}_{ML}} = -8 \frac{N^2}{\sum_i^N M_i^2} \quad B.23$$

is a negative quantity, given N and M_i are all real and positive values.

Due to the square-root operation however, $\hat{\sigma}_{ML}$ is biased, and following a series expansion has approximately the expectation value:

$$E[\hat{\sigma}_{ML}] \approx \sigma \left(1 - \frac{1}{8N} \right) \quad B.24$$

This bias and the bias-corrected estimator are shown Figure B.1 (a) for $N = 0$ to 100.

The variance of $\hat{\sigma}_{ML}$ may be estimated by substituting equations B.23 and B.24 into equation B.6 to compute the MVB:

$$MVB(\hat{\sigma}_{ML}) \approx \frac{\left(1 + \frac{d}{d\sigma} \left(\frac{\sigma}{8N} \right) \right)^2}{E \left[8 \frac{N^2}{\sum_i^N M_i^2} \right]} \quad B.25$$

Substituting equation B.16 (with $A=0$) into equation B.25:

$$MVB(\hat{\sigma}_{ML}) \approx \frac{\sigma^2 \left(1 - \frac{1}{8N} \right)^2}{4N} \quad B.26$$

For $N \gg 1$ we can approximate:

$$\text{var}(\hat{\sigma}_{ML}) \approx \frac{\sigma^2}{4N} \quad B.27$$

A plot of the ML and bias-corrected variances, as well as the approximate MVB given in equation B.26 are shown in Figure B.1 (b).

(a) Estimator bias

(b) Variance

Figure B.1 The ML estimator for σ

(a) The ML estimator, the predicted bias, and the estimator following bias correction. Note that bias is nearly eliminated for by the correction, and that the expectation for the ML estimator given in equation B.24 overestimates the bias.

(b) The approximate MVB, the variance of the ML estimator, and the variance of the bias-corrected estimator. Note that the ML variance is less than variance of the bias-corrected estimator, and that the MBV is less than both estimated variances.

Details: Rice distributed data were generated according to equation 3.12. Expectation values and variances are computed numerically in Matlab⁽²⁹⁾ from 10^5 samples for each N using the “mean” and “std” functions. Error bars range from (a) 0.14 % to 0.02% (left to right), (b) 0.11% to 0.01% and are not shown.

B.3.2 Estimating Magnitude

In magnitude MR images with low SNRs, the Rician PDF deviates significantly from the Gaussian PDF and leads to biased results. A variety of magnitude estimators that exploit the Rician PDF to reduce the bias were examined. The conventional estimator used for most MR [64] and the ML estimator are discussed in this Section. It is assumed that σ^2 is known or has been estimated using the information from the previous section.

B.3.2.1 Conventional Estimator

Most MR image analysis is conducted on images with sufficient SNR that Gauss and Rice-based estimators are virtually indistinguishable. For example, in Figure B.3 it can be seen that above a SNR of 7, Gaussian (i.e., $\bar{M}$) estimators and Rice estimators are both within 1% of an unbiased estimate. Above an SNR of 11 this difference becomes 0.1%. As a result, the magnitude ML estimator derived in the next section is rarely used as it is more demanding to compute. This Section describes the conventional MR estimator used.

For a group of N voxels with true signal A , and magnitudes M_i , the expectation of M^2 can be computed by a spatial average within a region of interest (ROI):

$$\langle M^2 \rangle = \frac{1}{N} \sum_{i=1}^N M_i^2 \quad \text{B.28}$$

Since it can be shown that:

$$E[\langle M^2 \rangle] = E[M^2]. \quad \text{B.29}$$

Substituting equation B.16, an unbiased estimator of A^2 may be constructed as:

$$\hat{A}^2 = \langle M^2 \rangle - 2\sigma^2. \quad \text{B.30}$$

Taking the square root of equation 2.49 gives the conventional estimator of A .

$$\hat{A}_c = \sqrt{\langle M^2 \rangle - 2\sigma^2}. \quad \text{B.31}$$

Note however, that A is known *a priori* to be real valued and non-negative. Both a negative value for A^2 or an imaginary value of A are physically meaningless. Therefore, typically one sets $\hat{A}_c$ to zero should it become imaginary.

B.3.2.2 Maximum Likelihood Estimator

To find the magnitude ML estimator for A , the likelihood function $L(\{M_i\}|A, \sigma)$ is constructed as in B.19, this time without forcing A to zero, for a sample of N independent Rice-distributed magnitudes $\{M_i\}$:

$$L = \prod_{i=1}^N p_{\text{Rice}}(M_i|A) = \prod_{i=1}^N \frac{M_i}{\sigma^2} e^{-\frac{M_i^2 + A^2}{2\sigma^2}} I_0\left(\frac{AM_i}{\sigma^2}\right). \quad \text{B.32}$$

Transforming to the log-likelihood function:

$$\log L = \sum_{i=1}^N \log\left(\frac{M_i}{\sigma^2}\right) - \sum_{i=1}^N \frac{M_i^2 + A^2}{2\sigma^2} + \sum_{i=1}^N \log\left(I_0\left(\frac{AM_i}{\sigma^2}\right)\right). \quad \text{B.33}$$

Those terms not containing A are constants and hence are not required in the maximization procedure. Reducing equation B.33 gives:

$$\log L = \sum_{i=1}^N \log\left(I_0\left(\frac{AM_i}{\sigma^2}\right)\right) - \frac{NA^2}{2\sigma^2} \quad \text{B.34}$$

The ML estimate is the global maximum of $\log L$, so we now compute the derivative of equation B.34 with respect to A :

$$\frac{\partial \log L}{\partial A} = \sum_{i=1}^N \frac{M_i}{\sigma^2} \frac{I_1\left(\frac{AM_i}{\sigma^2}\right)}{I_0\left(\frac{AM_i}{\sigma^2}\right)} - \frac{NA}{\sigma^2}. \quad \text{B.35}$$

Setting the left side of equation B.35 to zero and rearranging yields:

$$\hat{A}_{ML} = \frac{1}{N} \sum_{i=1}^N M_i \frac{I_1\left(\frac{\hat{A}_{ML} M_i}{\sigma^2}\right)}{I_0\left(\frac{\hat{A}_{ML} M_i}{\sigma^2}\right)} \quad \text{2.44}$$

A enters the equation 2.44 in a non-trivial way, and as a result $\hat{A}_{ML}$ cannot be solved for directly, but rather must be evaluated using numerical methods. It can be shown however that the log-likelihood function has only one maximum for positive values of A and M .

The magnitude, conventional estimator, and ML estimator are compared in Figure B.2, Figure B.3, and Figure B.4.

Figure B.2 Expected bias as a function of SNR for the magnitude, ML and conventional estimators for $N = 1$. An unbiased estimator would produce the value 100 regardless of SNR.

Details: For each point 10^7 Rice distributed variables were generated according to equation 3.12. Values were placed in a histogram using the Matlab⁽²⁹⁾ “hist” function with 10^4 bins. Bin values were re-computed according to equations 2.44 and B.27, and histograms were integrated to give the resulting estimates. Uncertainties are indistinguishable from the data, and are not shown.

Figure B.3 Expected bias as a function of SNR for the magnitude, shown as the absolute difference from the unbiased magnitude for magnitude, ML and conventional estimators with $N = 1$. An unbiased estimator would produce the value of 0 regardless of SNR. Data are the same as in Figure B.2. It can be seen the ML estimator converges to the unbiased value more rapidly than the other two estimators, and above an SNR of ~ 0.7 is always less-biased. 68% confidence error bars are indicated for the ML estimator, but are indistinguishable for the other estimators and not shown.

At a SNR of ~ 25 missing points and a discontinuity in the ML data are shown. These phenomena are artefacts of the calculation procedure: Missing points correspond to “perfect” estimates (i.e., 0) subject to the precision of the stored values and cannot appear on the log scale used. Following the discontinuity the ML estimator is seen to overlap the Conventional estimator and the magnitude. This is because the difference between the Conventional estimator (used as an input value in the numerical method) and the ML estimator was sufficiently small to truncate the Matlab₍₂₉₎ “fsolve” function.

Figure B.4 Estimating expectations via re-computing of histogram axes for SNR values of (a) 0, (b) 3 and (c) 5. Computed means and variances for the distributions are given for comparison. Note in (b) and (c) that the ML estimator outperforms the conventional estimator and the mean magnitude. In (a), the correct estimate is 0, which leads to the asymptotic behaviour of Figure B.2 at low SNR (division by zero). Estimated magnitudes are however, finite and are therefore given.

Each histogram was generated from 10^7 Rice-distributed data points, and placed in 100 bins. Data points are shown as opposed to bar graphs to facilitate distinguishing the trends. Note that for the conventional and ML estimator, bin widths increase towards low SNR.