INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA

UMI[®]
800-521-0600

**Magnetic Resonance Imaging
of Hyperpolarized ^{129}Xe :
A Feasibility Study for Biomedical Applications**

by

Pascale Sévigny.
B.Sc. (Université de Sherbrooke) 1996

A thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfillment of
the requirements for the degree of
Master of Science

Department of Physics
Carleton University
Ottawa, Ontario
August 11, 1999

©1999. Pascale Sévigny

National Library
of Canada

Acquisitions and
Bibliographic Services

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale
du Canada

Acquisitions et
services bibliographiques

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-48494-7

Canada

The undersigned recommend to
the Faculty of Graduate Studies and Research
acceptance of the thesis

"Magnetic Resonance Imaging of Hyperpolarized ^{129}Xe :
A Feasibility Study for Biomedical Applications"

submitted by Pascale Sévigny.
B. Sc. (Université de Sherbrooke) 1996
in partial fulfillment of the requirements for
the degree of Master of Science

Chair, Department of Physics

Thesis Supervisor

Carleton University
September 7, 1999

Abstract

Nuclear polarization of ^{129}Xe can be enhanced by 4 to 5 orders of magnitude by optical pumping and spin exchange. The resulting magnetization can be used as a powerful probe for Magnetic Resonance (MR) imaging. Since xenon is highly soluble in body fluids and lipids, hyperpolarized ^{129}Xe can be used as a tracer for MR imaging of tissues and blood flow.

This thesis describes the procedures used, developed and/or optimized for studying both hyperpolarized ^{129}Xe gas and dissolved phases. Gas phase is studied spectroscopically for relaxation time measurements. 2D gas phase imaging results are presented using gradient-echo sequences with different flip angle sequences and phase-encode strategies.

For the purpose of using injection delivery, different biocompatible carriers for hyperpolarized ^{129}Xe are explored. A compartmental model discusses the signal-to-noise ratios achievable for hyperpolarized ^{129}Xe imaging in tissues following intracarotid or intravenous injection. This model shows that intracarotid injection delivery could provide a SNR of 28% the proton SNR, as compared with 2% for continuous inhalation of hyperpolarized ^{129}Xe . The model also shows that the tissue magnetization following intravenous injection delivery is lower due to dilution and excretion of ^{129}Xe at the lungs, resulting in a SNR of 0.0063% the proton SNR, emphasizing the need for novel biocompatible carrier solutions for injection delivery of hyperpolarized ^{129}Xe .

Acknowledgements

I would like to thank my supervisor, Giles Santyr, for his support and the tremendous amount of confidence he has put in me throughout this project. I would like to acknowledge the opportunities he gave me to attend conferences. I would also like to thank all the Carleton Magnetic Resonance Facility (CMRF) people: in particular Julia Wallace for being a friend, for her continuous help and for all the useful discussions about this project. Greg Cron for his availability. Albert Cross for solving my noise problems.

All the people in the collaboration at the Steacie Institute for Molecular Sciences (SIMS) of the National Research Council (NRC) are gratefully acknowledged for the technical and scientific support they provided for the project. In particular, Steve Breeze and Steve Lang, for their patience and help in setting up the gas manifold, for providing pumping cells, and for carrying some frozen xenon for experiments at Carleton.

Teresa Fortin and W. Dale Stevens, from the Life Sciences, are acknowledged for their help with the rat experiments. A special thanks to Dr. Jim Cheetham, for his extraordinary enthusiasm and availability which made the work on liposomes and blood substitutes possible.

Thanks to Tháo, Maria, Valérie and Yvan, for taking me away from my thesis once in a while.

I would like to thank Jean-François Mercier, for his invaluable support and love. All this would not have been possible without him.

Finally, financial assistance from the National Sciences and Engineering Research Council of Canada (NSERC) is gratefully acknowledged.

Contents

Abstract	iii
Acknowledgements	iv
Table of Contents	v
List of Tables	x
List of Figures	xi
List of Abbreviations	xiv
1 Introduction	1
1.1 Historical Background	1
1.1.1 Magnetic Resonance Imaging	1
1.1.2 Hyperpolarized Noble Gases	2
1.2 MR Imaging of Hyperpolarized Noble Gases for Medical Applications	3
1.2.1 Gas Phase Imaging	4
1.2.2 Dissolved Phase Imaging	5
1.3 Thesis Overview	7
2 Theory	8
2.1 The Nuclear Magnetic Resonance Signal	8
2.1.1 The Nuclear Spin	9
The Nuclear Spin in a Magnetic Field	9

	Resonance of the Nuclear Spin	9
2.1.2	Bulk Magnetization	10
	The Bulk Magnetization in a Magnetic Field	11
	The Effect of an RF Pulse	11
	Relaxation	14
	Bloch Equations	16
	Spin Echoes	17
2.1.3	The Look-Locker Convention for Hyperpolarized ^{129}Xe	18
2.1.4	Signal Acquisition	21
2.1.5	Variable Flip Angle (VFA) Sequences	23
2.1.6	NMR Spectroscopy	23
2.2	2D Spin-Warp MR Imaging	25
2.2.1	Slice Selection	25
	Non-ideal Soft RF Pulses	28
2.2.2	Frequency Encoding	28
2.2.3	Phase Encoding	29
	Strategies for Phase-Encoding	30
2.2.4	Gradient Echoes	31
	T_2^* Weighting	31
2.2.5	Spin Echoes	31
2.2.6	3DFT Imaging	32
2.3	Laser Polarization	32
2.3.1	Optical Pumping of Rubidium Atoms	32
2.3.2	Spin Exchange	33
2.3.3	Role of Nitrogen	33
2.3.4	Relaxation	33
2.3.5	^{129}Xe Polarization Achievable	34
3	Materials and Methods	37
3.1	Laser Polarization Setup	37
3.1.1	Factors Affecting the Polarization	39

	Rubidium Polarization	39
	Spin Exchange	41
	Relaxation	41
3.1.2	Experimental Determination of the Polarization	41
3.1.3	Characterization and Optimization of the Laser Polarization	42
	Rubidium Polarization	42
	Rubidium Oxidation	43
	Polarization versus Time of Laser Polarization	43
	Polarization versus Temperature	44
	Polarization versus Pressure	49
3.2	Gas Handling	49
3.2.1	Gas Manifold and Accessories	50
	Pumping System	50
	Calibration of the Gas Manifold	52
3.2.2	Filling the Pumping Cells	52
3.2.3	Dissolving Hyperpolarized ^{129}Xe	53
3.3	NMR Methods and Sequences	58
3.3.1	Flip Angle Calibration	58
3.3.2	Relaxometry	60
	T_1 relaxometry	60
	T_2 relaxometry	60
4	Gas Phase Spectroscopy and Imaging	62
4.1	Flip Angle Calibration	63
4.1.1	Hard Pulses	63
4.1.2	Soft Pulses	63
4.2	Longitudinal Relaxation Time Measurement	64
4.2.1	Effect of Temperature	64
4.2.2	Deceased and <i>in vivo</i> Longitudinal Relaxation Time Measure- ments in Rat Lungs	67
	Deceased Rat Lung Experiment	67

	<i>In vivo</i> Experiment	69
	Oxygen Effect	70
4.3	Transverse Relaxation Time Measurement	71
4.4	Constant versus Variable Flip Angles	72
4.5	2D Imaging	72
4.5.1	CFA versus VFA Sequences	72
4.5.2	Simulations	75
4.5.3	Experimental Results	83
4.6	3D Imaging	84
4.6.1	Multislice Imaging	84
4.6.2	3DFT Imaging	86
4.7	Discussion	88
5	Dissolved Phase Spectroscopy and Imaging	90
5.1	Saline Solution	92
5.1.1	Chemical Shift	92
5.1.2	Flip Angle Calibration	92
5.1.3	T_1 Measurement	94
	Effect of Dissolved Oxygen	95
5.1.4	T_2 Measurement	97
5.2	Liposomes	97
5.2.1	Chemical Shift	98
5.2.2	T_1 Measurement	98
5.3	Perfluorocarbons	101
5.3.1	NMR Spectroscopy	103
5.4	Dissolved Phase Imaging	105
6	Optimizing the Injection Delivery Methods for Hyperpolarized ^{129}Xe:	
	Discussion and Future Work	107
6.1	Applications of Injection Delivery of Hyperpolarized ^{129}Xe	107
6.1.1	Angiography	107

6.1.2	Blood Flow Imaging	108
6.1.3	Tumour Imaging	108
6.1.4	Tissue Characterization	109
6.2	Cost Comparison	109
6.3	A Model of Injection Delivery	109
6.3.1	Intracarotid Injection	111
6.3.2	Intravenous Injection	112
6.4	The Parameters	115
6.5	Expected SNR	116
6.6	The Results	116
6.7	Discussion and Future Work	117
6.7.1	Injection Methods	122
	Intracarotid Injection	122
	Intravenous Injection	123
6.7.2	Injectable Solutions	124
	Saline	124
	Liposomes	125
	PFOB Emulsions	125
	Other Biocompatible Solutions	128
6.8	Thesis Summary	128

Bibliography	130
---------------------	------------

List of Tables

3.1	Saturation values for the polarization and time to reach the saturation for several oven temperatures.	45
3.2	Volumes of the manifold	52
4.1	Deceased rat lung experiments.	68
4.2	Summary of results for the rat lung experiments.	70
4.3	CPMG T_2 results for hyperpolarized ^{129}Xe gas.	71
6.1	Parameters used in the compartmental model.	114

List of Figures

2.1	Precession of the nuclear magnetic dipole $\vec{\mu}$ in the presence of a magnetic field $\vec{B}_0$	10
2.2	Classical view of the bulk magnetization.	12
2.3	Rotating magnetic field in the transverse plane.	12
2.4	Longitudinal and transverse magnetizations prior to and after an RF pulse of flip angle α	14
2.5	T_1 relaxation towards equilibrium.	16
2.6	T_2 relaxation towards equilibrium.	17
2.7	Spin echo	19
2.8	Train of RF pulses.	22
2.9	Free induction decay.	22
2.10	RF pulse of duration τ and its associated frequency distribution . . .	24
2.11	Spin-echo imaging timing sequence.	26
2.12	Gradient-echo imaging timing sequence.	27
2.13	Ideal soft RF pulse and its associated frequency distribution	27
2.14	Soft RF pulse and its associated frequency distribution	28
2.15	Fourier space of an object	35
2.16	3DFT gradient-echo imaging timing sequence.	36
2.17	Energy diagram of a rubidium atom and optical pumping.	36
3.1	Laser-polarization setup	38
3.2	Collisionally-broadened Rb resonance line.	40
3.3	MR signal as a function of the diode temperature.	45

3.4	Decrease of signal due to Rb oxidation as a function of time.	46
3.5	Polarization as a function of laser polarization time	47
3.6	Polarization at saturation as a function of oven temperature.	48
3.7	Time to reach 95% saturation as a function of oven temperature. . . .	48
3.8	Gas manifold.	51
3.9	Pumping cell filling.	54
3.10	Gas transfer process	55
3.11	Pumping system.	57
3.12	Mixing cell.	58
3.13	Mixing process	59
3.14	CPMG pulse sequence	61
4.1	Flip angle calibration for hard pulses.	65
4.2	Flip angle calibration for soft pulses.	65
4.3	T_1 measurement of hyperpolarized ^{129}Xe in the cylindrical gas phantom. .	66
4.4	Effect of cell temperature on T_1 measurement.	66
4.5	Series of ^{129}Xe spectra obtained from rat lungs.	69
4.6	CFA and VFA sequences spectroscopically.	73
4.7	Weighting of k-space with a CFA sequence for several phase-encode strategies	74
4.8	Profiles along the phase-encode direction for CFA sequentially and centrically ordered.	77
4.9	Signal as a function of RF pulse number for mis-calibrated VFA. . . .	78
4.10	Profiles along the phase-encode direction for VFA sequentially and centrically ordered.	79
4.11	Profiles along the phase-encode direction for ZP sequential CFA of 7° and 20% overestimated VFA.	80
4.12	Signal of simulated images with ZP centric.	81
4.13	Uniformity of simulated images with ZP centric.	82
4.14	Experimental images and profiles along the phase-encode direction obtained with centric CFA, sequential CFA and sequential VFA. . . .	83

4.15	Comparison between experimental and simulated images for signal intensity and artifacts.	85
4.16	Slice profile time evolution.	87
5.1	NMR spectra of hyperpolarized ^{129}Xe dissolved in saline.	93
5.2	T_1 measurement of hyperpolarized ^{129}Xe dissolved in saline.	95
5.3	$1/T_{1eff}$ versus $1/TR$ from all measurements of ^{129}Xe dissolved in degassed saline.	96
5.4	T_2 measurement of hyperpolarized ^{129}Xe dissolved in saline.	99
5.5	Schematic of the liposome solution.	99
5.6	NMR spectrum of hyperpolarized ^{129}Xe dissolved in a liposome solution.	100
5.7	Optical micrograph and schematic of the PFOB emulsion.	102
5.8	NMR spectrum of hyperpolarized ^{129}Xe dissolved in a PFOB emulsion.	103
5.9	Series of spectra from hyperpolarized ^{129}Xe dissolved in a PFOB emulsion.	104
6.1	Schematic of the blood circulation.	111
6.2	Time course of the hyperpolarized ^{129}Xe magnetization following an intracarotid injection.	118
6.3	Time course of the hyperpolarized ^{129}Xe magnetization following an intravenous injection.	119
6.4	Maximal tissue concentration as a function of intracarotid injection duration.	120
6.5	Maximal tissue concentration as a function of intravenous injection duration.	121
6.6	Model of ^{129}Xe exchange at the lung capillaries.	127

List of Abbreviations

CFA	Constant flip angles
CPMG	Carr-Purcell-Meiboom-Gill
CSI	Chemical shift imaging
EPI	Echo-planar imaging
FOV	Field of view
GE	Gradient-echo
MR	Magnetic resonance
NMR	Nuclear magnetic resonance
PFC	Perfluorocarbons
PFOB	Perfluorooctyl bromide
RF	Radiofrequency
SE	Spin-echo
SNR	Signal-to-noise ratio
T_1	Longitudinal relaxation time
T_2	Transverse relaxation time
TE	Echo time
TR	Repetition time
VFA	Variable flip angles
ZP	Zero phase encode number

Chapter 1

Introduction

1.1 Historical Background

1.1.1 Magnetic Resonance Imaging

For a long time, understanding the physiology and anatomy of the human body has relied on indirect methods such as external observations or dissections on cadavers. Modern imaging technologies now provide a variety of methods which allow the interior of the human body to be seen and understood, diseases to be detected, and treatments to be planned. Among them, Magnetic Resonance (MR) imaging is a non-invasive and non-ionizing modality, famous for its soft tissue contrast and its invaluable multi-planar cross-sectional views.

MR imaging is an extension of the Nuclear Magnetic Resonance (NMR) methods, developed in 1946 by Bloch[1] and Purcell[2]. NMR is a method for studying a population of nuclear spins in an external magnetic field by means of an excitation with a radiofrequency (RF). The first MR images using linear gradients were reported by Lauterbur in 1973[3]. Since then, the field of MR imaging has shown tremendous growth in the medical community, specifically in finding new applications, quantitating information, diminishing costs, etc.

1.1.2 Hyperpolarized Noble Gases

The vast majority of clinical MR imaging relies on imaging protons of water molecules (i.e. the nuclei of hydrogen atoms of water molecules). Since 60 to 80% of the body weight is composed of water[4], protons yield a high signal. Non-proton imaging suffers from the low density and low sensitivity of the nuclei *in vivo*. For example, ^{23}Na and ^{31}P are the best candidates for non-proton MR imaging. The natural abundance of both isotopes is 100%, however their densities in the human body are typically about 80 mM (1 mM = 1 mmol/liter) and 10 mM respectively, compared to a typical proton density of 10^5 mM in most tissues[5]. Furthermore, their sensitivity is only about 9.25×10^{-2} and 6.63×10^{-2} the proton sensitivity. As a result, non-proton imaging with nuclei occurring naturally in the human body is not practical clinically because of the long acquisition times (hours) required to compensate for low sensitivity and density. However, other nuclei can be introduced in the human body for the purpose of non-proton imaging. Recently, Albert et al. have reported images of excised lungs of a mouse obtained in a time of 600 ms with ^{129}Xe gas of which the nuclear polarization had been increased by five orders of magnitude by methods of optical pumping and spin exchange[6]. This paper preceded a large effort towards developing new applications for MR imaging using hyperpolarized noble gases.

In 1950, increasing the nuclear polarization of noble gases was of interest to nuclear physics. Kastler first described that the ground state of nuclear spins could be populated by optical pumping using circularly polarized light in a magnetic field[7]. In the 1960's, Colegrove et al reported on the polarization of ^3He by metastability exchange[8], while Bouchiat was measuring the nuclear polarization of ^3He obtained by spin exchange from optically pumped rubidium atoms, for the purpose of measuring the rubidium polarization[9].

An understanding of spin exchange and an improvement of the technique's efficiency was provided by Happer's group during the 1980's[10, 11, 12]. With the most recent developments in laser technologies, the technique of optical pumping

and spin exchange has spread to many research laboratories around the world, making hyperpolarized noble gases more available. Research is currently being pursued in the following areas: production of highly polarized noble gases (either continuous flow[13, 14, 15] or batch-mode[16, 17] production), separation of xenon from other gases[17], noble gas delivery [18], and recycling systems[19] as a few examples. This basic research contributes to the development of a wide range of new applications making use of the huge nuclear polarization (5, 10, and up to 70% polarization) now available. Current applications benefit the material sciences[20, 21] and medical imaging. The next section illustrates the challenge and the potential of the applications of hyperpolarized noble gases for medical imaging.

1.2 MR Imaging of Hyperpolarized Noble Gases for Medical Applications

Hyperpolarization of noble gases can provide a huge magnetization which can largely counterbalance the low density of the nuclei. However, hyperpolarization produces a very non-equilibrium state of the system of spins. Therefore, the large magnetization decays to its equilibrium value with a characteristic time called the T_1 relaxation time. This is analogous to the exponential decay of a radioisotope with a given half-life. As a result, the magnetization of the hyperpolarized noble gases is non-renewable (unless they are laser-polarized again) and must then be used in a relatively short time compared to T_1 . It also means that imaging hyperpolarized noble gases is a one-shot procedure.

Among the noble gases, two nuclei have T_1 relaxation times on the order of hours in the gas phase: ^{129}Xe and ^3He . The other noble gas nuclei have relaxation times too short to be useful for medical imaging[22].

1.2.1 Gas Phase Imaging

The first application developed for MR imaging of hyperpolarized noble gases is lung imaging. The lungs are mainly composed of alveoli and house the respiratory passage ways[4]. Respiratory membranes surround the numerous alveoli, resulting in a high surface to volume ratio (S/V) for the lung tissue. The lungs are extremely difficult to image with all modalities. X-ray imaging and Computed Tomography (CT), for example, are based on contrast produced by different tissue densities, and are not sensitive to the lungs. Nuclear medicine lung scintigraphy is possible with radioactive ^{133}Xe and ^{81}Kr , but suffers from low resolution. Also, multi-planar imaging is difficult with lung scintigraphy, and the resulting projection images reduce the contrast. The proton signal for MR imaging in the lung parenchyma, *a priori* very small, is further decreased by susceptibility effects at the tissue-air interfaces. However, rapid imaging on modern scanners allows anatomical information to be obtained from the lungs.

Hyperpolarized ^3He and ^{129}Xe gas are well-suited for providing a high signal from gas spaces. Both gases can be inhaled safely, but xenon must be inhaled in low concentrations (about 30%) since it is an anesthetic at concentrations larger than 70%[23]. By 1997, the feasibility of lung and airways imaging using hyperpolarized noble gases was demonstrated in animal models[6, 24, 25] and human volunteers[26, 27, 28, 29, 30]. Helium has a longer relaxation time than ^{129}Xe , i.e. its magnetization decays more slowly. This characteristic can be advantageous for gas space imaging. However, xenon dissolves in the lung tissue, due to its high lipid solubility, and can provide information from both gas spaces and lung tissue. Dissolved ^{129}Xe spectra in the chest have been demonstrated by several investigators[31, 32, 33].

Since 1998, the field of lung imaging has moved towards clinical applications, for studying lung ventilation[34, 35], lung microscopy[36, 37], and lung diseases such as emphysema[38] and asthma[39]. Furthermore, hyperpolarized ^{129}Xe is foreseen for measuring the surface to volume (S/V) ratio of the lungs[40] and the measurement of the matching of ventilation to blood flow (V_A/Q matching)[41] with spatial discrimination, two important determinants of lung physiology and pathologies.

1.2.2 Dissolved Phase Imaging

Helium solubility in most solvents is very low (it is about 20 times less soluble than xenon). As a result, helium can hardly be used for dissolved phase imaging[42]. Hyperpolarized helium has been encapsulated in microbubbles, where helium is still in the gas phase, and injected intravenously to show the feasibility of vascular imaging and angiography with ^3He [43, 44]. This emphasizes that hyperpolarized ^3He is probably limited to gas phase imaging and some vascular imaging.

The high solubility of xenon in blood and lipids permits its use as a tracer for applications beyond the lungs. Inhaled xenon gas is taken up by the blood circulation at the lung capillaries, and carried to the tissues. The uptake of inhaled hyperpolarized ^{129}Xe in blood and subsequently in tissues has been modeled theoretically and by simulations[45, 42]. Blood T_1 relaxation measurements have been performed[46, 47, 48], as well as T_1 relaxation measurements in tissue homogenates[49], to study the feasibility of *in vivo* dissolved ^{129}Xe imaging. Finally imaging and spectroscopy have been demonstrated in rat brain, blood and kidney tissue[50, 51, 52]. Hyperpolarized ^{129}Xe can also be dissolved in a biocompatible compound and be injected intravenously, as shown *in vivo* in rats[53, 54, 55].

Xenon is known to be a quasi-freely diffusible tracer, since it leaks easily through the capillaries to enter the tissues. For a freely diffusible tracer, the tissue concentration is directly related to the blood flow coming to the tissues, according to the Fick principle. Kety first described how to measure blood flow with this principle[56]. Although it is possible to measure the blood flow with tracers which are not freely diffusible, a freely diffusible tracer simplifies the measurements and increase the accuracy by decreasing the number of assumptions. Therefore, hyperpolarized ^{129}Xe could become a contrast agent of choice for measuring blood flow with MR imaging.

Imaging blood flow *in vivo* is a valuable tool for assessing functional activity, stroke, myocardial infarct and tumour metastasis. The relationship between physiological function and local blood flow in the brain is now well established[57], and methods of measuring the regional cerebral blood flow help distinguish normal and abnormal cerebral activities. Also, knowledge of blood flow is essential to assess any

damage to the brain and plan an adequate therapeutic procedure in the case of a stroke[58], or myocardial infarct[59]. By accurately measuring normal and abnormal perfusion, the diagnosis and management of those patients with ischemic disease is facilitated[60].

Finally, capillary permeability and vascularity assessments can provide diagnostic information for differentiating malignant from benign tumours[61, 62]. In fact, malignant tumours often show persistent angiogenesis, which is the development of new vessels from the existing vascular bed, resulting in increased blood flow. Hyperpolarized ^{129}Xe , as a quasi-diffusible tracer, is studied by our group with the long-term goal of developing a new method of blood flow imaging for tumour detection, in particular for breast cancer. Breast cancer is the second leading cause of cancer-related deaths for Canadian women[65]. Early detection with X-ray mammography has helped increase the five-year survival rate[66]. However, the limited tissue contrast of this technique prevents some women from being correctly diagnosed[67]. Also, surgical biopsy, an invasive procedure, is required to confirm whether a lesion is benign or malignant[68]. For those reasons, other methods, including blood flow imaging with hyperpolarized ^{129}Xe , are currently being developed for early detection of breast cancer.

Accurate blood flow measurement requires a knowledge of both the tissue concentration and the arterial concentration of a tracer. No modality can measure both simultaneously, and assumptions reduce the accuracy of the measurements. Current methods of measuring blood flow include MR imaging with contrast agents, usually Gd-DTPA (gadolinium chelated with diethylenetriamine pentaacetic acid)[62]. This tracer is not freely diffusible, and does not provide a direct measure of blood flow. Also, one method to measure both the tissue and arterial concentrations requires two injections, with Gd chelated with two molecules of different molecular weights. Hyperpolarized ^{129}Xe could provide the two measurements at once. In fact, xenon is very sensitive to its environment: its large electron cloud is deformed differently depending on its neighborhood. As a result, the ^{129}Xe nuclei resonate slightly differently depending on whether they are in a blood compartment or in a

tissue compartment, and this can be monitored by NMR. With one study of hyperpolarized ^{129}Xe , concentrations in both compartments could be measured, leading to a direct measure of blood flow. Swanson et al[63] reported preliminary spectroscopic studies of tissue perfusion, measuring both the tissue and the blood concentrations as a function of time. Injection delivery of ^{129}Xe in a suitable blood pool agent could also provide this kind of measurement, as discussed by Wolber et al[64].

1.3 Thesis Overview

The work presented in this thesis is a feasibility study of hyperpolarized ^{129}Xe for medical applications. A methodology, suitable for our research group and our installation, was developed and tested. NMR and MR imaging techniques were implemented and studied. Both gas and dissolved phases were examined, with the ultimate goal of imaging the dissolved phase by injection delivery.

The thesis is presented in approximately chronological order, in steps of increasing complexity. Chapter 2 presents the theory underlying this project. Chapter 3 explicitly describes the methods used for the thesis, from laser-polarization to gas handling and then to NMR techniques. Chapter 4 presents a study of ^{129}Xe gas phase in imaging phantoms. The phantoms were extremely useful for implementing the NMR and MR imaging sequences and testing the theory. Then, some dissolved phase work is presented in Chapter 5. Finally, a theoretical study of injection delivery, included in Chapter 6, provides a basis for a discussion of dissolved phase imaging and highlights future directions for the project.

Chapter 2

Theory

This chapter contains the theoretical framework necessary to understand the powerful combination of NMR, MR imaging and laser polarization for medical applications. Firstly, principles of NMR are reviewed in Section 2.1. Next, MR imaging is briefly explained (Section 2.2). Finally, the theory of laser polarization is explained in Section 2.3.

2.1 The Nuclear Magnetic Resonance Signal

Nuclear Magnetic Resonance, as the name implies, involves a nuclear magnetic system undergoing resonance. In this section, magnetic properties of nuclear spins are reviewed(2.1.1). To do so, both classical and quantum treatments are useful and complementary. The classical treatment is particularly useful for visualizing how the bulk magnetization behaves in a magnetic field(2.1.2). Resonance due to an RF pulse and relaxation are then introduced, leading to the Bloch equations and spin echoes. A notation is also defined for a train of RF pulses, useful for studying hyperpolarized ^{129}Xe . Finally, the basics of signal acquisition (2.1.4) and NMR spectroscopy are explained(2.1.6).

2.1.1 The Nuclear Spin

A nucleus of mass number A is composed of Z protons and N neutrons, where $A = Z + N$. The nucleus possesses a nuclear magnetic dipole moment $\vec{\mu}$ due to both the intrinsic magnetic dipole moments of the nucleons and the currents circulating in the nucleus resulting from the movement of protons. Moreover, the nucleus has a total angular momentum $\vec{J}$ resulting from the intrinsic spin angular momenta of the nucleons and the motion of particles (the orbital angular momenta of the nucleons). In the nuclear field, the total angular momentum of the nuclei is most often referred to as the nuclear spin, i.e. $J = \hbar I$ where I is commonly called the nuclear spin.

The nuclear magnetic dipole moment $\vec{\mu}$ and the total angular momentum $\vec{J}$ are related by the relation $\vec{\mu} = \gamma \vec{J}$ where γ is the gyromagnetic ratio of the nucleus. For example, the gyromagnetic ratios of the hydrogen nucleus (^1H) and ^{129}Xe are respectively 267.51 and 73.992×10^6 rad/s/T[69].

The Nuclear Spin in a Magnetic Field

In the presence of a magnetic field $\vec{B}_0$, the nuclear magnetic dipole moment $\vec{\mu}$ experiences a torque

$$\vec{\tau} = \frac{d\vec{J}}{dt} = \vec{\mu} \times \vec{B}_0. \quad (2.1)$$

The result of this torque is a precession of the nuclear magnetic dipole around the external magnetic field $\vec{B}_0$ at the angular frequency $\omega_0 = \gamma B_0$, as illustrated classically in Fig. 2.1. By definition, the Larmor frequency ν_0 is

$$\nu_0 = \frac{\omega_0}{2\pi} = \frac{\gamma}{2\pi} B_0. \quad (2.2)$$

Resonance of the Nuclear Spin

The Hamiltonian $\mathcal{H}$ associated with the nuclear spin in a magnetic field is

$$\mathcal{H} = -\vec{\mu} \cdot \vec{B} = -\gamma \vec{J} \cdot \vec{B} \quad (2.3)$$

or, for a magnetic field $\vec{B} = B_0 \hat{z}$:

$$\mathcal{H} = -\gamma \hbar B_0 I_z \quad (2.4)$$

Figure 2.1: Precession of the nuclear magnetic dipole $\vec{\mu}$ in the presence of a magnetic field $\vec{B}_0$

The allowed energies of the Hamiltonian are:

$$E = -\gamma \hbar B_0 m \quad m = I, I - 1, \dots, -I \quad (2.5)$$

For a spin $I = \frac{1}{2}$, two states are possible (commonly known as the Zeeman splitting) of energies $E = \pm \frac{1}{2} \gamma \hbar B_0$. The lowest and highest energy levels are usually referred to as the spins parallel ($\uparrow$) and anti-parallel ($\downarrow$) to the magnetic field respectively. The spin resonates when it absorbs energy such that a transition from the lowest to the highest energy level occurs. The amount of energy ΔE absorbed must correspond to the Larmor frequency ν_0 :

$$\nu_0 = \frac{\Delta E}{h} = \frac{\gamma}{2\pi} B_0 \quad (2.6)$$

2.1.2 Bulk Magnetization

At a given non-zero temperature T , the thermal energy is sufficient for some of the spins to occupy the higher energy level. The relative populations of the lowest ($n_{\uparrow}$) and highest energy states ($n_{\downarrow}$) is given by the Boltzmann distribution:

$$\frac{n_{\downarrow}}{n_{\uparrow}} = e^{-\Delta E/k_B T} = e^{-\hbar \omega_0/k_B T} \quad (2.7)$$

where k_B is Boltzmann's constant.

The polarization P is defined as the fraction of spins in excess[70]:

$$P = \frac{n_{\uparrow} - n_{\downarrow}}{n_{\uparrow} + n_{\downarrow}} = \frac{1 - e^{-\hbar\omega_0/k_B T}}{1 + e^{-\hbar\omega_0/k_B T}} \quad (2.8)$$

The bulk magnetization $\vec{M}$ is defined as the volume density of magnetic dipole moments. i.e. $\vec{M} = \sum \vec{\mu}$ for a volume of unity. This is illustrated classically in Fig. 2.2. In this figure, the individual magnetic dipole moments, represented as arrows, are precessing around the external magnetic field, some being in the lower energy state (parallel to $\vec{B}_0$) and some being in the higher energy state (antiparallel to $\vec{B}_0$). Since all spins precess with different phases, a net magnetization $\vec{M}$ appears parallel to the external magnetic field.

At equilibrium, the magnitude of the bulk magnetization M_{eq} is directly proportional to the polarization P (eq. 2.8) and can be calculated for a sample containing N spins with the approximation that $\frac{\gamma\hbar B_0}{k_B T}$ is very small:

$$M_{eq} = \frac{N}{2} \gamma \hbar P \simeq \frac{N \gamma^2 \hbar^2}{4 k_B T} B_0 \quad (2.9)$$

The Bulk Magnetization in a Magnetic Field

Similar to the single magnetic dipole moment $\vec{\mu}$, the bulk magnetization $\vec{M}$ experiences a torque in the presence of a magnetic field:

$$\frac{d\vec{M}}{dt} = \gamma \vec{M} \times \vec{B}_0 \quad (2.10)$$

At equilibrium in a static magnetic field, the magnetization is parallel to the magnetic field, and no precession occurs.

The Effect of an RF Pulse

For the purpose of NMR and MR imaging, resonance in a system of spins is induced by a Radiofrequency (RF) pulse. This is simply a magnetic field $\vec{B}_1$ rotating at an angular frequency ω in the plane perpendicular to the static magnetic field, as illustrated in Fig. 2.3a.

Figure 2.2: Classical view of the bulk magnetization.

Figure 2.3: Rotating magnetic field in the transverse plane.

The magnetic field seen by the magnetization is now the sum of static and rotating magnetic fields:

$$\vec{B}_{tot} = \vec{B}_0 + \vec{B}_1 \quad (2.11)$$

where $\vec{B}_1 = B_1 [\cos(\omega t)\vec{i} + \sin(\omega t)\vec{j}]$. Eqn. 2.10 becomes:

$$\frac{d\vec{M}}{dt} = \gamma \vec{M} \times \vec{B}_{tot} \quad (2.12)$$

A convenient way to analyse the behaviour of the magnetization in the presence of both static and rotating magnetic fields is to use a frame of reference rotating about the z -axis at frequency ω . In this frame of reference, $\vec{B}_1$ is static, and $\vec{B}_0$, by an appropriate transformation, becomes $(\vec{B}_0 - \frac{\vec{\omega}}{\gamma})$. The net magnetic field in the rotating frame is therefore, as shown in Fig. 2.3b:

$$\vec{B}_{eff} = \left(\vec{B}_0 - \frac{\vec{\omega}}{\gamma} \right) + \vec{B}_1 \quad (2.13)$$

The “on-resonance” case will be considered for simplicity, i.e. when the RF pulse frequency is exactly the resonant frequency of the spins or $\omega = \omega_0$. The effective magnetic field is entirely along B_1 , along the y' -axis of the rotating frame of reference. For the duration of the RF pulse, the magnetization $\vec{M}$ precesses around $\vec{B}_1$ along the y' -axis, with an angular frequency $\omega_1 = \gamma B_1$. The magnetization is thus tipped by an angle α towards the transverse plane as a result of the RF pulse. The flip angle α depends on the strength (B_1) and duration (τ) of the magnetic field:

$$\alpha = \int_0^\tau \omega_1 dt = \int_0^\tau \gamma B_1 dt \quad (2.14)$$

Following an RF pulse, the longitudinal and transverse magnetizations are respectively

$$M_z^+ = M_z^- \cos(\alpha) \quad (2.15)$$

$$\text{and} \quad M_{xy}^+ = M_z^- \sin(\alpha), \quad (2.16)$$

where M_z^- and M_z^+ are the longitudinal magnetization prior to and after the RF pulse, and M_{xy}^+ is the transverse magnetization after the RF pulse. This is illustrated in Fig. 2.4.

Figure 2.4: Longitudinal and transverse magnetizations prior to and after an RF pulse of flip angle α .

In particular, a 90° pulse tips all the longitudinal magnetization into the transverse plane, whereas a 180° pulse inverts the magnetization. Small flip angles are also commonly used for imaging.

Relaxation

Whether an RF pulse is used to excite a system of spins or, as will be seen shortly (Section 2.3), laser polarization is used to create a very non-equilibrium state of a system of spins, the magnetization returns to equilibrium by relaxation mechanisms.

Relaxation is due to couplings between nuclear spins, or between magnetic dipole moments. For a monoatomic gas like ^{129}Xe , couplings are extremely weak except during collisions (with other atoms or with the walls), where magnetic dipole-dipole interactions occur. Also, when paramagnetic impurities are present (the best example being the oxygen molecule O_2), their electronic magnetic dipole moments couple with the nuclear magnetic dipole moments. Since the electron dipole moment is about three orders of magnitude larger than the nuclear magnetic dipole moment, this type of coupling is very important.

The couplings can be visualized as fluctuations of magnetic field at the vicinity

of a nucleus by other atoms or nuclei. The fluctuations usually arise from rapid rotational and translational motions of molecules or atoms surrounding the nucleus. If the fluctuations are in the transverse plane and at the resonant frequency of the nucleus, an energy transition can be induced, and the nuclear spins can relax to the lowest energy state, causing the magnetization to relax towards equilibrium.

Spin-lattice relaxation, also called longitudinal or T_1 relaxation, characterizes this return to equilibrium. This relaxation involves exchange of energy between the nuclei and the surrounding lattice. For the case of ^{129}Xe , it is due to collisions between atoms, collisions with walls, and is dominated by electronic paramagnetic relaxation if oxygen is present. The spin-lattice relaxation is characterized by the T_1 relaxation time, and the time dependence of the longitudinal magnetization can be expressed as:

$$\frac{dM_z}{dt} = -\frac{M_z - M_{eq}}{T_1} \quad (2.17)$$

where M_z is the z -component of the magnetization at any time t and M_{eq} is the thermal magnetization, as defined by Eqn. 2.9. In the case of hyperpolarized ^{129}Xe , the non-equilibrium magnetization $\bar{M}_0$ created by laser polarization returns to equilibrium by T_1 relaxation. This is illustrated in Fig. 2.5a and expressed as the solution to the previous equation for $M_z(t=0) = M_0 \gg M_{eq}$:

$$M_z = (M_0 - M_{eq})e^{-t/T_1} + M_{eq}. \quad (2.18)$$

In Fig. 2.5b, the case of thermally polarized nuclei is illustrated following a 90° pulse (i.e. $M_z(t=0) = 0$).

Spin-spin relaxation, also called transverse or T_2 relaxation, involves interactions between nuclei. T_2 relaxation mechanisms include T_1 relaxation mechanisms as well as spin diffusion and chemical exchange. After an RF pulse is applied, all spins precess coherently and a transverse magnetization M_{xy} is produced. This magnetization disappears exponentially with a time constant called the T_2 relaxation time. This relaxation represents a loss of coherence between nuclei due to the slightly different magnetic fields seen by a nucleus and its neighbours. The time dependance

Figure 2.5: T_1 relaxation towards equilibrium for (a) hyperpolarized ^{129}Xe nuclei and (b) thermally polarized nuclei.

of the transverse magnetization is characterized by:

$$\frac{dM_{xy}}{dt} = -\frac{M_{xy}}{T_2} \quad (2.19)$$

Following an RF pulse, the solution to the previous equation is illustrated in Fig. 2.6 and is given by:

$$M_{xy}(t) = M_{xy}(0)e^{-t/T_2} \quad (2.20)$$

Static magnetic field inhomogeneities further enhance transverse relaxation. This causes the transverse magnetization to relax according to an apparent spin-spin relaxation time, called the T_2^* relaxation time, which is shorter than T_2 ($T_2^* < T_2$). The T_2^* relaxation can be expressed as in Eqn. 2.19 and 2.20, but replacing T_2 by T_2^* .

Bloch Equations

Combining Eqn. 2.10, 2.17 and 2.19, the phenomenological Bloch equations describe the behaviour of the bulk magnetization in the presence of a magnetic field and governed by relaxation mechanisms:

Figure 2.6: T_2 relaxation towards equilibrium.

$$\frac{d\vec{M}}{dt} = \gamma \vec{M} \times \vec{B}_{tot} - \frac{M_x \vec{i} + M_y \vec{j}}{T_2} - \frac{(M_z - M_{eq}) \vec{k}}{T_1} \quad (2.21)$$

Spin Echoes

The magnetization tipped into the transverse plane is rapidly defocussed due to field inhomogeneities resulting in T_2^* relaxation. In fact, viewed from the rotating frame of reference, parts of the magnetization precess at larger frequencies and others at lower frequencies according to the slightly different magnetic field that they see. After a time $TE/2$, where TE stands for echo-time, the phase accumulated is proportional to the magnetic field seen

$$\phi(TE/2^-) = \gamma B \frac{TE}{2}. \quad (2.22)$$

A 180° pulse can be applied after a time $TE/2$ to refocus the transverse magnetization. After this pulse, the phases are flipped, becoming

$$\phi(TE/2^+) = \pi - \phi(TE/2^-) = \pi - \gamma B \frac{TE}{2}. \quad (2.23)$$

The magnetizations continue their precession at the same frequencies, and after another time $TE/2$, the phase is

$$\phi(TE) = \phi(TE/2^+) + \gamma B \frac{TE}{2} = \phi(TE/2^+) + \phi(TE/2^-) = \pi, \quad (2.24)$$

independent of the magnetic field present. The 180° pulse thus reverses all the effects of field inhomogeneities, creating a spin echo at a time TE , when the transverse magnetization is refocussed. This is illustrated in Fig. 2.7.

Although this technique compensates for field inhomogeneities, the transverse magnetization still decays according to T_2 relaxation and the magnetization at the spin echo (at $t = TE$) is weighted by a factor e^{-TE/T_2} .

2.1.3 The Look-Locker Convention for Hyperpolarized ^{129}Xe

Immediately after laser polarization, ^{129}Xe nuclei collectively produce a large magnetization $\vec{M}_0$ parallel to the magnetic field $\vec{B}_0$. This magnetization is much larger than the thermal magnetization $\vec{M}_{eq}$:

$$M_0 \gg M_{eq}. \quad (2.25)$$

Bloch equations (2.21) describe the behaviour of the magnetization in the presence of a static magnetic field $\vec{B}_0$ and an oscillating magnetic field due to an RF pulse $\vec{B}_1$, as discussed above.

Following these equations, two general considerations for hyperpolarized ^{129}Xe must be highlighted. First, in the absence of an RF pulse, the magnetization $\vec{M}_0$ created by laser polarization relaxes to the equilibrium value $\vec{M}_{eq}$ according to T_1 relaxation, as given by Eqn. 2.18. Therefore, the huge magnetization due to laser polarization must be used in a relatively short time compared to T_1 . Second, following an RF pulse, the magnetization is tipped by an angle α towards the transverse plane. The transverse magnetization M_{xy} relaxes according to T_2 relaxation. The longitudinal magnetization continues its relaxation towards equilibrium. As a result, each time an RF pulse is applied, an amount of longitudinal magnetization, equal

Figure 2.7: Spin echo

to $M_z(1 - \cos \alpha)$, is lost. Small flip angles must then be used in order to spare the magnetization.

Look and Locker introduced, in the late 1960s, a useful method for one-shot T_1 estimation using a periodic train of RF pulses separated by a repetition time TR , represented schematically in Fig. 2.8[71]. Following their notation, consider M_n^+ and M_n^- to be the longitudinal magnetization just before and after the n th RF pulse of tip angle α_n , respectively. For hyperpolarized ^{129}Xe :

$$M_n^+ = M_n^- \cos \alpha_n \quad (2.26)$$

$$M_{n+1}^- = M_n^+ e^{-TR/T_1} \quad (2.27)$$

The combination of these two equations leads to:

$$M_{n+1}^- = M_n^- \cos(\alpha_n) e^{-TR/T_1} \quad (2.28)$$

A recursive equation can be obtained:

$$\begin{aligned} M_0^- &= M_i \\ M_1^- &= M_0^- \cos(\alpha_0) e^{-TR/T_1} = M_i \cos(\alpha_0) e^{-TR/T_1} \\ M_2^- &= M_1^- \cos(\alpha_1) e^{-TR/T_1} = M_i \cos(\alpha_0) \cos(\alpha_1) e^{-2TR/T_1} \\ &\dots \\ M_{n+1}^- &= M_i \left(\prod_{j=0}^n \cos(\alpha_j) \right) e^{-(n+1)TR/T_1} \end{aligned} \quad (2.29)$$

where M_i is the initial longitudinal magnetization prior to the train of RF pulses. In the particular case where all RF pulses are of the same flip angle α :

$$M_{n+1}^- = M_i (\cos \alpha)^{(n+1)} e^{-(n+1)TR/T_1} \quad (2.30)$$

Since the $(n + 1)$ th pulse takes place at a time $t = (n + 1)TR$, Eqn. 2.30 can be rewritten as:

$$M_{n+1}^- = M_i (\cos \alpha)^{t/TR} e^{-t/T_1} \quad (2.31)$$

or:

$$M_{n+1}^- = M_i e^{-t \left(\frac{1}{T_1} - \frac{\ln(\cos \alpha)}{TR} \right)} = M_i e^{-t/T_{1eff}} \quad (2.32)$$

where

$$\frac{1}{T_{\text{eff}}} = \frac{1}{T_1} - \frac{\ln(\cos \alpha)}{TR} \quad (2.33)$$

2.1.4 Signal Acquisition

An RF coil is used to produce the oscillating magnetic field ($\vec{B}_1$) necessary to tip the bulk magnetization. The coil is positioned such that the magnetic field produced lies in a plane perpendicular to the static magnetic field ($\vec{B}_0$). The coil can take various forms, from a simple solenoid to a Helmholtz coil or a quadrature coil. The coil is essentially an electronic circuit designed to resonate at a given frequency. Two variable capacitors, one in parallel and one in series with the circuit, are used for fine tuning the circuit to the Larmor frequency of the nuclei and matching to 50Ω .

The RF coil serves also as a receiver. The part of the magnetization tipped into the transverse plane is oscillating in the laboratory frame. Fluctuations in the magnetic flux induce a current in the coil according to Faraday's law. This current is the actual NMR signal. Since the magnetization is rotating in the transverse plane at a frequency ω_0 , the current induced in the coil oscillates as a function of time at the frequency ω_0 . The current is also attenuated exponentially due to T_2^* relaxation of the transverse magnetization. The resulting signal is called a "free-induction decay" or FID, and is represented in Fig. 2.9.

Since the portion of the magnetization tipped into the transverse plane is responsible for the signal detection, the strength of the signal measured is actually proportional to $M_{xy}(t)$.

Eqn. 2.29 and 2.30 describe the behaviour of the longitudinal magnetization as a function of time for a train of RF pulses. The signal measured (S_n) after the n th RF pulse is:

$$S_n = M_n^- \sin \alpha_n \quad (2.34)$$

Therefore, the signals measured for the train of RF pulses are, for variable and

Figure 2.8: Train of RF pulses.

Figure 2.9: Free induction decay.

constant flip angles respectively:

$$(S_{n+1})_{VFA} = M_i \sin \alpha_{n+1} \left(\prod_{j=0}^n \cos(\alpha_j) \right) e^{-t/T_1} \quad (2.35)$$

$$(S_{n+1})_{CFA} = M_i \sin \alpha (\cos \alpha)^{t/TR} e^{-t/T_1} \quad (2.36)$$

2.1.5 Variable Flip Angle (VFA) Sequences

According to Eqn. 2.36, a series of Constant Flip Angles (CFA) leads to a diminishing signal over time. A sequence of Variable Flip Angles (VFA) can be designed such that the measured signal remains constant over time.

By forcing the measured signals (Eqn. 2.35) to be constant for a total of N RF pulses, and using a 90° pulse at the end of the sequence for employing all the remaining magnetization, the VFA sequence is the following[72]:

$$\alpha_n = \tan^{-1} \left(e^{-(N-n)TR/T_1} \prod_{j=n+1}^{N-1} \cos(\alpha_j) \right) \quad (2.37)$$

$$= \tan^{-1} \left(\frac{e^{-(N-n)TR/T_1}}{\sqrt{N-n}} \right) \quad (2.38)$$

2.1.6 NMR Spectroscopy

In response to an applied magnetic field, all substances exhibit diamagnetism: currents in the electron clouds induced by the application of a magnetic field oppose that field. If a paramagnetic substance is present however, diamagnetism is masked by paramagnetism. As a result of diamagnetism, a nucleus placed in a given environment is shielded from the external magnetic field to some extent and sees a magnetic field equal to $B_0(1 - \sigma)$ where σ is the shielding constant. The amount of shielding depends on the environment. Therefore, two identical nuclei placed in two different environments have distinct resonant frequencies.

NMR spectroscopy provides chemical and environmental information by sampling all the resonant frequencies of a sample. To do so, a pulse of radio-frequency at a carrier frequency ω and of duration τ can be used, as illustrated in Fig. 2.10a.

The pulse being of finite duration, a spectrum of frequencies is carried by the pulse, as shown by the Fourier transform of the RF pulse, in Fig. 2.10b. If the pulse is relatively short, the bandwidth of the frequencies carried is large, and most or all of the resonant frequencies of the nuclei are equally excited. This type of RF pulse, in NMR terminology, is called a “hard” pulse.

Figure 2.10: RF pulse of duration τ (a) and its associated frequency distribution (b).

The signal acquired from the sample as a function of time or FID is a superposition of all the signals at different resonant frequencies. A Fourier transform leads to a frequency spectrum, showing peaks at the resonant frequencies of the nuclei. The peaks are usually Lorentzian, due to the exponential decay of the transverse magnetization. The full width at half maximum (FWHM) is:

$$FWHM = \frac{2}{\pi T_2^*}. \quad (2.39)$$

The frequency axis is usually expressed in terms of chemical shifts. The chemical shift (δ) is a measure of the shift in resonant frequency, with respect to a reference

frequency ω_{ref} :

$$\delta = \frac{\omega_s - \omega_{ref}}{\omega_{ref}} \times 10^6 = \frac{\sigma_{ref} - \sigma_s}{1 - \sigma_{ref}} \times 10^6 \quad (2.40)$$

The units of the chemical shift are in parts per millions (ppm). With ^{129}Xe , the gas peak is usually taken as the reference frequency. The advantage of this scale is that the chemical shift is independent of the carrier frequency and is therefore the same for any static magnetic field.

2.2 2D Spin-Warp MR Imaging

MR imaging consists of exciting a sample with an RF pulse, and encoding the transverse magnetization prior to and during data acquisition in order to localize the information in three dimensions. The first paragraphs of this section (2.2.1.2.2.2.2.3) explain in general terms how the magnetization is encoded. Next, Sections 2.2.4 and 2.2.5 describe more specifically how gradient echoes and spin echoes can be employed to encode the magnetization. Fig. 2.11 and 2.12 illustrate the timing of the 2D spin-echo and gradient-echo sequences, respectively. Finally, 3D imaging is introduced in 2.2.6.

2.2.1 Slice Selection

In order to excite only the spins contained in a particular slice of a sample, a “soft” RF pulse accompanied by a slice-selective gradient is used. A soft pulse, in MR imaging terminology, means a sinc-modulated RF pulse, as shown in Fig. 2.13a. The Fourier transform of the RF pulse (Fig. 2.13b) shows that a range of frequencies, from $(\omega_1 - \frac{\Delta\omega}{2})$ to $(\omega_1 + \frac{\Delta\omega}{2})$, are uniformly excited. A linear gradient of magnetic field is applied perpendicular to the desired slice, by convention, in the z -direction. The static magnetic field is therefore:

$$B(z)\hat{z} = B_0\hat{z} + (G_z z)\hat{z} \quad (2.41)$$

where G_z is the gradient of magnetic field and z is the linear position along the z -axis. Only spins located where the magnetic field has a value between $[B_1 - \frac{\Delta B}{2}, B_1 + \frac{\Delta B}{2}] =$

Figure 2.11: Spin-echo imaging timing sequence.

Figure 2.12: Gradient-echo imaging timing sequence.

Figure 2.13: Ideal soft RF pulse (a) and its associated frequency distribution (b).

$\gamma[\omega_1 - \frac{\Delta\omega}{2}, \omega_1 + \frac{\Delta\omega}{2}]$ are excited. For given soft RF pulse and gradient G_z , those spins are located in a slice of thickness Δz :

$$\Delta z = \frac{\Delta\omega}{\gamma G_z} \quad (2.42)$$

For example, with a 1 Gauss/cm gradient and $\Delta\omega = 6.3 \times 10^3$ rad/s, 8.5 mm slice thickness is obtained.

Non-ideal Soft RF Pulses

A perfect sinc-shaped RF pulse along with a slice-selective gradient leads to a sharp slice profile. However, truncated sinc RF pulses are used in MR imaging due to timing constraints. Three or five lobe soft pulses are commonly used, and they result in smeared slice profiles, as illustrated in Fig. 2.14.

Figure 2.14: Soft RF pulse (a) and its associated frequency distribution (b).

2.2.2 Frequency Encoding

A frequency-encoding gradient is applied during the read-out of the signal. This gradient is in the plane of the selected slice, by convention in the x -direction. The

magnetic field, still pointing in the z -direction, has a varying magnitude along the x -axis:

$$B(x)\hat{z} = B_0\hat{z} + (G_x x)\hat{z} \quad (2.43)$$

where G_x is the gradient of magnetic field and x is the linear position along the x -axis.

As a result, spins located in different x locations resonate at different frequencies, and the read-out is a superposition of all frequencies. A Fourier transform of the signal gives a frequency distribution of the spins, i.e. a spatial distribution of the spins along the x -axis.

2.2.3 Phase Encoding

Finally, a third gradient of magnetic field is applied along the y -direction, for a duration τ , between the end of the excitation RF pulse and the beginning of the read-out. During the application of this gradient, spins located at different y locations precess at different frequencies: the spins acquire a phase according to their y location. When the gradient is turned back off, the spins precess all with the same frequency, but with different phases. Now, when the signal is read with a frequency-encoding gradient, not only is the signal a superposition of several frequencies, but also with different phases. For a given phase-encode gradient strength and duration, this signal corresponds to one line of the Fourier transform of the object.

In order to obtain a complete two-dimensional (2D) image, the sequence of applying an RF pulse along with a slice-selective gradient, phase-encoding, and reading-out with a frequency-encoding gradient is repeated N times with N different phase-encoding gradients. Each signal read corresponds to one line of the Fourier transform of the object, and the whole field-of-view (FOV) in Fourier space is covered by a set of N views, this is referred to as k -space. A two-dimensional Fourier transform of the entire data set provides an image of the object. Fig. 2.15 illustrates the Fourier space of the object, where k_x and k_y are spatial frequencies.

Strategies for Phase-Encoding

Several strategies can be employed to map the Fourier or k-space of an object. For some applications, it can be useful to fill the central part of k-space first, although some other applications benefit from other types of coverage. Amongst the possible strategies, we have:

- Sequential phase-encode ordering handles the phase-encode gradients such that k-space is covered sequentially:

$$k_y = \left(n - \frac{N-1}{2} \right) \Delta k_y \quad n = 1, 2, 3 \dots N \quad (2.44)$$

where

$$\Delta k_y = \frac{2k_{y\max}}{N} \quad (2.45)$$

is the k-space resolution, i.e. the spacing between two lines of k-space.

- For centric phase-encode ordering, $k_y = 0$ is sampled first, and k-space is then covered by going alternately up and down:

$$k_y = \begin{cases} n \frac{\Delta k_y}{2} & \text{if } n = 1, 3, 5 \dots (N-1) \\ -(n-1) \frac{\Delta k_y}{2} & \text{if } n = 2, 4 \dots N \end{cases} \quad (2.46)$$

The sequential and centric ordering can be modified such that any line of k-space is read first and the line of zero phase (ZP) encode is read at $n = ZP[73]$.

- ZP sequential phase-encode ordering follows:

$$k_y = \begin{cases} \left(n - ZP + \frac{1}{2} \right) \Delta k_y & \text{if } n = 1, 2, 3 \dots \left(\frac{N}{2} + ZP - 1 \right) \\ \left(n - N - ZP + \frac{1}{2} \right) \Delta k_y & \text{if } n = \left(\frac{N}{2} + ZP \right) \dots N \end{cases} \quad (2.47)$$

For the regular sequential ordering, $ZP = \frac{N}{2} + 1$.

- For ZP centric phase-encode ordering (ZP odd):

$$k_y = \begin{cases} (n - ZP + 1) \frac{\Delta k_y}{2} & \text{if } n = 1, 3, 5 \dots (N-1) \\ -(n + ZP - 2) \frac{\Delta k_y}{2} & \text{if } n = 2, 4 \dots (N - ZP + 1) \\ (2N - ZP + 2 - n) \frac{\Delta k_y}{2} & \text{if } n = (N - ZP + 3) \dots N \end{cases} \quad (2.48)$$

The regular centric ordering occurs for $ZP = 1$.

2.2.4 Gradient Echoes

Each time a gradient of magnetic field is applied during an imaging sequence, the transverse magnetization is dephased by an amount depending on the gradient strength (G) and duration (τ):

$$\phi_G(x, y, z, \tau) = \gamma \int_0^\tau \vec{G}(t) \cdot \vec{r} dt \quad (2.49)$$

In the case of the phase-encode gradients, this dephasing is desired for spatial localization. However, for slice-selective and frequency-encode gradients, the dephasing effect has to be compensated. A compensation gradient is applied after the slice-selective gradient with a total area of approximately $-G_z \tau_{ss}/3$, where G_z and τ_{ss} are the slice-selective gradient strength and duration respectively. Another compensation gradient is applied prior to the frequency-encode gradient, with an area $-G_x \tau_{fe}/2$, where G_x and τ_{fe} are the frequency-encode gradient strength and duration respectively. As a result, when acquisition begins, the transverse magnetization is already dephased by an amount $\phi_G = -\gamma G_x x \tau_{fe}/2$. This corresponds to $k_x = -k_{xmax} = -\gamma \pi G_x \tau_{fe}$. Mid-way through the acquisition, the phase is compensated and all the spins are back in phase. This is called the gradient-echo, occurring at $k_x = 0$. Dephasing further continues up to a phase $\phi_G = +\gamma G_x x \tau_{fe}/2$ corresponding to $k_x = +k_{xmax}$.

T₂* Weighting

Since the transverse magnetization decays according to the relaxation time T₂*, the gradient-echo occurring at a time TE is attenuated by an amount equal to e^{-TE/T_2^*} , producing a T₂* weighted-image.

2.2.5 Spin Echoes

Spin echoes (Section 2.1.2) can be used for imaging in order to compensate for field inhomogeneities and produce a T₂-weighted image. As shown in Fig. 2.11, a 90° pulse is followed by a 180° which refocuses the transverse magnetization at a time TE . The spin echo is used along with the gradient echo for mapping k-space.

2.2.6 3DFT Imaging

3D Fourier-Transform (3DFT) imaging sequences are also available using gradient echoes. The 3DFT sequence is very similar to the 2DGE (Fig. 2.12), except that the slice-selective gradient is replaced by a second phase-encode gradient. Briefly, all the magnetization is tipped by an angle α (not only the spins contained in a selected slice) and the transverse magnetization is encoded in both y and z directions prior to being read in the x direction. The whole 3D k -space is sampled by N_y y -phase-encodes and N_z z -phase-encodes, and a 3D Fourier transform of the data provides a 3D image, displayed as N_z slices along the z -direction. The 3DFT sequence is illustrated in Fig. 2.16.

2.3 Laser Polarization

Polarization of the noble gas ^{129}Xe can be increased by several orders of magnitude by laser polarization of the nuclei. The technique combines optical pumping of rubidium atoms and spin-exchange, in the presence of a magnetic field, and is described in detail elsewhere[74, 75].

2.3.1 Optical Pumping of Rubidium Atoms

As a first step, rubidium atoms are excited optically using a circularly polarized laser emitting at 794.8 nm. Photons carry one unit of angular momentum ($m = 1$): for an interaction to occur, the angular momentum must be conserved and the selection rule $\Delta m = +1$ must be obeyed. The D_1 ($5S_{-1/2} \rightarrow 5P_{1/2}$) transition of rubidium is thus the only one allowed. As a result, the level $5S_{1/2}$ becomes populated (see 2.17).

Rubidium polarization, defined as $\frac{F}{2}$, is achieved very rapidly, on the order of milliseconds.

2.3.2 Spin Exchange

In a second step, rubidium atoms can collide with ^{129}Xe and form a van der Waals complex for a mean time τ . During that time, spin exchange via hyperfine coupling can occur between the atomic spin of rubidium and the nuclear spin of ^{129}Xe , creating a population of hyperpolarized ^{129}Xe nuclei[12]:

The probability of forming a van der Waals complex and of spin exchange depend on the relative velocities of ^{129}Xe and rubidium ($\bar{v}$) and the ^{129}Xe spin-exchange cross-section (σ_{Xe})[76], respectively.

2.3.3 Role of Nitrogen

Nitrogen gas is added to the ^{129}Xe and rubidium mixture. Its effect is two-fold. The probability of creating a van der Waals complex is higher when three-body collisions occur between ^{129}Xe , rubidium and nitrogen. Furthermore, deexcitation of rubidium atoms create an unwanted population of photons (fluorescence photons) emitted in all directions and not polarized. Nitrogen acts as a quenching gas by absorbing those photons[17, 12].

2.3.4 Relaxation

Polarized ^{129}Xe nuclei relax through collisions. ^{129}Xe collides with other atoms (nitrogen, rubidium and other ^{129}Xe atoms) and with the walls of the pumping cell. During a collision, magnetic interactions can induce the nuclear spin to relax. Relaxation is magnetic field dependent, and is more important at low fields.

Relaxation can be expressed as[12]:

$$\frac{1}{T_1} = C_1[\text{Rb}] + \gamma_{\text{wall}} + C_2[\text{others}] \quad (2.51)$$

where C_1 and C_2 are constants, γ_{wall} is a cell-dependant wall relaxation rate, and [others] are the ^{129}Xe and nitrogen concentrations.

2.3.5 ^{129}Xe Polarization Achievable

The ^{129}Xe polarization achievable is an equilibrium between pumping through spin exchange on the one hand and relaxation on the other hand. In simple terms, the increase in polarization depends on the “pumping rate” $1/T_{\text{pump}}$, i.e. how many ^{129}Xe nuclei get polarized in a time dt , and the relaxation, i.e. how many ^{129}Xe nuclei get depolarized in a time dt . The pumping rate is related simply to the number of polarized rubidium atoms and the spin exchange probability, i.e.:

$$\frac{1}{T_{\text{pump}}} = \frac{\Gamma}{2}[\text{Rb}]\bar{\nu}\sigma_{\text{Xe}} \quad (2.52)$$

The pumping rate is independent of the number of polarized nuclei. The nuclear relaxation rate is related to the spin-lattice relaxation (T_1) and to the number of polarized nuclei. In a simple mathematical form,

$$\frac{dP}{dt} = \frac{1}{T_{\text{pump}}} - \frac{P}{T_1} \quad (2.53)$$

where P is the ^{129}Xe polarization.

The solution is of the form:

$$P = \frac{T_1}{T_{\text{pump}}}(1 - e^{-t_{HP}/T_1}) \quad (2.54)$$

where t_{HP} is the laser polarization time.

The maximum ^{129}Xe polarization is[16]:

$$P(t_{HP} \rightarrow \infty) = \frac{T_1}{T_{\text{pump}}} \quad (2.55)$$

Figure 2.15: Fourier space or k-space of an object. k_x is the frequency-encode direction, and k_y is the phase-encode direction. One line along k_x is read for each data acquisition.

Figure 2.16: 3DFT gradient-echo imaging timing sequence.

Figure 2.17: Energy diagram of a rubidium atom and optical pumping.

Chapter 3

Materials and Methods

Probing materials, tissues, or blood flow with hyperpolarized ^{129}Xe requires a complex procedure containing many steps. Initially, ^{129}Xe gas is laser polarized, then hyperpolarized gas is handled and carried into the magnet room to be injected or inhaled, then imaging or spectroscopy is performed. Finally, the data is processed and analysed in order to obtain quantitative information or an image. This chapter addresses the methods developed and currently used in our laboratory to study hyperpolarized ^{129}Xe spectroscopically and by imaging. It covers the laser polarization setup (Section 3.1), the gas handling facilities (Section 3.2), and the NMR techniques (Section 3.3). It also includes the optimization of the temperature and time of laser polarization. In this chapter, laser polarized ^{129}Xe is used to specifically refer to the hyperpolarized ^{129}Xe obtained by the laser polarization technique.

3.1 Laser Polarization Setup

^{129}Xe was laser polarized using a 30 W Al-Ga-As diode array laser (Opto-Power, Tucson AZ) emitting at 794.8 nm. Fig. 3.1 shows a schematic of the set-up used. The laser beam was polarized and widened into a large parallel beam by a set of lenses and then directed onto the gas cell to be hyperpolarized. The laser beam was directed parallel to the magnetic field (i.e. the z -axis in Fig. 3.1).

The cell containing the ^{129}Xe gas to be laser polarized was made of glass coated

Figure 3.1: Laser-polarization setup, placed in the fringe field of the MRI magnet.

with SurfaSil (Pierce Chemical Laboratories) and contained typically around 800 mbar of natural abundance xenon (26.4% of ^{129}Xe), 200 mbar of nitrogen and a few milligrams of rubidium. The glass cell was positioned in a home-made oven having an opening for the laser beam. The temperature of the oven was typically set between 70 and 95°C and kept constant using a temperature controller. The high temperature allowed part of the rubidium metal to vaporize in the pumping cell, creating a vapor pressure of rubidium.

The cell was laser polarized in the most homogeneous part of the fringe field of an Oxford 30 cm bore imaging magnet (operating at 1.89 T), i.e. at a distance of about 2 m off-axis, at a magnetic field of 30 Gauss. The laser polarization time varied between 20 and 60 minutes depending on the level of polarization desired and the cell used, as described shortly.

As described in Section 3.1.1 the polarization achievable is an equilibrium between pumping and relaxation of the ^{129}Xe nuclei, and depends on a number of

factors. In order to improve the polarization achievable with our simple laser polarization setup, the procedure was characterized and optimized with respect to the following factors: the rubidium polarization, the time of laser polarization, the temperature of laser polarization, and the pumping cell pressure. To do so, a completely depolarized pumping cell containing ^{129}Xe was positioned in the oven for at least 20 minutes, allowing the cell temperature to equilibrate to the oven temperature. The laser was subsequently turned on for a specific period of time, then the cell was placed in the RF coil for signal acquisition. The polarization was then measured, using the method described in 3.1.2. The measurements are a lower limit of the polarizations achieved by laser polarization, since some polarization was most likely lost during the transit time between the oven and the RF coil.

3.1.1 Factors Affecting the Polarization

Below are listed the contributors to the ^{129}Xe polarization and their relative importance.

Rubidium Polarization

Rubidium polarization saturates very rapidly, in a time on the order of milliseconds[12]. The rubidium polarization is directly related to the optical pumping, which depends simply on good matching between the laser light and the rubidium available. Therefore, it depends on the tuning, the alignment and the power of the laser.

The diode laser emits photons with a mean energy corresponding to the energy gap between the conduction and the valence bands of the semi-conductor composing the diodes. The energy gap depends upon the temperature of the diodes. A fine tuning of this temperature allows one to match the laser energy to the resonance line of the rubidium, and maximizes the rubidium polarization.

The efficiency of the optical pumping depends also of the alignment of the laser beam with the magnetic field.

Increasing the laser power improves the rubidium polarization, as long as the

rubidium density is high enough to take advantage of a larger number of photons available. A way to increase the laser power effectiveness is to broaden the Rb resonance line. In fact, this line is much narrower than the emission line of current lasers, and the Rb resonance line is broadened by adding noble gases in the pumping cells, resulting in a better match between the two lineshapes. This is illustrated in Fig. 3.2. Xenon gas itself does broaden the Rb emission line, but helium gas is often added due to its effectiveness[13, 77].

Figure 3.2: Collisionally-broadened Rb resonance line.

Optical pumping is also reduced if rubidium is outside the laser beam. This unpolarized rubidium participates in ^{129}Xe relaxation but not in spin exchange. For this reason, pumping cells were designed with diameters the same or smaller than the laser beam diameter at its focal point (i.e. about 15 mm).

Spin Exchange

Spin exchange depends on the number of collisions between polarized rubidium atoms and unpolarized ^{129}Xe nuclei leading to a van der Waals complex, and the spin-exchange cross-section[11]. Therefore, it depends on the relative concentrations of rubidium vapour [Rb], and of the third-body gas [N_2], and their kinetic energy. The issue of temperature and the role of pressure are discussed in Section 3.1.3.

Relaxation

^{129}Xe collides with other atoms (nitrogen, rubidium and other ^{129}Xe atoms) and with the walls of the pumping cell. The number of collisions depends on temperature and pressure. Also the walls of the pumping cell are coated with a silicon-based material to minimize interactions, i.e. to minimize γ_{wall} in Eqn. 2.51[78, 79, 80]. This results in increased T_1 and therefore higher polarizations.

3.1.2 Experimental Determination of the Polarization

The polarization achieved by laser polarization was determined by comparing the experimental signals obtained from two cells, one containing a known amount (volume and pressure) of hyperpolarized ^{129}Xe gas, and the second one containing a known amount of ^{129}Xe gas at thermal equilibrium. The signals were corrected for different pressures. The two cells were of the same geometry so that no corrections for the volume and for the filling factor of the RF coil were required.

The theoretical polarization of the thermal gas was calculated using Eqn. 2.8. knowing the temperature and the resonant frequency. For example, a cell containing 5 atm of thermal ^{129}Xe resulted in a relative signal of 8.09×10^{-4} while a pumping cell with the exact same geometry but containing 800 mbar of hyperpolarized ^{129}Xe gave a relative signal of 4.52. The theoretical thermal polarization being 1.7852×10^{-6} . the experimental polarization was determined to be:

$$\begin{aligned}
 P_{HP} &= P_{therm} \left(\frac{S_{HP}}{S_{therm}} \right)_{\text{same volume}} & (3.1) \\
 &= 1.7852 \times 10^{-6} \left(\frac{4.52}{8.09 \times 10^{-4}} \right) \times 5\text{atm} \times 1013\text{mbar/atm} \\
 &= 6.3\%
 \end{aligned}$$

3.1.3 Characterization and Optimization of the Laser Polarization

Rubidium Polarization

The temperature of the diodes can be controlled to tune the laser light to the absorption energy of the rubidium atoms. A crude tuning was first performed by studying the magnetization for several temperatures of the diodes. Fig. 3.3 shows a signal peak for a diode temperature of 25.6°C. The tuning was later confirmed by comparing the spectrum from the laser with the D_1 line from a Rb lamp.

Some time was spent establishing a good alignment of the laser beam with the magnetic field. To do so, the magnetic field was mapped in the laser polarization area. It was noticed that large ferromagnetic objects at the vicinity of the oven were modifying considerably the magnetic field, resulting in inhomogeneous and unpredictable field lines. Those objects were removed. The alignment of the laser beam with the magnetic field did not seem to be a large issue, and misaligning the laser beam by 5-10° did not lead to a major decrease in the polarization. In fact, the laser used consists of two diode arrays. The two laser beams cross each other at the working distance, where the pumping cell is positioned. The angle between the

main axis and the laser beams is of 6° , as quoted by the manufacturer. Therefore, it is expected that a range of 12° would be permissible for the mis-alignment of the main axis of the laser with the magnetic field.

Rubidium Oxidation

Observations from day to day and over prolonged periods indicated that the polarization levels decreased over time. The polarization depends highly on rubidium quality. This material oxidizes easily after exposure to even traces of oxygen. The presence of rubidium oxides reduces the rubidium vapor pressure and melting point, resulting in reduced spin transfer[17]. The maximal polarization, as given by Eqn. 2.55, is therefore lower in the presence of oxidized rubidium.

The oxidation was monitored qualitatively by observing the apparent colours of the rubidium droplets. Upon oxygen contamination, the metallic appearance gradually changed to yellow, blue, purple and black colors with increasing oxidation. Any manipulation (e.g. filling and emptying the cells) can potentially contribute to their degradation. The cells were considerably oxidized after about 15 emptying and refilling procedures and had to be replaced, i.e. after about three months. Fig. 3.4 illustrates qualitatively the oxidation of an open pumping cell as a function of time, by showing the decreasing signals obtained over a few months.

Polarization versus Time of Laser Polarization

The polarization obtained was studied as a function of laser polarization time. As expected from Eqn. 2.54, the polarization increased rapidly with time of laser polarization, up to a saturation point. Fig. 3.5 shows the polarization obtained as a function of time for two different oven temperatures.

The curves on Fig. 3.5 represent the best fit of the data to Eqn. 2.54. In examining this equation, it is noted that the plateau value is maximal for a high pumping efficiency (short pumping time) and a long relaxation time T_1 . The shoulder is mainly due to the T_1 value: when T_1 is short, the equilibrium between pumping and relaxation is rapidly established and the curve exhibits a narrow shoulder.

Polarization versus Temperature

Curves of polarization versus time of laser polarization can be studied for several temperatures of the oven. When temperature increases, the Rb vapour pressure is increased resulting in a higher Rb density $[Rb]$ and therefore a higher pumping efficiency. In fact, the vapor pressure of rubidium follows the empirical formula $[Rb] = 10^{(23.97-4132/T)} \text{atoms/cm}^3$ [76]. On the other hand, when temperature is increased, the number of volatile particles in the cell ($[others]$ and $[Rb]$) and their mean velocity ($\bar{v}$) are more important: as a result, the number of collisions and the probability of depolarization for the ^{129}Xe nuclei are increased dramatically, in other words the T_1 relaxation time is decreased. Therefore, a pumping cell is characterized by an optimal temperature for which the polarization achievable is maximal. Different pumping cells have different optimum temperatures due to the variability in the rubidium quality from cell to cell, therefore an optimum temperature needs to be determined for each pumping cell.

Fig. 3.6 and Table 3.1 show the maximum polarization achieved (polarization at saturation) as a function of oven temperature. For this particular cell, an oven temperature between 70 and 85°C was appropriate.

The last column of Table 3.1 indicates the approximate time required to reach 95% of the saturation point (t_{sat}). This time reflects the temperature dependence of the relaxation time T_1 . When examining Eqn. 2.51, the temperature dependence is due to the rubidium density $[Rb]$ and to the velocities of the gas particles in the cell, γ_{wall} and C_1 being very weakly temperature dependent [10]. Rubidium density increases more and more rapidly as the temperature is increased (logarithmic behavior), and the density becomes very important at temperatures higher than 95°C. For high temperatures, T_1 drops drastically and saturates. At lower temperatures however, T_1 is mainly due to collisions with other atoms and the temperature dependence is a velocity dependence, dominated by a $\sqrt{T}$ behaviour [81]. T_1 thus decreases with increasing temperature, but more slowly. Fig. 3.7 shows the approximate time to reach saturation as a function of temperature.

The temperature data give a qualitative estimate for the temperature and time

Figure 3.3: MR signal as a function of the diode temperature.

Table 3.1: Saturation values for the polarization and time to reach the saturation for several oven temperatures.

Temperature	Polarization at saturation	Approximate time to reach 95% saturation
T °C	$P(t_{HP} \rightarrow \infty)$ %	t_{sat} min.
60	4.5	65
70	6.3	60
80	5.8	30
95	4.5	15

Figure 3.4: Decrease of signal due to Rb oxidation as a function of time. The four symbols represent the signals from four different open pumping cells.

Figure 3.5: Polarization as a function of laser polarization time for two different oven temperatures.

Figure 3.6: Polarization at saturation as a function of oven temperature.

Figure 3.7: Time to reach 95% saturation as a function of oven temperature.

to use for an optimal polarization. The range of temperatures between 70 and 85°C seemed most reasonable and was thus chosen for experiments. Lower temperatures required longer times of laser polarization (60 minutes down to 30 minutes for this range of temperature).

Polarization versus Pressure

Other parameters, such as ^{129}Xe and nitrogen pressures could also have been studied. Reducing the pressure in the pumping cells greatly increases the relaxation time T_1 . A polarization of 70% was obtained by Ruth et al.[17] by using a total pressure of 100 mbar including a few mbar of ^{129}Xe only. However, for medical applications, large quantities of hyperpolarized ^{129}Xe have to be produced. Hyperpolarized gas produced at low pressures thus has to be produced by a flow system and accumulated by a freeze-thaw method. This process causes losses of polarization and was not practical with our installation. Two different total pressures were investigated for the pumping cells: 1 atm and 2.5 atm. A total pressure of 2.5 atm resulted in very poor polarization levels. We thus have chosen to routinely use a total pressure of 1 atm (800 mbar of ^{129}Xe and 200 mbar of nitrogen).

3.2 Gas Handling

Imaging hyperpolarized ^{129}Xe gas in glass phantoms requires minimal manipulation. Closed pumping cells are used, i.e. cells that have been filled once and then sealed afterwards. This type of cell can be laser polarized, and then immediately placed into the magnet for imaging. The presence of rubidium is not a problem for those applications, and ^{129}Xe can be re-used as long as the cell is not broken.

Some other applications, however, require a transfer of hyperpolarized ^{129}Xe from the pumping cell to some other vessel. Imaging ^{129}Xe gas *in vivo* or looking at the dissolved phase are examples of applications requiring the use of these open pumping cells. The open pumping cells are laser polarized, next they are opened via a high vacuum Teflon valve to let the hyperpolarized gas fill another vessel, and

then they are closed. Those manipulations must be performed quickly and carefully to minimize any depolarization. The pumping cells also have to be refilled after each or a few utilizations.

The next sections describe the gas manifold, the pumping system, and other accessories allowing the transfer of hyperpolarized ^{129}Xe gas from open pumping cells to other vessels for the purpose of dissolved phase imaging.

3.2.1 Gas Manifold and Accessories

An efficient and simple way to force an amount of gas to move from one vessel to another is to use pressure gradients. To do so, a gas manifold was designed for our specific needs. A schematic of the gas manifold is shown in Fig. 3.8.

The gas manifold was made of glass and high vacuum Teflon valves. Teflon and glass materials were used because they are non-ferromagnetic: they can be handled safely in the vicinity of the magnet, and minimal depolarization of the hyperpolarized ^{129}Xe nuclei is induced by magnetic interactions.

The gas manifold had a number of outlets where other accessories can be attached and detached easily. Amongst the accessories are two different pressure gauges. A Penning gauge (Edwards) allowed high vacuum monitoring, for vacuums ranging between 10^{-7} to 10^{-2} mbar. A vacuumeter (VM1500, Ebro) was used for pressures ranging from 0 mbar up to a few atmospheres. The latter was useful for monitoring gas transfer.

Pumping System

The gas manifold was pumped down to pressures of about 8×10^{-6} Torr using a diffusion pump backed by a roughing pump (Alcatel). A high vacuum was essential for all manipulations involving rubidium. This metal oxidizes rapidly in the presence of any trace of oxygen. It also becomes reactive when in contact with water.

Figure 3.8: Gas manifold.

Table 3.2: Volumes of the manifold. The volumes description refer to Fig. 3.8

Volume delimited by ...	Volume
V#1 and V#2	145 ml
V#2, V#3, V#4 and V#5	38.5 ml
V#3, V#6, V#7 and the cold trap	15.5 ml
V#5 and the outlet	4 ml
V#4, V#8 and V#9	8 ml

Calibration of the Gas Manifold

The different volumes of the gas manifold were calibrated using the following method. A known volume (V_{known}) at atmospheric pressure ($P_1 = 1 \text{ atm} = 1013 \text{ mbar}$) was attached to the previously evacuated manifold. The gas was allowed to fill one part of the manifold (V_{calib}) and a pressure measurement was made (P_2) with the vacuumeter. The ideal gas law ($PV = nRT$) was used to compute the volumes of the various sections according to:

$$V_{calib} = \left(\frac{P_1 - P_2}{P_2} \right) V_{known} \quad (3.2)$$

The volumes of interest measured with this method are indicated in Table 3.2.

3.2.2 Filling the Pumping Cells

As previously mentioned, rubidium oxidizes very quickly in the presence of oxygen. Therefore, precautions must be taken especially when filling a pumping cell with ^{129}Xe and nitrogen gases because of the inflow of gases which can introduce impurities into the cell. A high vacuum is required, so overnight pumping was done prior to filling. Furthermore, the gases must be clean and dry. To ensure that, the gases were stored separately within special bottles. The bottles contained potassium metal which react with oxygen and contaminants, keeping the gases clean and dry. The bottles were attached to the gas manifold as shown in Fig. 3.8.

A pumping cell was filled in two steps. The process is illustrated in Fig. 3.9. First, the ^{129}Xe storage bottle was slowly opened to let a desired amount of ^{129}Xe fill the manifold and the pumping cell which had been previously evacuated (Fig.3.9A and B). The pumping cell was then frozen by immersion in liquid nitrogen, and all ^{129}Xe was condensed in the pumping cell (Fig.3.9C). In a second step, nitrogen gas was allowed to fill the manifold and the pumping cell up to a desired pressure (Fig.3.9D). The pumping cell was then closed and thawed (Fig.3.9E).

3.2.3 Dissolving Hyperpolarized ^{129}Xe

For the study of dissolved phase ^{129}Xe , hyperpolarized gas was transferred from the pumping cell to a glass mixing cell previously evacuated, as shown in Fig. 3.10. The transfer line was at room temperature, preventing rubidium from exiting the pumping cell. In fact, rubidium solidifies quickly when cooled down, therefore it was assumed that only traces of rubidium were actually leaving the pumping cell to solidify in the transfer line and possibly in the mixing cell. For the purpose of administering ^{129}Xe *in vivo*, a cold trap should be added to the transfer line to ensure that the ^{129}Xe is free of rubidium at the end of the transfer line. The resulting ^{129}Xe pressure in the mixing cell was less than 1 atm, ranging from about 0.5 atm to 1 atm.

For the purpose of transferring hyperpolarized gas from the pumping cell to the mixing cell (emptying the pumping cell), a high vacuum was not essential, as long as the pumping cell was rapidly closed after the transfer to avoid any contamination. When hyperpolarized ^{129}Xe was transferred to a clean and dry mixing cell, the vacuum was provided by the diffusion pump, i.e. the transfer line was connected to the gas manifold (outlet A of Fig. 3.10 was connected to outlet B of Fig. 3.11). For some experiments however, the mixing cell was already filled with a biological material or an aqueous solution prior to being filled with hyperpolarized ^{129}Xe . In those cases, it was preferable not to pump the mixing cell via the gas manifold, to avoid any contamination of the latter by water molecules or biological substances. Instead, the mixing cell was pumped to lower vacuums ($\sim 10^{-2}$ mbar) by connecting

Figure 3.9: Pumping cell filling.

Figure 3.10: Schematic of the gas transfer process. The mixing cell is evacuated while the pumping cell is hyperpolarized. At the time of the transfer, the vacuum line is closed, the pumping cell is opened, and hyperpolarized ^{129}Xe gas fills the mixing cell.

outlet A of Fig. 3.10 to outlet C of Fig. 3.11.

In a simplified view, the mixing cell was a glass container with two openings, a first one with a glass stopcock for introducing hyperpolarized ^{129}Xe , and a second one for introducing and extracting biological samples (see Fig. 3.12). Once the mixing cell was filled with hyperpolarized ^{129}Xe , it was detached from the transfer line and placed in the magnet. The biological sample was injected in the mixing cell with a syringe, and then the mixing cell was vigorously shaken to ensure ^{129}Xe was dissolved in the solution, as illustrated in Fig. 3.13. 1 or 2 ml of the solution was extracted in a 3 cc plastic syringe from the mixer for analysis by NMR. This procedure provided a sample with or without ^{129}Xe gas on top of the solution.

In more detail, the opening of the mixing cell for liquid samples was closed by a self-sealing septum pierced by a catheter connected to a Luer stop-cock, as shown in Fig. 3.12. With this type of closing, a vacuum of about 7×10^{-4} mbar was achieved in the mixing cell. The syringe needle was not used to pierce the septum once ^{129}Xe was in the mixing cell, because oxygen would have been introduced into the mixing cell due to pressure gradients and hyperpolarized ^{129}Xe was rapidly depolarized. Instead, the syringe was connected to the Luer stop-cock to deliver and extract the liquid solution.

To reduce any temperature effect on the data, all measurements were made with solvents at room temperature. In fact, temperature affects the gas solubilities. For example, ^{129}Xe solubility is decreased by about 55% by going from 4 to 23°C[82]. For experiments with solutions stored at 4°C, gas bubbles were observed to appear in the syringe during the course of a T_1 measurement. The apparent T_1 measured was thus the true T_1 and the decrease of the dissolved signal due to decreased solubility. Furthermore, T_1 relaxation is related to the correlation time of the dipolar couplings between dissolved ^{129}Xe and protons. Increasing the temperature decreases the correlation time, and could increase the relaxation rate[83]. This has actually been shown for ^{129}Xe dissolved in benzene[84].

Figure 3.11: Pumping system.

Figure 3.12: Mixing cell.

3.3 NMR Methods and Sequences

All NMR and MR imaging experiments were performed using a SMIS (Surrey Medical Imaging Systems, Surrey, UK) MR5000 console and Bruker Biospec gradients.

3.3.1 Flip Angle Calibration

As mentioned in Section 2.1.3, working with hyperpolarized ^{129}Xe necessitates the use of small flip angles to spare the longitudinal magnetization. The flip angle by which the magnetization is tipped is the result of the energy deposited in the sample by the oscillating magnetic field B_1 for the duration of the RF pulse. The flip angle must be calibrated experimentally, because it depends on several factors. A first factor is the output power of the transmitter. The tuning of the RF coil to the resonant frequency (a perfect tuning being a $50\ \Omega$ impedance with a null phase) can also modify the amount of power actually transferred to the coil. Finally, the loading of the RF coil and the type of sample are important factors. They determine how well the RF energy is transferred to the sample.

Figure 3.13: Schematic of the mixing process. Liquid and hyperpolarized ^{129}Xe gas are combined and mixed together. 1 or 2 cc of the resulting liquid is extracted for analysis. Shaking and extraction steps can be repeated a few times.

A train of RF pulses of unknown but constant flip angle α separated by a time $TR \ll T_1$ was used as a flip angle calibration[85]. Following Eqn. 2.36, the signal measured as a function of time is:

$$S_{n+1} = M_i \sin \alpha (\cos \alpha)^{t/TR} \quad \text{for } t \ll T_1 \quad (3.3)$$

A fit of the preceding equation to the experimental data provided an estimation of the flip angle used. Typically, 10-12 RF pulses were used separated by 500 ms, resulting in a total time of 5-6 s. For a T_1 of about 100 s or more, the approximation that $t \ll T_1$ was sufficiently valid.

3.3.2 Relaxometry

T_1 relaxometry

T_1 relaxation times were measured by applying a series of RF pulses of known flip angle separated by a repetition time TR . The signal decays as a function of time due to both T_1 relaxation and the use of RF pulses to tip the magnetization. The signal measured is given by Eqn. 2.36.

Alternatively, when the flip angle was not accurately known and/or the measurements were scattered (for the dissolved phase in our case), several T_1 measurements with the same flip angle were performed using different TR s. All measurements were fitted for T_{1eff} , as in Eqn. 2.32 and 2.33. The intercept of the graph of $1/T_{1eff}$ versus $1/TR$ was used to calculate T_1 .

T_2 relaxometry

The exponential decay of an FID follows a T_2^* relaxation time, as explained in Sections 2.1.2 and 2.1.4. The T_2 relaxation time can be measured by using spin echoes to refocus the magnetization. The most popular sequence is the Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence and is illustrated in Fig. 3.14. The CPMG sequence uses a 90° pulse to tip all the magnetization into the transverse plane. Then a train of 180° pulses, applied at times $t = (n - \frac{1}{2})TE$, periodically refocuses

Figure 3.14: CPMG pulse sequence

the transverse magnetization at times $t = nTE$, for $n = 1, 2, 3 \dots$. The amplitude of the spin echoes decays according to T_2 . The CPMG sequence allows the T_2 relaxation time to be measured in a one shot manner[69].

Chapter 4

Gas Phase Spectroscopy and Imaging

Gas phantoms, with their ease of use and the good Signal-to-Noise Ratio (SNR) they provide, give an opportunity to establish NMR and MRI procedures and to study their limitations in a quantitative and quick manner. These procedures can then be modified for probing materials or for lung imaging with hyperpolarized ^{129}Xe . They can also be extended to the study of dissolved hyperpolarized ^{129}Xe , which differ from gas phase by lower SNR, different chemical shifts, and shorter T_1 relaxation times.

This chapter describes a study of hyperpolarized ^{129}Xe in gas phantoms. Calibrations and spectroscopic measurements are presented, as well as some *in vivo* results. Both two-dimensional (2D) and three-dimensional (3D) imaging were studied, and results from numerical simulations and experiments are presented and compared. The simulations were useful to compare the experimental results with the theory and to guide experiments.

The experimental results presented in this chapter were obtained from a 7 cm long cylindrical closed cell, of external diameter 1.7 cm. The cell contained 800 mbar of ^{129}Xe , 200 mbar of nitrogen, and a few milligrams of rubidium. The results were obtained with a birdcage quadrature RF transmit/receive coil (i.d. 10 cm, length

11 cm. homogeneous volume $\sim 385 \text{ cm}^3$). The gas phantoms were positioned entirely in the homogeneous part of the coil, avoiding any replenishment of hyperpolarized ^{129}Xe from outside the coil via diffusion, which could complicate the measurements.

4.1 Flip Angle Calibration

The flip angle was calibrated using trains of RF pulses, as described in Section 3.3.1. Both hard (rect-shaped) and soft (sinc-shaped) pulses were calibrated.

4.1.1 Hard Pulses

Fig. 4.1 shows the results from a typical flip angle calibration, where the signal intensity measured is displayed as a function of time. The error bars on the individual measurements are smaller than the symbol size and are thus not shown. The measurements were made following a train of hard RF pulses separated by a repetition time of 500 ms. A non-linear least-squares fit, using a Levenberg-Marquardt method[86], of Eqn. 3.3 to the experimental data allows a determination of the flip angle used. In this case, the flip angle was determined to be $18.64^\circ(\pm 0.20)$. The best fit is represented in Fig. 4.1 by the line.

4.1.2 Soft Pulses

Soft pulses along with a slice-selective gradient were used for imaging to excite only the spins in one particular slice. The flip angle was calibrated using a series of soft RF pulses in the same manner as a hard pulse calibration. An example of soft pulse calibration, using a series of five-lobe soft RF pulses separated by 500 ms, is shown in Fig. 4.2, where the best fit is represented by the line. The error bars on the individual measurements are smaller than the symbol size and are thus not shown. The flip angle used was determined to be $27.75^\circ(\pm 0.05)$.

Without an applied gradient, all spins from the sample are excited and participate in the signal. If the sample is larger than the homogeneous part of the coil,

some spins can be excited with less power and this will affect the calibration. In our case however, the calibration was very robust since the samples used were small compared to the coil size.

4.2 Longitudinal Relaxation Time Measurement

T_1 measurements of hyperpolarized ^{129}Xe gas were performed using the method described in Section 3.3.2. Fig. 4.3 shows a typical T_1 measurement from the cylindrical cell, where the signal measured is displayed as a function of time. The repetition time TR was 300 seconds, and the flip angle was 6.33° (± 0.07). The error bars on the individual measurements are smaller than the symbol size and are thus not shown. A three-parameter fit resulted in a T_{1eff} of 30.3 (± 3.6) minutes, as shown by the line in the figure. Correction for the flip angle leads to a T_1 measurement of 31.5 (± 3.9) minutes. This result is of the same order as other reported T_1 measurements: at 2.0 T, T_1 from cells with 1051 and 1191 mbar of hyperpolarized ^{129}Xe were measured to be 155 and 66 min respectively[85].

4.2.1 Effect of Temperature

Fig. 4.4 illustrates the effect of temperature on a T_1 measurement. The cell was at a high temperature (95°C) in the oven prior to the T_1 measurement, and was cooling down to room temperature during the experiment. As can be seen on the figure, the magnetization drops more quickly between the first two points. This is due to a shorter T_1 relaxation time at high temperature, as discussed in Sections 3.1.1 and 3.1.3. To avoid this problem, the cells were routinely cooled down to room temperature by immersing the cells in a water bath for 30-40 s prior to any T_1 measurement. The loss of magnetization was minimized by performing this procedure in the bore of the magnet.

Figure 4.1: Flip angle calibration for hard pulses.

Figure 4.2: Flip angle calibration for soft pulses.

Figure 4.3: T_1 measurement of hyperpolarized ^{129}Xe in the cylindrical gas phantom.

Figure 4.4: Effect of cell temperature on T_1 measurement.

4.2.2 Deceased and *in vivo* Longitudinal Relaxation Time Measurements in Rat Lungs

Spectroscopic measurements of hyperpolarized ^{129}Xe in Sprague-Dawley rat lungs were performed. For these experiments, a large quantity of hyperpolarized ^{129}Xe gas was required to fill the rat lungs several times. About 100 ml of hyperpolarized ^{129}Xe gas was produced at the Steacie Institute for Molecular Sciences (SIMS) of the National Research Council of Canada (NRC), was transported to the Carleton Magnetic Resonance Facility (CMRF) as a solid (frozen to liquid nitrogen temperature) and was thawed in the bore of the CMRF magnet. The T_1 relaxation time of frozen ^{129}Xe is quite long (~ 100 minutes) even at magnetic fields of about 500 Gauss[87], therefore it can be transported over short distances, while immersed in liquid nitrogen in the magnetic field of small permanent magnets (at a field of about ~ 500 G).

Deceased Rat Lung Experiment

A first set of experiments was performed on a deceased rat. The experiments were performed within 2 hours of the death caused by an overdose of anesthetics. The rat had a tracheotomy which involved some tubing inserted into the trachea to facilitate mechanical ventilation and ^{129}Xe delivery. A syringe full of hyperpolarized ^{129}Xe was attached to the tubing. The air contained in the rat lungs was pushed out by applying some pressure on the rat chest. Hyperpolarized ^{129}Xe was then forced and maintained in the rat lungs with the aid of the syringe, while a measurement was acquired. Table 4.1 tabulates the flip angle and T_1 results obtained from this rat.

Since the filling of the RF coil was completely different for a rat compared to the gas phantom, the RF coil was re-tuned with the rat inside and the flip angle calibration was repeated. Two flip angle calibrations were successfully performed using the technique of repeated RF pulses separated by a TR of 500 msec. The fits resulted in T_{1eff} of 2.768 (± 0.026) s and 2.626 (± 0.034) s, for an average of 2.70 (± 0.03) s. Assuming $t \ll T_1$ here lead to a flip angle of 33.80 (± 0.18) $^\circ$.

Table 4.1: Deceased rat lung experiments.

Experiment	α ($^{\circ}$)	TR (s)	T_{1eff} (s)	
Flip angle calibration	33.8	0.5	Trial # 1	Trial # 2
			2.768 ± 0.026	2.626 ± 0.034
			Average 2.70 ± 0.03	
T_1 measurement	16.4	5.0	48.3 ± 0.5	

A T_1 measurement was performed using a TR of 5 seconds. T_{1eff} was $48.3 (\pm 0.5)$ s. Using the above flip angle calibration, T_1 in the *ex vivo* lungs was determined to be $80.4 (\pm 1.5)$ s. This result seems to be high compared to a value of 30 s obtained in excised mouse lungs by Albert[6], but could be due to low oxygen concentration, as discussed later. The T_1 measured is actually an apparent T_1 since some decay is due to the wash-out of ^{129}Xe dissolving in tissues and blood.

The resulting apparent T_1 in the lungs was on the order of tens of seconds, therefore the approximation that $t \ll T_1$ is not completely accurate here. To verify the validity of the approximation, T_1 was plotted as a function of the unknown flip angle according to Eqn. 2.33 knowing TR and T_{1eff} , for the average flip angle calibration and the T_1 experiment, correcting for the different RF power used. The intercept of the two lines yielded an estimation of the flip angle. With this method, it was found that the flip angle calibration was overestimated by 1% and, using this corrected flip angle, the apparent T_1 was estimated to be $78.6 (\pm 2.0)$ s. It is expected that the flip angle calibration is overestimated by assuming $t \ll T_1$ since all the decay is assumed to be due to the flip angle, whereas some decay is due to T_1 relaxation. Although the flip angle overestimation yielded an overestimation of T_1 , the approximation $t \ll T_1$ was valid within the limits of the uncertainty ($\pm 2\%$).

Figure 4.5: Series of ^{129}Xe spectra obtained from rat lungs.

In vivo Experiment

A second set of experiments was performed on a live rat weighting about 500 g. A tube was inserted into the rat's trachea for artificially ventilating the lungs using an animal ventilator (Benson, Minneapolis, USA). The rat was ventilated with 100% oxygen and Halothane (1-2%) for anesthesia. At the end of a ventilatory cycle, the ventilator was shut down and the lungs were inflated with about 5 cc of hyperpolarized ^{129}Xe using a syringe. ^{129}Xe remained in the lungs for a breath-hold of about 5-10 s, while a measurement was made. ^{129}Xe was then released from the lungs and the ventilator was turned back on. A series of spectra were obtained with this procedure, with $TR = 0.5$ s, and these are shown in Fig. 4.5. The SNR of the first spectrum is 77.

T_{1eff} of this series of spectra was $2.73 (\pm 0.10)$ s. Using the flip angle calibration from the previous experiment, the apparent T_1 was estimated to be $6.5 (\pm 0.6)$ s.

Table 4.2 summarizes the measurements obtained from the two rat experiments.

It seems reasonable to use the same flip angle calibration for both rat experiments. In fact, only 10% more RF power was needed to obtain a 90° pulse with a rat compared with a gas phantom, although those samples were completely different.

Table 4.2: Summary of results for the rat lung experiments.

Experiment	TR (s)	Flip angle ($^\circ$)	T_{1eff} (s)	Apparent T_1 (s)	$[O_2]$ %
Deceased	5	16.1 ± 0.1	48.3 ± 0.5	78.6 ± 2.0	2.5
<i>In vivo</i>	0.5	25.9 ± 0.2 (estimated)	2.73 ± 0.10	6.5 ± 0.6	30

Oxygen Effect

It is known that T_1 of ^{129}Xe in lungs depends mainly on the oxygen concentration, and this is not expected to differ for a deceased rat or *in vivo*[89]. The T_1 measurement in the lungs from the deceased rat was performed after the lungs had been emptied and flushed with ^{129}Xe 8 times. Therefore, very little oxygen was present in the lungs, which would depolarise ^{129}Xe and thus shorten T_1 . This can explain the surprisingly long T_1 of 78.6 s obtained compared to literature values. On the other hand, the T_1 measurement acquired in the live rat was performed while the rat was breathing 100% O_2 . Since the residual volume of a 500 g rat is 3.5 ml[88] and 5 ml of hyperpolarized ^{129}Xe were used, it can be assumed that about 30% of oxygen was present at the time of the T_1 measurement.

$1/T_1$ is directly proportional to the oxygen density[89], and the proportionality constant can be interesting to estimate for our magnetic field (1.89 T, Larmor frequency of 22.17 MHz for ^{129}Xe). From our data at 30% oxygen ($\rho_{O_2} = 0.30$ amagat), a proportionality constant of $0.5 \text{ s}^{-1}\text{amagat}^{-1}$ can be extracted, which agrees reasonably well with experimental data reported in gas phantoms corrected for 22.17 MHz[89]. This proportionality constant gives an estimate of 2.5% for

the oxygen concentration present in the lungs of the deceased rat at the time of the measurements. Furthermore, the apparent T_1 in a normally breathing subject ($\rho_{O_2} = 0.10 - 0.26$ amagat) can be estimated, using this proportionality constant, to range between 8 and 20 seconds. Apparent T_1 values from two human volunteers holding their breath with hyperpolarized ^{129}Xe were reported to be 16 and 22 s[33].

4.3 Transverse Relaxation Time Measurement

T_2 relaxation time measurements of the cylindrical gas phantom were performed to demonstrate the feasibility of measuring T_2 of hyperpolarized ^{129}Xe with a CPMG sequence. Table 4.3 summarizes two experiments using different echo times TE . The observed transverse relaxation time (T_2) depends upon the echo-time used due to the diffusion of the nuclei between pulses. In fact, it can be shown that for a CPMG sequence:

$$\frac{1}{T_2^{obs}} = \frac{1}{T_2} + \frac{1}{3}D\gamma^2g^2\left(\frac{TE}{2}\right)^2 \quad (4.1)$$

where D is the diffusion coefficient and g is the gradient of magnetic field (due to field inhomogeneities).

Since the two measurements were performed under the same conditions, D and g can be assumed to be the same for both experiments. The two results observed for T_2 can thus be combined, eliminating D and g from the previous equation, and the true T_2 can be estimated to be 5722 ms.

Table 4.3: CPMG T_2 results for hyperpolarized ^{129}Xe gas.

TE (ms)	T_2 (ms)
20	1807
30	974

4.4 Constant versus Variable Flip Angles

Fig. 4.6 illustrates the Constant and Variable Flip Angle (CFA versus VFA) techniques spectroscopically. Three experiments with 64 pulses were performed: a CFA with angles of 15° , a CFA of 10° , and finally a VFA sequence, as illustrated in Fig. 4.6a. The signals measured using the three techniques are shown in Fig. 4.6b with symbols, while the lines are the theoretical predictions from Eqns. 2.35 and 2.36.

The signals measured follow the theoretical predictions of the CFA very closely. However, some discrepancy appears for individual points in the VFA sequence. This is explained by the limited precision of the software of the NMR console: only integers can be encoded. As a result, an ideal sequence of angles like $[12.0000^\circ, 12.2722^\circ, 12.5638^\circ, 12.8773^\circ, 13.2155^\circ]$ is encoded as $[12^\circ, 12^\circ, 13^\circ, 13^\circ, 13^\circ]$. This is shown in Fig. 4.6a, where the symbols represent the flip angles actually encoded in the sequence, and the lines are the theoretical predictions (Eqn. 2.38 for VFA).

4.5 2D Imaging

For this study of gas phase hyperpolarized ^{129}Xe , image quality using different sequences was studied in terms of Signal-to-Noise Ratio (SNR) and image artifacts. All 2D simulations and experiments were performed with the 10 cc cylindrical cell described earlier. A transverse view of the cell was imaged with the Gradient-Echo technique explained in Section 2.2.

4.5.1 CFA versus VFA Sequences

Imaging can be performed using either a CFA or a VFA sequence. When using a CFA sequence, the signal decreases for each phase-encode step, according to Eqn. 2.36. Some parts of k-space in the phase-encode direction (k_y) are therefore emphasized, whereas other parts are lacking signal. Fig. 4.7 shows schematically the weighting of the different phase encodes due to a CFA sequence for sequential and centric

Figure 4.6: Illustration of the CFA and VFA methods. The flip angle used are shown in (a) and the signal obtained are shown in (b). For both graphs, the symbols represent the experimental data while the lines are the theoretical predictions.

orderings, and for $ZP = 15$. This inhomogeneous coverage of k-space is reflected by features, not belonging to the object, appearing in the image, i.e. artifacts. Those artifacts are only in the phase-encode direction, since the k-space is covered homogeneously in the frequency-encode direction (k_x). A VFA sequence results in a constant signal over time, and thus no artifact should appear in the image.

Figure 4.7: Weighting of k-space with a CFA sequence for (a) sequential, (b) centric, (c) sequential and $ZP = 15$, and (d) centric and $ZP = 15$.

4.5.2 Simulations

Transverse images of the cylindrical cell were simulated numerically for several flip angle sequences and phase-encode orderings. The simulations were performed in a manner very similar to a gradient-echo sequence, with the following algorithm:

For $n = 1$ to N , N being the matrix size.

- the object is created with a signal S_n given by Eqn. 2.35
- a line $k_y(n)$ of the 2D Fourier transform of the object, chosen to follow a given phase-encode strategy, is used to map k-space

When k-space is entirely mapped, an inverse Fourier transform is used to reconstruct the image.

All simulated images were noise-free and were reconstructed in the absence of any filter. Image profiles were generated by taking the pixel values along a line in the center of the object in the phase-encode direction. The signal at the center of the object was used to estimate the SNR of an image. For an artifact-free image, the signal at the center is proportional to the total signal measured, i.e. $S_{tot} = \sum_{i=1}^N S_n$. However, image artifacts alter the signal at the center of the image, therefore two images acquired using the same flip angle but with different k-space coverings will result in different image intensities at the center of the image.

Fig. 4.8a and b show simulated profiles along the phase-encode direction for CFA ordered sequentially and centrically respectively. The flip angles were varied from 3 to 15°. With CFA, the signal acquired decreases as a function of time, and the decrease is more significant for large flip angles. When using sequential phase-encode ordering, the total signal encoded is maximum for a certain optimum flip angle depending on the number of views. For 128 phase-encodes or views, the optimum flip angle which maximises the SNR is given by $\alpha_{opt} = \text{atan}\sqrt{\frac{2}{N}} = 7.125^\circ[90]$. In fact, in Fig. 4.8a, we see that the simulated image intensity increases with flip angle up to this optimum flip angle. Also, when using the sequential phase-encode ordering, the high frequency components of the object are emphasized. Edge enhancement

is thus apparent in the simulated phase profiles, and becomes more significant with larger flip angles. With centric ordering, the high frequency information is reduced resulting in obvious blurring, i.e. the edges are rendered indistinct and smeared. However, the relative signal at the center of the image is quite large and is increasing with increasing flip angles. In fact, the resulting signal of an image depends mainly on the signal acquired at the center of k-space. With centric ordering, the center of k-space is sampled first, and large signals are acquired for large flip angles, resulting in a high signal at the center of the image.

Sequential and centric phase-encode ordering slice profiles are shown in Fig. 4.10a and b respectively for VFA. For a perfect VFA, ordering sequentially or centrically leads to identical images since the signal over k-space is constant. Since a perfect VFA sequence relies on a good flip angle calibration, the effect of mis-calibrating the flip angle was also studied. Fig. 4.9 shows the expected measured signal for mis-calibrated VFA sequences. When the 90° pulse is overestimated, the flip angles used are larger than expected and most of the signals measured are larger than with a perfect VFA.

Image profiles from mis-calibrated VFA sequences are shown in Fig. 4.10. For the sequential ordering, the effect of miscalibrating the flip angle is not very important. Even a 10% underestimate causes minor artifacts and reduces the signal by only 4% relative to the perfect VFA. For centric ordering however, the signal can be increased more significantly from overestimation of the flip angle, although a small amount of ripple and blurring appear. In both cases however, underestimating the flip angle leads to reduced signals at the center of the image and to some artifacts, and is thus not desirable.

Overall, in terms of signal intensity, the centric CFA appears to perform best, although with the compromise of significant blurring. On the other hand, overestimated VFA with centric phase-encode ordering still has a reasonable signal without significant artifacts.

The image profiles were studied further by using the modified sequential and centric ordering for several ZP numbers. Fig. 4.11 shows the result for ZP sequential encoding. For both VFA and CFA, significant artifacts occur with this method, and

Figure 4.8: Profiles along the phase-encode direction for CFA (top) sequentially and (bottom) centrically ordered.

Figure 4.9: Signal as a function of RF pulse number for mis-calibrated VFA.

this is simply because of the large discontinuity in the coverage of k -space, as shown in Fig. 4.7. The ZP centric has the advantage of being smooth over k -space. Centric ZP was studied for a range of flip angles (CFA) and ZP numbers. The images were analyzed in terms of signal at the center of the object (mean of four pixels at the center of the image), and in terms of uniformity U of the entire object[83]:

$$U = 1 - \frac{(\text{maximum pixel value}) - (\text{minimum pixel value})}{(\text{maximum pixel value}) + (\text{maximum pixel value})} \quad (4.2)$$

for all pixels covered by the original object (with this definition, a uniformity of 100% is desired). Fig. 4.12 and 4.13 display contour plots of the resulting signal and uniformity. With the criteria of keeping the uniformity larger than 90 or 95% with a signal larger than what is achieved with a VFA sequence, it is found that a range of angles from 6 to 12° are acceptable with ZP ranging from 1 to 30.

Figure 4.10: Profiles along the phase-encode direction for VFA (top) sequentially and (bottom) centrically ordered.

Figure 4.11: Profiles along the phase-encode direction for (top) sequential CFA of 7° and (bottom) 20% overestimated VFA for several ZP numbers.

Figure 4.12: Signal of simulated images with ZP centric.

Figure 4.13: Uniformity of simulated images with *ZP* centric.

4.5.3 Experimental Results

Fig. 4.14 shows three transverse images of the same cell using the following sequences: (a) centrically phase-encode ordered CFA of 13° , (b) sequentially phase-encode ordered CFA of 13° , and (c) sequentially phase-encode ordered VFA. Gradient-echo imaging was used with a repetition time (TR) of 38 ms and an echo time (TE) of 16 ms. A matrix size of 128 by 128 pixels was used, with a total field-of-view of 160 mm x 160 mm. Two averages were acquired. The images were reconstructed from the original data without filtering. The profile along the phase-encode direction, represented by the dotted lines, is displayed for all images.

Figure 4.14: Experimental images and profiles along the phase-encode direction obtained with (a) centric CFA, (b) sequential CFA and (c) sequential VFA.

In (a), an important amount of blurring occurs along the phase-encode direction

due to a high signal in the low k -values of the data and a lack of signal in the high k -values. On the other hand, edge enhancement appears in (b), since most of the signal was collected for high values of k_y . As expected, the VFA sequence (c) results in a homogeneous image without artifact.

Although the experimental image profiles can be contrasted for artifacts, the resulting signals are difficult to compare because they depend on the initial magnetization (recall Eqn. 2.35 and 2.36). In order to rescale the images for the purpose of a quantitative comparison, the initial magnetization for each of them must be known. The initial magnetization can be estimated by analyzing the received signal at the center of k -space and back calculating to the initial magnetization, knowing the phase-encode strategy and the flip angle used. With this approximate technique, the relative signals can be compared. Fig. 4.15 shows the three experimental profiles without and with correction for the initial magnetization, as well as the simulated profiles corresponding to the experiments. Simulations and experiments are in fairly good agreement, for both image artifact and signal intensity. We notice however, that the blurring in the experimental centric CFA image is larger than expected.

4.6 3D Imaging

4.6.1 Multislice Imaging

For proton MR imaging, the method of choice for three-dimensional (3D) imaging is often multislice imaging. A first slice is excited and imaged, and while the magnetization recovers, other slices are imaged. Imaging a number of slices can therefore be as fast as imaging only one.

Artifacts due to overlapping of contiguous slices are well known and documented[91]. They result from imperfect RF pulses, as described in Section 2.2.1. Gaps between slices are commonly used to avoid artifacts.

For imaging hyperpolarized ^{129}Xe , time saving by interleaved slice imaging is not an advantage since TR is generally set as short as possible. Therefore, imaging N slices takes N times longer.

Figure 4.15: Comparison between experimental and simulated images for signal intensity and artifacts. The corrected experimental image profiles are only approximate, as explained in the text.

Furthermore, the slice profile resulting from imperfect RF pulses evolves as a function of the number of excitations. This evolution happens because ^{129}Xe nuclei on the edge of the slice profile see a smaller amount of RF power and are tipped by a smaller angle than nuclei in the center of the slice. Their loss of magnetization is therefore much less than for nuclei in the center of the slice. Whereas the signal from the center of the slice has almost disappeared after several RF pulses, signal from the edges may still be important. The slice profile evolution can be visualized experimentally by applying a slice-selective gradient during the RF pulse, and a gradient along the same direction during the read-out. The Fourier transform of the signal acquired is thus a projection of the entire cell along the slice. The experimental results are shown in Fig. 4.16, where the slice profile is plotted as a function of the RF pulse number of a CFA sequence. The slice profiles for the first and the 100th acquisitions are also shown in Fig. 4.16.

Mugler has estimated that slice-selective imaging, as opposed to non-selective imaging in 2D, results in a higher SNR[90]. We believe, however, that artifacts could also result from the evolving slice profile.

4.6.2 3DFT Imaging

Since the magnetization from the whole sample is tipped at each RF pulse and participates in the signal, a SNR improvement of $\sqrt{N_z}$ is usually obtained with the 3DFT sequence compared to multi-slice imaging with the same number of slices N_z .

One disadvantage of the sequence is the long acquisition time for proton imaging, however this is not a problem for hyperpolarized ^{129}Xe imaging. Another disadvantage is that a minimum number of “slices”, i.e. of phase-encodes along the z -axis, are required for an artifact-free Fourier transform along the slice direction. With our system, composed of older-generation gradients, only 16 z -phase-encodes could be obtained, resulting in significant artifacts due to the limited field of view sampled in k -space. Newer gradient systems should allow a demonstration of the feasibility and usefulness of 3DFT GE for hyperpolarized ^{129}Xe imaging.

Figure 4.16: Slice profile time evolution. On the right are shown the slice profiles for the first and the 100th RF pulses.

4.7 Discussion

The preceding sections demonstrate the feasibility of hyperpolarized ^{129}Xe gas phase spectroscopy and imaging. Flip angle calibrations, T_1 and T_2 measurements were successfully performed. 2D imaging was demonstrated and studied for different flip angle sequences and phase-encoding strategies. Comparisons between simulated and experimental data showed that the theory is well understood and that experiments can be predicted.

Our study of hyperpolarized ^{129}Xe gas phase imaging was limited to gradient-echo MR imaging. Gradient-echo imaging, as with all spin-warp imaging, has the advantage of producing a uniformly sampled k-space, reducing the complexity of the reconstruction to a simple 2D or 3D Fourier transform. Gradient-echo allows rapid scanning to be performed. This rapid scanning is essential for flow or vessel imaging, and for 3DFT imaging. It is thus becoming a method of choice for fast imaging, with sequences such as FLASH. Imaging hyperpolarized ^{129}Xe benefits from fast gradient-echo imaging, which minimizes losses of magnetization due to T_1 relaxation. Other MR imaging sequences are available and currently used by other investigators.

Projection reconstruction has been used by the group of Johnson[25] for hyperpolarized ^3He lung MR imaging. This technique uses the same reconstruction algorithm as the spatial encoding of x-ray Computed Tomography (CT), i.e. a filtered back projection. For MR imaging, projection encoding is performed by sampling k-space radially from the center, as opposed to the cartesian grid sampling of gradient-echo imaging. The technique does not require any gradient or spin echo, and the acquisition can start immediately after the RF pulse, shortening the acquisition times. If T_2^* is short, this can be an important advantage over gradient-echo imaging. Furthermore, the signal is not encoded at the beginning of all acquisitions (which are at the center of k-space), and thus provides a means of calibrating the flip angle while imaging. The problems associated with projection reconstruction techniques arise from oversampling the central part of k-space and result in image

artifacts. Filters are applied along with the reconstruction to interpolate the signal at large k -values and reduce the artifacts, at the expense of spatial resolution however[92].

Echo-Planar Imaging (EPI) has been investigated by Saam and his co-workers[93]. With this technique, the entire k -space is mapped with a single-shot acquisition, by tipping all the available magnetization into the transverse plane and using gradient-echoes. This sequence is performed in a very short time, but requires high gradient strength and speed.

Swanson et. al. have used Chemical-Shift Imaging (CSI) for imaging *in vivo* dissolved phase ^{129}Xe [50]. This technique provides chemical shift information, but suffers from long acquisition times and low resolution.

When imaging hyperpolarized ^{129}Xe , all MR imaging sequences have in common a k -space weighting due to the non-renewable magnetization. As shown experimentally and with simulations, significant artifacts result from such a weighting. Various phase-encode orderings and CFA were investigated, and it seems that a VFA sequence is preferable, provided that the flip angle is not underestimated.

Chapter 5

Dissolved Phase Spectroscopy and Imaging

The ^{129}Xe atom possesses a large electron cloud which gets easily deformed by its environment. As a result, ^{129}Xe does interact with other atoms and molecules, and it does get dissolved in various solvents. For example, ^{129}Xe dissolves in water with an Ostwald coefficient of 0.1051[94], which means that the concentration of ^{129}Xe in water is 0.1051 times the concentration of ^{129}Xe in the gas phase. Moreover, ^{129}Xe has a high affinity for lipids: the Ostwald coefficient of ^{129}Xe in lipids containing 96% egg phosphatidylcholine and 4% egg phosphatidic acid is 1.76[95]. Because of its high affinity for lipids, ^{129}Xe readily dissolves in the blood stream and in lipid-rich tissues. Therefore, hyperpolarized ^{129}Xe is a good candidate for *in vivo* dissolved phase imaging.

On the other hand, the relaxation rate of ^{129}Xe is increased in the dissolved phase, compared to the gas phase. Dissolved ^{129}Xe is constantly surrounded by molecules. As described in Section 2.1.2, relaxation of ^{129}Xe nuclei is induced by fluctuations of magnetic field due to coupling with other nuclear moments. Dipolar interactions with the surrounding nuclear moments (of protons generally), which vary as $1/r^6$, where r is the internuclear distance, are continually stimulating the ^{129}Xe nucleus

to relax. As a result, the T_1 relaxation time of ^{129}Xe dissolved in biological tissues varies between a few to 15 or 20 seconds[49], as opposed to hours in the gas phase. Furthermore, paramagnetic molecules contained in blood (dissolved molecular oxygen (O_2) and deoxyhemoglobin) considerably increase the relaxation rate, thus decreasing the T_1 relaxation time to values of $6.4 (\pm 0.5)$ s and $4.0 (\pm 0.4)$ s for oxygenated and deoxygenated blood respectively[48]. This relaxation time is of the same order as the transit time of ^{129}Xe in blood from the lungs to tissues, therefore some hyperpolarized ^{129}Xe can reach the target organs, however the magnetization is significantly diminished during that time.

Two methods can deliver ^{129}Xe beyond the lungs. Ventilation delivery relies on breathing a large amount of hyperpolarized ^{129}Xe , of which a certain quantity is taken up by the blood circulation at the lung capillaries. Afterwards, hyperpolarized ^{129}Xe travels within the vascular system throughout the entire body, and dissolves in tissues. This method requires a large amount of hyperpolarized gas to be produced, since the magnetization is reduced in the lungs where T_1 is approximately 20 seconds[33], and the concentration of ^{129}Xe inhaled is diluted in the blood stream. Furthermore, ^{129}Xe gas must be breathed in small concentrations (about 30%), since it is a general anesthetic at concentrations above 70%.

The second method of delivering hyperpolarized ^{129}Xe is to intravenously inject a biocompatible solution in which hyperpolarized ^{129}Xe had been previously dissolved. This method does not require a large amount of hyperpolarized gas, and could allow the targetting of ^{129}Xe to a particular area of the body.

A suitable solution would be chemically and biologically inert, and ideally would exhibit a high ^{129}Xe solubility, a long intrinsic T_1 relaxation time, and would protect hyperpolarized ^{129}Xe from the paramagnetic molecules of the blood.

The next sections describe the preliminary results obtained with NMR of dissolved hyperpolarized ^{129}Xe . In particular, several potential injectable solutions for hyperpolarized ^{129}Xe were studied: saline, liposomes and perfluorocarbons. All experiments were performed with the methodology described in Chapter 3, and using a 1 cm (i.d.) RF transmit/receive coil for NMR. Following the results, theoretical calculations explore the expected SNR and features of dissolved phase imaging in

phantoms. The following chapter (Chapter 6) discusses these results and attempts to compare different injection strategies for the purpose of dissolved hyperpolarized ^{129}Xe imaging *in vivo*.

5.1 Saline Solution

Hyperpolarized ^{129}Xe dissolved in a saline solution was studied for two reasons. First, it is certainly a potential injectable solution for hyperpolarized ^{129}Xe , since it is already commonly used for intravenous injections and it is inert. Second, because of its availability and low cost, it is ideal for developing dissolving procedures and studying the limitations of the NMR techniques already in place for the gas phase.

A saline solution (phosphate buffer saline (PBS), 10 mM) was prepared from distilled water. The saline solution was at room temperature prior to and during NMR experiments.

5.1.1 Chemical Shift

Fig. 5.1 shows two typical spectra obtained from samples of saline containing dissolved hyperpolarized ^{129}Xe . In Fig. 5.1a, hyperpolarized ^{129}Xe gas was above the saline solution for reference. The spectrum in Fig. 5.1b demonstrates that no gas peak from ^{129}Xe gas bubbles in saline appears when the gas on top of the saline is removed. For both spectra, the chemical shifts are referenced to the ^{129}Xe gas resonance. The chemical shift of ^{129}Xe in saline was found to be $194.7(\pm 1.7)$ ppm. This is in agreement with a chemical shift of 196 ppm for ^{129}Xe in water[96].

5.1.2 Flip Angle Calibration

The technique described in Section 3.3.1 can generally not be used for flip angle calibration of dissolved hyperpolarized ^{129}Xe . In fact, for the condition $t \ll T_1$ to be true within 1%, $T_1 > 600$ s is required since the measurements can last for 5-6 s. T_1 of ^{129}Xe dissolved in various solvents is generally not larger than 160 s[84]. Instead,

Figure 5.1: NMR spectra of hyperpolarized ^{129}Xe dissolved in saline. In (a), both gas and dissolved phases were present in the syringe. In (b), no gas phase was present in the syringe, and no gas phase peak can be observed, showing that no ^{129}Xe gas bubbles were stable in the liquid.

the flip angle was calibrated by a standard proton procedure, which is to tip the magnetization by different flip angles until no signal is measured, which corresponds to a flip angle of 180° . For hyperpolarized ^{129}Xe , this method is more difficult since the amplitude of the signal measured depends on the initial magnetization and the previous RF pulses applied. When the flip angle chosen was too large (larger than about $15\text{-}20^\circ$) and relatively large signals were obtained, a new sample was prepared.

5.1.3 T_1 Measurement

Working with dissolved ^{129}Xe is a multi-step process which introduces numerous uncertainties in addition to the NMR uncertainties. These include: sample preparation, temperature, oxygenation, and others. Furthermore, lower SNR is obtained with dissolved ^{129}Xe , making the measurements more difficult to reproduce.

For T_1 measurements, the repetition time (TR) and the flip angle (α) must be chosen such that the magnetization is sampled many times during its decay. Choosing a very large flip angle results in a very fast decay, whereas too small a flip angle results in noisy data. The most satisfying results were obtained, as shown next, for a flip angle of 23° and studying a wide range of repetition times to account for the additional uncertainties of dissolved phase ^{129}Xe .

For the results shown here, the saline was degassed before adding ^{129}Xe and the NMR measurement, by pumping directly on the liquid for about 2-3 minutes or as long as dissolved gases were bubbling out of the liquid.

Several different RF pulse series, separated by repetition times varying between 3 and 30 s, were used. All T_1 measurements were done with the same flip angle α of $23.4 (\pm 0.8)^\circ$. Fig. 5.2 shows a typical T_1 measurement of hyperpolarized ^{129}Xe dissolved in degassed saline, where the error bars represent the standard deviation of the noise in the baseline spectra. The following three-parameter equation was fitted to all T_1 measurements, by a non-linear least-squares fit using a Levenberg-Marquardt method[86]:

$$S_n = S_i e^{-t/T_{1eff}} + S_0 \quad (5.1)$$

where T_{1eff} is given by Eqn. 2.33.

Figure 5.2: T_1 measurement of hyperpolarized ^{129}Xe dissolved in saline.

Fig. 5.3 displays the inverse of T_{1eff} as a function of $1/TR$ for all measurements. The error bars represent the errors on the estimation of T_{1eff} . According to Eqn. 2.33, the relaxation rate ($1/T_1$) is given by the intercept of the graph, and $-\log(\cos \alpha)$ corresponds to the slope. In agreement with the flip angle calibration performed by the 180° method, the flip angle was determined to be $21.13 (\pm 0.12)^\circ$ using the graph. And T_1 was found to be $97.2 (\pm 1.2)$ seconds. T_1 of saline has been reported to be 66 s at 9.4 T[47]. Other investigators have measured T_1 values longer than a hundred seconds[97].

Effect of Dissolved Oxygen

Since molecular oxygen is paramagnetic, it is expected that dissolved oxygen will increase the T_1 relaxation rate of dissolved ^{129}Xe . T_1 was studied for three samples of saline: one at equilibrium with 1 atm of air (26% $[\text{O}_2]$), a second one in which nitrogen gas had been bubbled for more than an hour, and a third one degassed,

Figure 5.3: $1/T_{eff}$ versus $1/TR$ from all measurements of ^{129}Xe dissolved in degassed saline.

as explained above, by directly pumping on the liquid. No statistically significant change in the T_1 relaxation time was measured between the three saline samples. This is in agreement with the oxygenation effect of T_1 of ^{129}Xe dissolved in water[98]. This consistency in T_1 could be due to the relatively low gas solubilities in saline. At 25°C, the Ostwald coefficient of ^{129}Xe and O_2 in water are of 0.1051[94] and 0.031[99] respectively.

5.1.4 T_2 Measurement

T_2 of ^{129}Xe dissolved in saline was measured using a CPMG sequence (as explained in Section 3.3.2). Fig. 5.4 shows the results using an echo time (TE) of 32 ms. T_2 was found to be 48.5 (± 0.2) s. T_2 of dissolved ^{129}Xe in water has been studied as a function of oxygenation at 9.4 T[98]. Interpolating this reported data to a concentration of oxygen of 26% gives a T_2 of about 33 s. The disagreement between our T_2 and the reported T_2 could be due to the different echo time used (32 ms in our case compared to 200 to 1200 ms for the reported values) or the uncertainty in the reported data ($\pm 30\%$).

In summary, saline provided a good medium for dissolving ^{129}Xe and studying the T_1 and T_2 relaxation times in the dissolved phase. However, the low ^{129}Xe solubility prevents saline from being an efficient biocompatible carrier solution for injection delivery of hyperpolarized ^{129}Xe .

5.2 Liposomes

Solutions containing liposomes were studied as a medium for dissolving hyperpolarized ^{129}Xe . Liposomes are vesicles made of a bilayer lipid membrane. Liposomes can potentially trap ^{129}Xe atoms and carry them in the blood circulation with a longer relaxation time. Also, the affinity of ^{129}Xe for lipids could increase the solubility of ^{129}Xe as compared to saline, leading to improved signal. Furthermore, liposomes can be tagged with molecules or antibodies for targeting to specific organs or tumours.

Liposomes were made from phospholipids using the following method[100]. The

phospholipids, namely dioleoylphosphatidylcholine (DOPC) (Avanti Polar Lipids, Alabaster, AL), were first dissolved in a solution of chloroform/methanol. The solvent was evaporated with a stream of dry nitrogen gas and then placed under vacuum, while the phospholipids were deposited as a thin film on the surface of the glass vessel. The dry lipid films were then suspended in a saline solution (phosphate buffer saline (PBS), 10 mM). Unilamellar vesicles were produced by freeze-thawing the lipid suspension 5 times followed by extrusion through polycarbonate membranes 10 times. The pore size used was of 100 nm, resulting in liposomes of sizes around 167 (± 2) nm, measured by photon correlation spectroscopy using the Submicron Particle Sizer-Autodilute (Model 370, NICOMP Particle Sizing Systems, Santa Barbara, CA). Fig. 5.5 shows a schematic of the resulting saline solution containing saline-filled liposomes.

5.2.1 Chemical Shift

Once the liposome solution was prepared, hyperpolarized ^{129}Xe was dissolved in the liposome solution for NMR analysis. The spectrum obtained from hyperpolarized ^{129}Xe dissolved in a liposome solution, as shown in Fig. 5.6, resulted in one dissolved peak at 194.4 (± 2.0) ppm. The chemical shift of the dissolved peak is the same as the one observed in saline (Fig. 5.1, 194.7 (± 1.7) ppm).

5.2.2 T_1 Measurement

T_1 measurements of hyperpolarized ^{129}Xe dissolved in the liposome solution were performed using different repetition times. The liposomes are usually stored at 4°C, and the experiments were performed over a full day. Problems due to temperature changes and liposome degradation are believed to have caused reproducibility problems in the measurements. However, all measurements showed T_{1eff} ranging between 30-60 s, i.e. shorter or of the same order than the corresponding ones observed in saline.

Following the experimental results, we cannot conclude that any ^{129}Xe was effectively present inside the liposomes or in the lipid bilayer. If ^{129}Xe was present

Figure 5.4: T_2 measurement of hyperpolarized ^{129}Xe dissolved in saline.

Figure 5.5: Schematic of the liposome solution.

Figure 5.6: NMR spectrum of hyperpolarized ^{129}Xe dissolved in a liposome solution.

in the lipid bilayer, a different peak chemical shift would be expected in the spectrum. Even ^{129}Xe in the aqueous compartment inside the liposomes would produce a peak at a slightly different chemical shift. The T_1 relaxation study does not show any improvement over the saline. Also, even if the solubility was not quantitatively measured, no obvious increase in the signal was observed.

A few issues remain unresolved. The essential one being if, by any method, hyperpolarized ^{129}Xe can get trapped inside the liposomes, is the T_1 relaxation time going to be preserved in blood? To answer this question, an efficient method of trapping ^{129}Xe inside must be found, as well as a way of discriminating between ^{129}Xe inside and outside the liposomes. Then, mixtures of fresh blood and liposome solution can be studied to determine the exchange time between the compartments. This will be discussed further in Chapter 6.

5.3 Perfluorocarbons

Fluorocarbons, synthetic molecules consisting principally of fluorine and carbon atoms, were historically used for carrying oxygen *in vivo* because of their biological and chemical inertness, and their high O_2 and CO_2 solubility[101]. Typically, they can dissolve 40 to 50 vol. % of O_2 compared to 2.3% in the case of water. Intravenously administered fluorocarbons are excreted unmetabolized through exhalation[101].

The perfluorooctyl bromide (PFOB), also called perflubron, or *F*-octyl bromide, is one of the few fluorocarbon candidates for blood substitutes. Its molecular structure is:

Fluorocarbons are not miscible in water and must be administered as emulsions in an aqueous phase of physiological pH and osmotic pressure. A surface active agent, commonly egg yolk phospholipid (EYP), is used for emulsification. Highly concentrated emulsions can be produced, with more than 90% of the weight as fluorocarbons, producing efficient oxygen carriers[101].

Fluorocarbons are candidates for dissolving hyperpolarized ^{129}Xe , since they act as a simple solvent for dissolving any type of gas. In fact, the Ostwald solubility of ^{129}Xe in perfluorotributylamine is 1.354 compared to 0.08 in blood plasma and 0.0834 in water (at 37°C) [94, 82].

An emulsion was made by sonication of 90% w/v PFOB (Sigma-Aldrich, Canada), 4% egg yolk phospholipids (EYP) (Avanti Polar Lipids, Alabaster, AL) and water. The emulsion consists of tightly packed droplets of PFOB constrained by a monolayer of lipids, surrounded by water, as shown in Fig. 5.7. The droplets had a range of sizes, varying from 2 to $30\text{ }\mu\text{m}$.

Figure 5.7: Optical micrograph and schematic of the PFOB emulsion.

Figure 5.8: NMR spectrum of hyperpolarized ^{129}Xe dissolved in a PFOB emulsion.

5.3.1 NMR Spectroscopy

Hyperpolarized ^{129}Xe was dissolved in a PFOB emulsion for NMR measurements. Several spectra were acquired while a series of RF pulses were performed. Fig. 5.8 displays a spectrum of the PFOB emulsion with a ^{129}Xe gas phase for reference. A first dissolved peak, at 104 ppm, is due to ^{129}Xe dissolved in the PFOB droplets, and a second dissolved peak at 193 ppm corresponds to ^{129}Xe in the aqueous compartment. The fact that the two peaks are well resolved in the spectrum indicates that the two compartments are in medium or slow exchange relative to the chemical shift differences.

Fig. 5.9 shows a series of spectra obtained from the PFOB emulsion. Only the two dissolved peaks are shown, and the spectra were broadened for clarity. This series of spectra clearly shows the rapid decrease of ^{129}Xe magnetization in the aqueous compartment compared to the ^{129}Xe magnetization in the PFOB droplets.

Figure 5.9: Series of spectra from hyperpolarized ^{129}Xe dissolved in a PFOB emulsion.

The T_1 relaxation time in the aqueous compartment was estimated to be about 80 s. and in the PFOB between 100 and 200 s. T_1 of ^{129}Xe in PFOB is reported to be 110 s[102]. The different T_1 in the two compartments suggests that the chemical exchange takes place in a long time compared to the relaxation time. This is very surprising and should be further investigated, since the chemical exchange time has been estimated to be on the order of milliseconds[64], implying rapid exchange and hence a single T_1 relaxation time. This will be discussed further in Chapter 6.

In summary, the preliminary results with PFOB emulsions indicate that they have potential as biocompatible carrier solution for injection delivery of hyperpolarized ^{129}Xe . Some more work is required, as discussed in the next chapter.

5.4 Dissolved Phase Imaging

Dissolved phase ^{129}Xe adds the new challenge of short T_1 relaxation times. The available magnetization decays with a time constant on the order of seconds to minutes as opposed to tens of minutes and hours in the gas phase, as shown in the previous sections. This section discusses expectations for imaging the dissolved phase in phantoms, i.e. in a syringe for example. CFA versus VFA flip angle sequences, and centric versus sequential phase-encode ordering are examined, to compare with gas phase imaging presented in Chapter 4.

For given imaging parameters TR and N , the SNR per voxel of the resulting image is proportional to the signal acquired at the center of k-space:

$$\left(SNR\right)_{CFA}^{seq} \sim M_i[Xe]\Delta V \sin \alpha (\cos \alpha)^{N/2} e^{-(N/2)TR/T_1} \quad (5.2)$$

$$\left(SNR\right)_{CFA}^{cen} \sim M_i[Xe]\Delta V \sin \alpha \quad (5.3)$$

$$\left(SNR\right)_{VFA} \sim M_i[Xe]\Delta V \sin \alpha_0 = M_i[Xe]\Delta V \sin \left(\tan^{-1} \left(\frac{e^{-NTR/T_1}}{\sqrt{N}} \right) \right) \quad (5.4)$$

where M_i is the initial magnetization, $[Xe]$ the ^{129}Xe density and ΔV the voxel size. As expected, the largest SNR is obtained for centric phase-encode ordering since k-space is sampled first, while the magnetization has not decayed yet due to the RF pulses and T_1 relaxation. Furthermore, in the case of dissolved hyperpolarized ^{129}Xe imaging where T_1 is much shorter, the factor e^{-NTR/T_1} is small and reduces significantly the SNR of both the sequential and the VFA sequences. Centric ordering could then be a method of choice for dissolved phase imaging.

The SNR per voxel depends also on the number of ^{129}Xe atoms in the voxel, i.e. the ^{129}Xe density. According to Henri's law, the amount of gas dissolved in a liquid depends on the partial pressure of the gas. In fact, the Ostwald coefficient of solubility L is:

$$L = \frac{\text{Volume of the absorbed gas}}{\text{Volume of the absorbing liquid}} \quad (5.5)$$

and can be rewritten as

$$L = \frac{\text{Concentration of gas in the liquid phase}}{\text{Concentration of gas in the dissolved phase}}. \quad (5.6)$$

Therefore,

$$[^{129}\text{Xe}]_{dissolved} = L[^{129}\text{Xe}]_{gas} \quad (5.7)$$

at equilibrium. For saline, $L = 0.1178$ at 20° and the concentration of ^{129}Xe is much lower than in the gas phase[94]. For PFC however, $L = 1.513$ at 20° and the density is higher[94].

Overall, the SNR of dissolved ^{129}Xe is decreased due to shorter T_1 relaxation times but can be increased if the solubility is high. An image with $N = 128$ and $TR = 0.5$ s of gas phase (assuming a T_1 of 35 minutes) in equilibrium with ^{129}Xe dissolved in PFC (assuming a T_1 relaxation of 110 s) would give:

$$\frac{SNR_{dissolved}}{SNR_{gas}} = 1.15 \quad (5.8)$$

Now, imaging dissolved ^{129}Xe *in vivo* is a slightly different story. The ^{129}Xe atoms must be delivered to the tissues of interest by the blood circulation. The density of atoms in the tissues depends on the density in the blood pool and the partition coefficient of the tissues. The magnetization of the ^{129}Xe nuclei depends on the initial magnetization and the T_1 relaxation times *in vivo* in the different compartments (blood, tissues). Chapter 6 explores and discusses the expected SNR using injection delivery of hyperpolarized ^{129}Xe dissolved in a biocompatible carrier solution.

Chapter 6

Optimizing the Injection Delivery Methods for Hyperpolarized ^{129}Xe : Discussion and Future Work

6.1 Applications of Injection Delivery of Hyperpolarized ^{129}Xe

In Chapter 5, the feasibility of dissolving hyperpolarized ^{129}Xe in saline and PFOB emulsions was demonstrated, allowing NMR experiments to be performed. Also, liposomes were investigated, however some more work is needed to fully benefit from their targeting and encapsulating properties. The following sections illustrate some applications foreseen for MR imaging of hyperpolarized ^{129}Xe delivered *in vivo* by injection.

6.1.1 Angiography

Angiography is the imaging of blood vessels with the use of a contrast agent. The only signal of interest is the one coming from inside the blood vessels. In fact, an absence of background signal from the tissues increases the contrast of the blood

vessel images. Injection delivery of hyperpolarized ^{129}Xe tightly trapped in particles would be very useful for angiography. Particles like liposomes and PFOB droplets in an emulsion should be further investigated for this purpose.

6.1.2 Blood Flow Imaging

Blood flow is determined by measuring the concentration of a freely-diffusible tracer in a tissue as a function of time, knowing the arterial concentration of the tracer at all times. Accurate blood flow measurements thus require a measure of both the tissue concentration and the arterial concentration of a freely-diffusible tracer. PFOB emulsions could provide the two measurements at once. In fact, the two well resolved peaks of the emulsion (as shown in Section 5.3.1: the tissue peak at ~ 200 ppm and the PFOB peak at ~ 100 ppm) could provide the tissue and arterial concentrations respectively.

6.1.3 Tumour Imaging

Detection of tumours could be another application for hyperpolarized ^{129}Xe dissolved in PFOB emulsions. Detection of tumours has been reported with PFOB by ^{19}F MR imaging[103]. PFOB emulsions are known to circulate in the blood circulation without leaking in normal capillaries. They accumulate in the reticuloendothelial system. However, PFOB emulsions have been shown to leak through gaps in the tumour vascular endothelium, resulting in an accumulation in tumour extracellular space, allowing tumour imaging to be performed.

The SNR of hyperpolarized ^{129}Xe in a PFOB emulsion should be about 40 times the SNR from ^{19}F nuclei, as calculated using Eqn. 6.16, with the density of ^{19}F atoms in PFOB. Depending on the actual T_1 relaxation time of ^{129}Xe in PFOB *in vivo* and other losses *in vivo*, hyperpolarized ^{129}Xe imaging in PFOB could be very promising for tumour detection.

6.1.4 Tissue Characterization

Hyperpolarized ^{129}Xe in different tissues exhibits different chemical shifts and T_1 and T_2 relaxation times[49, 98]. Chemical shift imaging (CSI) of hyperpolarized ^{129}Xe *in vivo* could provide tissue characterization based on chemical shift differences. Also, tissue types could be differentiated by T_1 or T_2 -weighted images using GE imaging.

6.2 Cost Comparison

A comparison of the costs associated with inhalation and injection delivery methods of hyperpolarized ^{129}Xe further supports the feasibility of injection delivery. In fact, a typical inhalation study can require about 10 to 20 liters of, 80% enriched xenon. The actual market cost of 10 liters of 80% enriched ^{129}Xe is of 3000\$U.S. An injection study uses about half a liter of ^{129}Xe , for a cost of 150\$U.S. The cost of the biocompatible solution must be added to the cost of the ^{129}Xe gas. Using 30 ml of PFOB emulsions, for example, can cost around \$400. So, assuming that the costs of the laser-polarization technique would be identical for both delivery methods, an inhalation delivery can be about 7 times more expensive than an injection delivery.

6.3 A Model of Injection Delivery

Despite the interest of injection delivery, a crucial question remains: would this delivery method provide *in vivo* tissue magnetizations of hyperpolarized ^{129}Xe large enough to be imaged? Also, which characteristics of a novel biocompatible solution would maximize the tissue magnetization? To help answer these questions, a compartmental model was used to predict the hyperpolarized ^{129}Xe magnetization in the brain following different types of injection. The model is a modification of the one developed for continuous inhalation of hyperpolarized ^{129}Xe by Peled et al[45] and extended by Martin et al[42]. The model is as follows.

According to Fick's principle, the quantity of ^{129}Xe taken up by a tissue per unit time is equal to the quantity of ^{129}Xe delivered by the arterial blood minus the

quantity carried away by the venous blood[104]:

$$\frac{dC_i}{dt} = F_i(C_a - C_v) \quad (6.1)$$

where F_i is the blood flow (in ml/min) and C_i , C_a and C_v are the tissue, arterial and venous concentrations of ^{129}Xe respectively. It is generally assumed that the tissue concentration is in equilibrium with the venous concentration:

$$C_i = \lambda_i C_v \quad (6.2)$$

where λ_i is the partition coefficient for ^{129}Xe in the tissue, or the ratio of the solubility of ^{129}Xe in tissue and blood. Then:

$$\frac{dC_i}{dt} = F_i \left(C_a - \frac{C_i}{\lambda_i} \right). \quad (6.3)$$

In the case of hyperpolarized ^{129}Xe , the magnetization per unit of volume in the tissue is the parameter of interest, since it is directly proportional to the MR signal. The magnetization is related to the concentration of ^{129}Xe except that the T_1 relaxation of ^{129}Xe is taken into account. The following equation correctly describes the evolution of the magnetization in the tissue:

$$\frac{dM_i}{dt} = F_i M_a - \left(\frac{F_i}{\lambda_i} + \frac{1}{T_{1i}} \right) M_i. \quad (6.4)$$

where M_i and M_a are the tissue and arterial magnetizations per unit volume respectively.

For injection of a bolus, the arterial magnetization of ^{129}Xe is related to the magnetization of ^{129}Xe injected as a function of time and the path followed by ^{129}Xe between the injection site and the tissue. For hyperpolarized ^{129}Xe , where the magnetization decays rapidly *in vivo*, a first-pass model was developed, i.e. it is assumed that no more ^{129}Xe magnetization is carried in the second passage of blood in the tissue. For this model, it is assumed that a volume V_s of a solution containing a concentration C_s of xenon, polarized at P and containing a fraction f_E of ^{129}Xe (enriched versus natural abundance xenon), is injected in a time τ_{inj} . Following Eqn. 2.9, the magnetization per unit volume in the solution is therefore, :

$$M_s = \frac{1}{2} C_s \gamma \hbar P f_E. \quad (6.5)$$

Figure 6.1: Schematic of the blood circulation.

Two cases are considered, the intracarotid injection and the intravenous injection. Fig. 6.1 is a schematic of the blood circulation.

6.3.1 Intracarotid Injection

Blood is carried to the brain via the common left and right carotid arteries. They arise from the aortic arch and divide in external and internal carotid arteries. An intracarotid injection is done by injection into one of the common carotid arteries.

For an intracarotid injection, the arterial magnetization of hyperpolarized ^{129}Xe

feeding the brain tissues is:

$$M_a(t) = M_{inj}(t - \Delta_{car})e^{-\Delta_{car}/T_{lob}} \quad (6.6)$$

where Δ_{car} is the transit time between the injection site (in the carotid artery) and the brain tissues, and T_{lob} is the T_1 relaxation time of ^{129}Xe in oxygenated blood. $M_a(t)$ is also called the arterial input function.

The concentration of hyperpolarized ^{129}Xe in the blood at the injection site as a function of time is assumed to be:

$$M_{inj}(t) = \begin{cases} M_s \frac{V_s}{\tau_{inj} F_{car}} & \text{if } 0 < t < \tau_{inj} \\ 0 & \text{if } t > \tau_{inj} \end{cases} \quad (6.7)$$

where F_{car} is the blood flow in the carotid artery in ml/min. The magnetization injected is therefore proportional to the ratio of the quantity of hyperpolarized ^{129}Xe injected ($M_s V_s$) and the quantity of liquid flowing through the carotid artery during the time of the injection ($\tau_{inj} F_{car}$).

6.3.2 Intravenous Injection

Intravenous injections are performed in any vein. This type of injection is more complex. The injected bolus is directed towards the heart by the venous blood, travels through the pulmonary circulation before coming back to the heart, and finally reaches the tissue of interest. 90% of the ^{129}Xe is excreted in the lungs[104, 105]. Also, the concentration of ^{129}Xe is diluted since the blood containing ^{129}Xe is distributed throughout the entire body.

The arterial magnetization of hyperpolarized ^{129}Xe in the tissue is expressed as:

$$M_a(t) = M_{inj}(t - \Delta_{ven}) f_L f_i e^{-\Delta_{oxy}/T_{lob}} e^{-\Delta_{deoxy}/T_{ldb}} \quad (6.8)$$

where f_L is the fraction of ^{129}Xe remaining after the passage through the lung capillaries, and f_i is the fraction of the total blood volume in the tissue of interest. Δ_{deoxy} is the transit time from the injection site to the pulmonary capillaries where the blood gets oxygenated. During that time, hyperpolarized ^{129}Xe relaxes according to T_{ldb} , the T_1 relaxation in deoxygenated blood. During the transit time from

the pulmonary capillaries to the brain Δ_{oxy} . ^{129}Xe relaxes according to T_{lob} . T_1 in oxygenated blood. Δ_{ven} is the total transit time between the intravenous injection site and the brain, i.e. $\Delta_{ven} = \Delta_{deoxy} + \Delta_{oxy}$.

The hyperpolarized ^{129}Xe magnetization in the blood at the injection site as a function of time is:

$$M_{inj}(t) = \begin{cases} M_s \frac{V_s}{\tau_{inj} F_{tot}} & \text{if } 0 < t < \tau_{inj} \\ 0 & \text{if } t > \tau_{inj} \end{cases} \quad (6.9)$$

where F_{tot} is the total blood flow in ml/min. Rigorously, F_{ven} , the blood flow in the vein, should be used to express the concentration at the site of injection, but the concentration is divided at the heart by F_{tot}/F_{ven} . This step was omitted for simplicity.

Finally, the hyperpolarized ^{129}Xe tissue magnetization as a function of time, obtained by analytically solving the differential equation (Eqn. 6.4), is:

$$M_i(t) = \begin{cases} 0 & \text{if } t < \Delta \\ \left(\frac{F_i M_a}{\lambda_i + \frac{1}{T_{1i}}} \right) \left(1 - e^{-(t-\Delta)\left(\frac{F_i}{\lambda_i} + \frac{1}{T_{1i}}\right)} \right) & \text{if } \Delta < t < \Delta + \tau_{inj} \\ \left(\frac{F_i M_a}{\lambda_i + \frac{1}{T_{1i}}} \right) \left(1 - e^{-\tau_{inj}\left(\frac{F_i}{\lambda_i} + \frac{1}{T_{1i}}\right)} \right) e^{-(t-(\Delta+\tau_{inj}))\left(\frac{F_i}{\lambda_i} + \frac{1}{T_{1i}}\right)} & \text{if } t > \Delta + \tau_{inj} \end{cases} \quad (6.10)$$

where

$$\Delta = \begin{cases} \Delta_{car} & \text{for intracarotid injection} \\ \Delta_{ven} & \text{for intravenous injection} \end{cases} \quad (6.11)$$

and

$$M_a = \begin{cases} M_s \frac{V_s}{\tau_{inj} F_{car}} e^{-\Delta_{car}/T_{lob}} & \text{for intracarotid injection} \\ M_s \frac{V_s}{\tau_{inj} F_{tot}} f_L f_i e^{-\Delta_{deoxy}/T_{ldb}} e^{-\Delta_{oxy}/T_{lob}} & \text{for intravenous injection} \end{cases} \quad (6.12)$$

Table 6.1: Parameters used in the compartmental model.

Parameter	Symbol	Value	Reference
Brain (Gray Matter)			
T_1 relaxation time in tissue	T_{1i}	20 s	[49]
Partition coefficient	λ_i	0.85	[42, 45]
Blood flow	F_i	80 ml/min/100ml or 0.8 min^{-1}	[42]
Blood and Circulation			
T_1 in oxygenated blood	T_{1ob}	6.4 s	[48]
T_1 in deoxygenated blood	T_{1db}	4.0 s	[48]
Transit time carotid-brain	Δ_{car}	2 s	
Transit time vein-lung	Δ_{deoxy}	4 s	
Transit time lung-brain	Δ_{oxy}	4 s	
Blood flow in the carotid artery	F_{car}	375 ml/min	[4]
Total blood flow	F_{tot}	5800 ml/min	[4]
Fraction of total blood volume going to the brain	f_i	0.129	[4]
Lungs			
Fraction of ^{129}Xe remaining in the blood after the lungs	f_L	0.1	[104, 105]
Variable Parameters			
^{129}Xe polarization	P	0.5	
Enrichment of ^{129}Xe	f_E	0.8	
Concentration of ^{129}Xe in the solution	C_s	55 mM	
Volume of the injection	V_s	16 ml	
Time of injection	τ_{inj}	2.6 s	

6.4 The Parameters

Table 6.1 displays the parameters used to make the calculations. A value of 20 s was used for T_1 in the brain. This is the mid-range value obtained with rat tissue homogenates[49]. The partition coefficient is the average of the values used by Peled[45] and by Martin[42]. The blood flow values to the brain are the same as the ones used by Martin et al[42].

The T_1 relaxation times in arterial blood and venous blood are from the measurements of Bifone et al[48]. The transit times are based on estimations. A transit time of 2 s is estimated from the carotid artery to the brain. 4 s from the vein to the lungs and 4 s from the lungs to the brain, as used by Peled[45]. The blood flow in the carotid artery was estimated as follows. The blood flow to the entire brain was taken to be 750 ml/min[4]. Since the two carotid arteries (left and right) are almost the exclusive supply to the brain, the carotid artery blood flow was estimated to be half of the entire brain blood flow. The total blood flow is given to be 5800 ml/min at rest [4]. The fraction of the total blood volume going to the brain was estimated by dividing the blood flow to the entire brain by the total blood flow.

The fraction of ^{129}Xe leaving the blood circulation at the pulmonary capillaries is 90%[105, 104].

The ^{129}Xe polarization was assumed to be 50%, a value that is desirable and probably achievable routinely using optimized laser polarization. Enriched xenon (80% of ^{129}Xe) was used for the calculations. The injection volume was chosen to be 16 ml, a typical injection volume. The injection duration was chosen to match the blood flow in the blood vessel used, i.e. $\tau_{inj} = F_{car}/V_s = 2.6$ s. The concentration of ^{129}Xe in the biocompatible solution was based on a solvent with an Ostwald solubility of 1.5, typical of a lipid-rich or hydrophobic (e.g. PFOB) solvent, and the amount of ^{129}Xe dissolved was calculated as if an equilibrium with 1 atm of ^{129}Xe was established.

6.5 Expected SNR

The signal of an image is proportional to the signal acquired at the center of k-space[106]. In fact,

$$S \propto \omega_0 M_{xy} \quad (6.13)$$

where ω_0 is the Larmor frequency and M_{xy} is the transverse magnetization producing the signal at the center of k-space.

The noise at high fields ($B_0 > 1.0$ T) is due to thermal fluctuations of dipoles in the sample, and is proportional to the resistance in the sample R_s :

$$N \propto \sqrt{R_s} \propto \omega_0 \quad (6.14)$$

This noise is referred to as Johnson noise or thermal noise.

The SNR, i.e. S/N , is thus proportional to the magnetization. For protons in thermal equilibrium, the longitudinal magnetization is given by the thermal equilibrium value (eq. 2.9):

$$M_H = \frac{N_H \gamma_H^2 \hbar^2}{4k_B T} B_0 \quad (6.15)$$

For hyperpolarized ^{129}Xe , the longitudinal magnetization *in vivo* is calculated with Eqn. 6.10 and 6.12. The transverse magnetizations are determined by the flip angle used by the imaging sequence ($M_{xy} = M \sin \alpha$).

For the case of EPI imaging, which tips all the longitudinal magnetization into the transverse plane and samples the entire k-space with this transverse magnetization, the ratio of expected SNR for proton and hyperpolarized ^{129}Xe images is:

$$\frac{(SNR)_{Xe}}{(SNR)_H} = \frac{M_i}{N_H \gamma_H^2 \hbar B_0 / 4k_B T} \quad (6.16)$$

6.6 The Results

Figs. 6.2 and 6.3 show the time course of the hyperpolarized ^{129}Xe magnetizations at the site of the injection, in the cerebral arteries, and in the brain tissue, for an injection of 5 s. An injection duration of 5 s was chosen to better illustrate the

build-up of the magnetization in the brain tissue. The injected bolus reaches the cerebral arteries after a delay Δ determined by the transit time between the site of injection and the brain. The tissue concentration increases exponentially while the bolus is in the cerebral arteries, and then decreases exponentially due to T_1 relaxation mainly and clearance through the venous circulation.

The maximal concentration in the tissue occurs at a time $t = \Delta + \tau_{inj}$ and can be studied as a function of the duration of the injection τ_{inj} , for constant injection volumes V_s . Figs. 6.4 and 6.5 show that the tissue concentration is larger for tighter boluses. In fact, for the time the bolus passes in the cerebral capillaries, the concentration builds up in the tissues, but at the same time T_1 relaxation occurs. Tighter boluses leave less time for hyperpolarized ^{129}Xe nuclei to relax resulting in a larger maximal tissue concentration.

For an injection duration of 2.6 s, the expected SNR for hyperpolarized ^{129}Xe imaging of the human brain is 28% of the proton SNR for intracarotid injection, and is 0.0063% of the proton SNR for intravenous injection. The difference between intracarotid and intravenous injections is mainly due to clearance at the lungs and dilution in the body blood pool.

6.7 Discussion and Future Work

The simple model used for this study of injection delivery provides estimates of the concentration of hyperpolarized ^{129}Xe which can be expected in brain tissues and in arterial blood following an injection delivery. Not all the parameters are accurately known, and some were based on estimations only. Furthermore, some assumptions were made. In particular, the calculations were performed as if the bolus was very delimited, i.e. the arterial magnetization as a function of time followed a perfect rectangular pulse. For a more realistic bolus, the tissue concentration would start building up more slowly and the time course would be more smooth in general. Also, the decay of the magnetization in the syringe, during the injection protocol, was not accounted for. For short injection durations, the decay is minimal since T_1

Figure 6.2: Time course of the hyperpolarized ^{129}Xe magnetizations at the injection site, in the cerebral arteries, and in the brain tissue following an intracarotid injection. Note: the vertical axes are scaled differently.

Figure 6.3: Time course of the hyperpolarized ^{129}Xe magnetizations at the injection site, in the cerebral arteries, and in the brain tissue following an intravenous injection. The magnetization at the injection site is in fact diluted by the total blood flow and represents the magnetization after the passage through the heart. Note: the vertical axes are scaled differently.

Figure 6.4: Maximal tissue concentration as a function of intracarotid injection duration.

Figure 6.5: Maximal tissue concentration as a function of intravenous injection duration.

in biocompatible solutions is usually quite long (over one minute). For long injection durations, this effect could become more important. Despite the assumptions and the uncertainties of the parameters, the results can still provide a basis for a discussion on the feasibility and usefulness of injection delivery.

For simplicity, the expected SNR values were calculated on the basis of EPI imaging. More sophisticated calculations could be performed for GE imaging taking into account the repetition time between pulses. For GE imaging, it would be interesting to study whether long injection durations are suitable or not, since tissues could be replenished with hyperpolarized ^{129}Xe between RF pulses.

The calculated results of the tissue magnetization and expected SNR for injection delivery are very different depending on the type of injection. As a comparison, using a similar model, Peled[45] has predicted a SNR for brain hyperpolarized ^{129}Xe imaging of 2% the SNR of protons for continuous inhalation of hyperpolarized ^{129}Xe gas. Our calculations predict 28% for intracarotid injection, but only 0.0063% for intravenous injection.

The next sections discuss the advantages and disadvantages of both injection methods, and how the tissue concentration could be improved. A discussion of possible biocompatible carrier solutions for ^{129}Xe follows.

6.7.1 Injection Methods

Intracarotid Injection

Using an intracarotid injection, hyperpolarized ^{129}Xe is directed exclusively to the brain in a very short time. The tissue concentrations achieved with this method can thus be very high. Furthermore, no hyperpolarized ^{129}Xe is present in any other tissue, therefore absolutely no signal background interferes with the tissue signal, resulting in high contrast.

On the other hand, this method necessitates puncture of the carotid artery, a procedure which is invasive and hazardous[104]. A similar method was developed in nuclear medicine with radioactive ^{133}Xe , however it has not found many clinical

applications due to its invasiveness. It is likely that despite the high tissue concentrations of hyperpolarized ^{129}Xe achievable with this method, the disadvantages will prevent the technique from becoming clinically important in humans. However, this technique could be useful for research purposes on animals.

Intravenous Injection

Intravenous injections are done routinely in clinical practice and are considered very safe. This injection technique would have the advantage of being more acceptable for imaging of hyperpolarized ^{129}Xe .

The tissue concentrations achieved with intravenous injection are quite deceiving at first. An SNR of a fraction of a percent relative to the proton SNR is very difficult to image and its applications would be limited. Nevertheless, this is actually of the same order as the SNR of *in vivo* ^{23}Na images[45], which has found some usefulness in MR imaging.

Eqn. 6.12 can be examined for the purpose of improving the tissue magnetization for intravenous injection. The transit times are not well known and could be taken to be maximal limits. If both Δ_{oxy} and Δ_{deoxy} are set to 3 s instead of 4 s, for a total transit time of 6 s, the expected SNR increases from 0.0063% to 0.0094% of the proton SNR. T_1 of deoxygenated and oxygenated blood are not accurately known, and there is still some controversy about those numbers. If they are set to 6 and 10 s respectively, the expected SNR increases from 0.0063% to 0.011% of the proton SNR. The polarization was assumed to be 50%, a value still not achieved in every laboratory, and 90% enriched ^{129}Xe was assumed. Changing the injection protocol (C_s , V_s and/or τ_{inj}) might increase the tissue concentration by a factor of 2, 3 or 5 perhaps, giving an SNR of 0.032% of the proton SNR but this value is still lower than the one achieved by inhalation delivery for example.

The preceding analysis highlights the need for a different intravenous injectable solution which would overcome some of these limitations.

First, a solution which would encapsulate or protect ^{129}Xe from free oxygen and deoxyhemoglobin present in blood would increase the tissue concentrations.

For example, if ^{129}Xe , while being transported in the blood circulation, undergoes relaxation with a T_1 of 60 s, the maximal tissue concentration is increased by a factor of 4.5, resulting in a SNR of 0.028% relative to the proton SNR.

Second, targetting of ^{129}Xe towards specific regions of the body could increase the fraction of hyperpolarized ^{129}Xe going to the tissue, f_i . This could be achieved, for example, by encapsulating hyperpolarized ^{129}Xe in liposomes, with the use of targetting ligands. A variety of targetting ligands are already under development for increasing the selectivity of delivery of liposomal drugs[107].

Third, the fraction of hyperpolarized ^{129}Xe remaining after excretion in the lungs f_L could possibly be increased. We can imagine hyperpolarized ^{129}Xe trapped by a carrier while transported in the blood in such a way that very few ^{129}Xe atoms are lost at the pulmonary capillaries.

The following sections explore some possible candidates as biocompatible carrier solutions for intravenous delivery of hyperpolarized ^{129}Xe based on results of Chapter 5. Future research directions are also suggested.

6.7.2 Injectable Solutions

Saline

The calculations of the expected SNR were performed for a biocompatible solution with an Ostwald solubility of 1.5. Repeating the calculations, but for saline (Ostwald solubility of 0.1 based on the solubility of ^{129}Xe in water[82]), the expected SNR values are smaller by a factor of about 15, yielding a SNR of 1.9% the proton SNR for intracarotid injection.

Saline does not seem to be a good candidate for injection delivery for the purpose of hyperpolarized ^{129}Xe tissue imaging. Its ^{129}Xe solubility is low, and it does not encapsulate ^{129}Xe or target any specific area of the body. Furthermore, its T_1 of 97 s, as reported in Section 5.1.3, is not particularly large.

Liposomes

Our preliminary results with a liposome solution are not conclusive. However, some future work can be outlined, since they are of interest for targetting the delivery of hyperpolarized ^{129}Xe . As well, they could reduce the losses of hyperpolarized ^{129}Xe at the lung capillaries.

The liposome results in Section 5.2 suggest that ^{129}Xe is not dissolving efficiently in the lipid membrane. The first objective should be to develop a procedure for trapping ^{129}Xe efficiently inside liposomes. Gas-filled liposome microbubbles are already in use as vascular ultrasound contrast agents and more recently as pressure-sensitive MR contrast agents[108]. This technique should be investigated for MR imaging of hyperpolarized ^{129}Xe . Another proposed technique is to use phosphatidylethanolamines as the phospholipids to form the liposomes. These phospholipids have the characteristic of undergoing a bilayer to inverted hexagonal phase transition at temperatures of about 40-60°C. The liposomes would be formed following the normal procedure. Then, hyperpolarized ^{129}Xe would be dissolved while the liposomes would be heated above their critical temperature and destabilized. By cooling down the solution, the liposomes would reform and could trap hyperpolarized ^{129}Xe inside. Very high concentrations of liposomes should be used to dissolve as much hyperpolarized ^{129}Xe as possible. The solution can be diluted afterwards using the same buffer.

PFOB Emulsions

PFOB emulsions have the potential to increase concentrations in tissues. They are composed of droplets of PFOB encapsulated by a monolayer of lipids, surrounded by water, as described in Section 5.3. ^{129}Xe dissolved in PFOB exhibits a long T_1 relaxation time and a high solubility: the T_1 relaxation time of ^{129}Xe in pure PFOB was measured to be 110 s[102], and the solubility of ^{129}Xe in perfluorocabons is about 15 times the solubility of ^{129}Xe in water[94]. The NMR spectrum of ^{129}Xe dissolved in a PFOB emulsion reveals two peaks for the two compartments: the aqueous compartment and the PFOB compartment, as shown in Section 5.3. ^{129}Xe

in the PFOB compartment was measured *in vivo* to be 10 s after an emulsion was injected in a rat by Wolber et al[64]. This demonstrated that ^{129}Xe magnetization can be detected in the PFOB compartment after an injection.

A lot of work is still needed to determine whether the emulsions are of any value to increase the tissue concentrations using injection delivery. Of primary importance is the exchange time between the two compartments, and this must be studied. Wolber et al estimated the exchange time to range between 0.01 to 10 ms depending on particle size and ageing or degradation, using an analysis of the lineshape broadening[64]. The exchange time should be confirmed by other methods. One possible method is a saturation-recovery, where all the magnetization in the aqueous compartment is destroyed by a frequency-selective 90° pulse, then the recovery of the signal is sampled by small flip angles[109]. Alternatively, studying the T_2 relaxation times in both compartments as a function of the echo-time TE (recall Section 3.3.2) in a CPMG sequence is another method to measure the exchange time[110]. If the echo-time is shorter than the exchange time, the two compartments should exhibit distinct T_2 relaxation times since the refocusing happens before any exchange has occurred. If the echo-time is larger than the exchange time, the two compartments exchange between refocusing pulses, and a single T_2 relaxation time should be measured for both compartments. This method should provide a second independent measurement of the exchange time.

The exchange time between compartments determines how well ^{129}Xe is trapped in the droplets. It could determine whether PFOB would prevent ^{129}Xe from exiting the blood circulation at the lungs or not, and if the relaxation time is affected by the blood compartment. It is expected that the exchange time will vary with particle size. It could also be speculated that exchange time could vary for different lipids forming the monolayer. Designing a PFOB emulsion optimized for injection delivery of hyperpolarized ^{129}Xe should take into account the desired exchange time between the two compartments. A desirable exchange time would be long enough to minimize ^{129}Xe losses at the lung capillaries. In fact, we can model the exchange at the lung capillaries as in Fig. 6.6, where ^{129}Xe exchanges between the aqueous (blood) compartment and the alveoli, and between PFOB droplets and the aqueous

Figure 6.6: Model of ^{129}Xe exchange at the lung capillaries.

(blood) compartment, but not directly between the PFOB droplets and the alveoli. Following such a model, a fraction (90%) of ^{129}Xe in the aqueous compartment would leave the blood circulation. If the aqueous compartment is replenished due to a short exchange time between PFOB and aqueous compartments compared to the transit time in the lung capillaries, then a significant fraction of the total ^{129}Xe could be lost. If, however, the exchange time is long, the amount of ^{129}Xe lost could be minimized. With an exchange time of 10 ms[64] and assuming a transit time in capillaries of less than 1 s[45], the fraction of ^{129}Xe remaining after the lungs is probably larger than 0.1.

It should be noted that some PFOB droplets are also excreted at the lung capillaries, however the rate of excretion ($T_{1/2} \sim \text{days}$ [101]) is negligible here.

In summary, a long exchange time is desirable to minimize losses at the lungs.

On the other hand, a long exchange time could result in very small ^{129}Xe tissue magnetizations, since tissues would be fed exclusively by the aqueous compartment. An optimal exchange time for achieving high tissue magnetizations could be studied by refining our simple model. Second and higher passes should also be considered since T_1 in PFOB is much longer than the total circulation time (about 10 s).

Other Biocompatible Solutions

Other biocompatible solutions could be designed for the specific use of intravenous injection of hyperpolarized ^{129}Xe . For example, we can think of a solution containing unstable particles trapping ^{129}Xe . If the particles were stable just long enough to traverse the lungs, and were then disaggregated, the losses at the lungs would be minimized and the tissue uptake would be increased. Moreover, ^{129}Xe would retain its characteristics as a freely diffusible tracer allowing direct blood flow measurements.

Overall, for any intravenous injectable solution, it should be emphasized that even doubling the injection volume V_i , with a T_1 during the transit time of 110 s, and no loss at the lungs ($f_L = 1$), the expected SNR for tissue imaging with hyperpolarized ^{129}Xe is 0.59% relative to the proton SNR.

6.8 Thesis Summary

MR imaging of hyperpolarized ^{129}Xe is a very new technique for which not all the possibilities have been explored or even thought of. At this stage, feasibility studies of hyperpolarized ^{129}Xe are emerging in many laboratories, creating a very dynamic field full of new ideas and new applications. This thesis was a feasibility study which was, in fact, the first step in the outline of developing a method for breast cancer detection and characterization using hyperpolarized ^{129}Xe .

First, all the procedures required for studying hyperpolarized ^{129}Xe in both gas and dissolved phases were implemented. The laser-polarization method was optimized. A gas manifold and the associated pumping system were installed and tested.

Finally a procedure for dissolving hyperpolarized ^{129}Xe in liquids was developed.

Second, hyperpolarized ^{129}Xe gas phase was studied. Spectroscopic measurements, like T_1 and T_2 relaxation measurements, were performed. 2D GE imaging was studied for several flip angle sequences and phase-encode strategies. 3D issues were explored, especially the effect of using slice-selective excitations.

Third, preliminary work on the dissolved phase showed the feasibility of dissolving hyperpolarized ^{129}Xe in biological liquids to perform NMR experiments. To better understand what the needs and expectations are for dissolved phase imaging of hyperpolarized ^{129}Xe following injection delivery, a compartmental model was used to calculate the expected SNR *in vivo*. This model showed that intracarotid injection delivery of hyperpolarized ^{129}Xe provides a large tissue magnetization, and could be very useful for basic research with animals. The model also showed that the tissue magnetization following intravenous injection delivery of hyperpolarized ^{129}Xe is much smaller due to dilution and excretion of ^{129}Xe at the lungs, emphasizing the need for novel biocompatible carrier solutions for injection delivery of hyperpolarized ^{129}Xe .

From the results presented in this thesis, two parallel projects are emerging.

One is the imaging of the dissolved phase, in phantoms and ultimately *in vivo*. Based on what was learned with gas phase imaging, flip angle sequences and phase-encode ordering strategies should be investigated for dissolved phase imaging. Imaging sequences, such as GE and EPI, could be compared.

Another project would be to develop and optimize biocompatible carriers for injection delivery of hyperpolarized ^{129}Xe , based on the preliminary results presented in this thesis and the compartmental model developed for injection delivery. Here the possibilities are as varied as the number of applications foreseen for hyperpolarized ^{129}Xe , ranging from angiography to perfusion studies.

Finally, many more steps and studies are required to explore the benefits of hyperpolarized ^{129}Xe . But clearly MR imaging of hyperpolarized ^{129}Xe is a powerful technique and it is worth pursuing further research towards applications in biomedicine.

Bibliography

- [1] Bloch F., Nuclear induction *Phys. Rev.* 70:460-473 (1946)
- [2] Purcell E. M., Torrey H. C. and Pound R. V., Resonance absorption by nuclear magnetic moments in a solid, *Phys. Rev.* 69:37-38 (1946)
- [3] Lauterbur P. C., Image formation by induced local interactions: Examples employing nuclear magnetic resonance, *Nature*, 242:190-191 (1973)
- [4] Marieb E. N., *Human anatomy and physiology*, 3rd edition, Benjamin/Cummings (1995)
- [5] Webb S., *The Physics of Medical Imaging*, Institute of Physics (1996)
- [6] Albert M. S., Cates G. D., Driehuys B., Happer W., Saam B., Springer C. S. Jr and Wishnia A., Biological magnetic resonance imaging using laser-polarized ^{129}Xe , *Nature* 370:199-201 (1994)
- [7] Kastler A., *J. Phys. Radium* 11, 225 (1950)
- [8] Colegrove F. D., Schearer L. D. and Walters G. K., Polarization of ^3He gas by optical pumping, *Phys. Rev.* 132(6):2561-2572 (1963)
- [9] Bouchiat M. A., Carver T. R. and Varum C. M., Nuclear polarization in ^3He gas induced by optical pumping and dipolar exchange *Phys. Rev. Lett.* 5:373-375 (1960)
- [10] Bhaskar N. D., Happer W., Larsson M. and Zeng X., Slowing down of rubidium-induced nuclear spin relaxation of ^{129}Xe gas in a magnetic field, *Phys. Rev. Lett.* 50(2):105-108 (1983)

- [11] Happer W., Miron E., Schaefer S., Schreiber D., van Wijngaarden W. A. and Zeng X., Polarization of the nuclear spins of noble-gas atoms by spin exchange with optically pumped alkali-metal atoms, *Phys. Rev. A* 29:3092-3110 (1984)
- [12] Zeng X., Wu Z., Call T., Miron E., Schreiber D. and Happer W., Experimental determination of the rate constants for spin exchange between optically pumped K, Rb, and Cs atoms and ^{129}Xe nuclei in alkali-metal-noble-gas van der Waals molecules, *Phys. Rev. A* 31(1):260-278 (1985)
- [13] Driehuys B., Cates G. D., Miron E., Sauer K., Walter D. K. and Happer W., High-volume production of laser-polarized ^{129}Xe , *Appl. Phys. Lett.* 69(12):1668-1670 (1996)
- [14] Hattori M., Hiraga T. and Moriya T., Continuous-flow apparatus for hyperpolarization of ^{129}Xe : optimized structure of cell efficient spin exchange at a high concentration of optically pumped rubidium, *Eur. Radiol.* 9:B14 (1999)
- [15] Hasson K. C., Cella P., Deaton D., Kameya G. and Driehuys B., Continuous-flow production of polarized ^{129}Xe , *Eur. Radiol.* 9:B10 (1999)
- [16] Rosen M. S., Chupp T. E., Coulter K. P., Welsh R. C. and Swanson S. D., Polarized ^{129}Xe optical pumping/spin exchange and delivery system for magnetic resonance spectroscopy and imaging studies, *Rev. Sci. Instr.* 70(2):1546-1552 (1999)
- [17] Ruth U., Hofmann T., Schmidt J., Fick D. and Jansch H. J., Production of nitrogen-free, hyperpolarized ^{129}Xe gas, *Appl. Phys. B* 68:93-97 (1999)
- [18] Venkatesh A. K., Zhao L., Pausak T., Ward C. F., Jolesz F. A. and Albert M. S., Hyperpolarized gas imaging with a simple programmable gas delivery system, *Eur. Radiol.* 9:B34 (1999)
- [19] Spiegelman J. J., Venkatesh A. K. and Albert M. S., Recycling system for hyperpolarized noble gases, *Eur. Radiol.* 9:B38 (1999)
- [20] Pietrass T., Gaede H. C., Bifone A., Pines A. and Ripmeester J. A., *J. Am. Chem. Soc.* 117:7520-7525 (1995)

- [21] Song Y.-Q., Gaede H. C., Pietraß T., Barrall G. A., Chingas G. C., Ayers M. R. and Pines A., *J. Magn. Reson. Series A* 115:127-130 (1995)
- [22] Walker T. G. and Happer W., Spin-exchange optical pumping of noble-gas nuclei, *Rev. Mod. Phys.* 69(2):629-642 (1997)
- [23] Yonas H., Grundy B., Gur D., Shabason L., Wolfson S. K. Jr and Cook E. E., Side effects of xenon inhalation, *J. Comput. Assist. Tomogr.* 5:591-592 (1981)
- [24] Middleton H., Black R. D., Saam B., Cates G. D., Cofer G. P., Guenther R., Happer W., Hedlund L. W., Johnson G. A., Juvan K. and Swartz J., MR imaging with hyperpolarized ^3He gas, *Magn. Reson. Med.* 33:271-275 (1995)
- [25] Shattuck M. D., Gewalt S. L., Glover G. H., Hedlund L. W. and Johnson G. A., MR microimaging of the lung using volume projection encoding, *Magn. Reson. Med.* 38:938-942 (1997)
- [26] Albert M. S., Tseng C. H., Williamson D., Oteiza E. R., Walsworth R. L., Kraft B., Kacher D., Holman B. L. and Jolesz F. A., Hyperpolarized ^{129}Xe MR imaging of the oral cavity, *J. Magn. Reson. B* 111:204-207 (1996)
- [27] Johnson G. A., Cates G., Chen X. J., Cofer G. P., Driehuys B., Happer W., Hedlund L. W., Saam B., Shattuck M. D., Swartz J., Dynamics of magnetization in hyperpolarized gas MRI of the lung, *Magn. Reson. Med.* 38:66-71 (1997)
- [28] Bachert P., Schad L. R., Bock M., Knopp M. V., Ebert M., Großmann T., Heil W., Hofmann D., Surkau R. and Otten E. W., Nuclear magnetic resonance imaging of airways in humans with use of hyperpolarized ^3He , *Magn. Reson. Med.* 36:192-196 (1996)
- [29] Kauzcor H.-U., Ebert M., Kreitner K.-F., Nilgens H., Surkau R., Heil W., Hofmann D., Otten E. W. and Thelen M., Imaging of the lungs using ^3He MRI: preliminary clinical experience in 18 patients with and without lung disease, *J. Magn. Reson. Imaging* 7:538-543 (1997)

- [30] Rizi R. R., Dimitrov I. E., Thompson A., Jones G., Gentile T. R., Ishii M., Reddy R., Schnall M. D. and Leigh J. S., MRI of hyperpolarized ^3He gas in human paranasal sinuses. *Magn. Reson. Med.* 39:865-868 (1998)
- [31] Sakai K., Bilek A. M., Oteiza E., Walsworth R. L., Balamore D., Jolesz F. A. and Albert M. S., Temporal dynamics of hyperpolarized ^{129}Xe resonances in living rats. *J. Magn. Reson. B* 111:300-304 (1996)
- [32] Wagshul M. E., Button T. M., Li H. F., Liang Z., Springer C. S., Zhong K., Wishnia A., *In vivo* MR imaging and spectroscopy using hyperpolarized ^{129}Xe . *Magn. Reson. Med.* 36:183-191 (1996)
- [33] Mugler J. P. III, Driehuys B., Brookeman J. R., Cates G. D., Berr S. S., Bryant R. G., Daniel T. M., de Lange E. E., Downs J. H. III, Erickson C. J., Happer W., Hinton D. P., Kassel N. F., Maier T., Phillips C. D., Saam B. T., Sauer K. L., Wagshul M. E., MR imaging and spectroscopy using hyperpolarized ^{129}Xe gas: preliminary human results. *Magn. Reson. Med.* 37:809-815 (1997)
- [34] Chen X. J., Chawla M. S., Cofer G. P., Hedlund L. W., Möller H. E. and Johnson G. A., Hyperpolarized ^3He NMR lineshape measurements in the live guinea pig lung. *Magn. Reson. Med.* 40:61-65 (1998)
- [35] Schreiber W. G., Markstaller K., Eberle B., Kauczor H.-U., Weiler N., Surkau R., Hanisch G. and Thelen M., Ultrafast MR-imaging of lung ventilation using hyperpolarized $^3\text{Helium}$. *Eur. Radiol.* 9:B28 (1999)
- [36] Chen X. J., Chawla M. S., Hedlund L. W., Möller H. E., MacFall J. R. and Johnson G. A., MR microscopy of lung airways with hyperpolarized ^3He . *Magn. Reson. Med.* 39:79-84 (1998)
- [37] Viallon M., Cofer G. P., Suddarth S. A., Möller H. E., Chen X. J., Chawla M. S., Hedlund L. W., Crémillieux Y. and Johnson G. A., Functional MR microscopy of the lung using hyperpolarized ^3He . *Magn. Reson. Med.* 41:787-792 (1999)
- [38] Saam B., Yablonskiy D. A., Gierada D. S., Cooper J. D., Lefrak S. S. and Conradi M. S., Measuring diffusivity of ^3He in human lung: preliminary study of patients with emphysema. *Eur. Radiol.* 9:B22 (1999)

- [39] Altes T. A., Rakes G., Knight-Scott J., Powers P., Mugler J. P. III, Christopher J. M., Tustison N., de Lange E. E., Mata J. F., Alford B. A. and Brookeman J. R., Hyperpolarized ^3He MR lung ventilation imaging in asthmatics: preliminary results *Proceedings of the International Workshop on Hyperpolarized Gases in Magnetic Resonance*, Les Houches 29 (1999)
- [40] Butler J., Patz S., Hoffmann D., Mair R., Topulos G. and Walsworth R., Measurement of surface area to volume ratio with ^{129}Xe NMR, *Eur. Radiol.* 9:B24 (1999)
- [41] Hedenstierna G., Lung physiology and physiopathology: V/Q matching, *Proceedings of the International Workshop on Hyperpolarized Gases in Magnetic Resonance*, Les Houches 19 (1999)
- [42] Martin C. C., Williams R. F., Gao J.-H., Nickerson L. D. H., Xiong J. and Fox P. T., The pharmacokinetics of hyperpolarized xenon: implications for cerebral MRI, *J. Magn. Reson. Imaging* 7:848-854 (1997)
- [43] Chawla M. S., Chen X., J., Möller H. E., Cofer G. P., Wheeler C. T., Hedlund L. W. and Johnson G. A., *In vivo* magnetic resonance vascular imaging using laser-polarized ^3He microbubbles, *Proc. Natl. Acad. Sci. USA* 95:10832-10835 (1998)
- [44] Möller H. E., Chawla M. S., Chen X. J., Driehuys B., Hedlund L. W., Wheeler C. T. and Johnson G. A., Magnetic resonance angiography with hyperpolarized ^{129}Xe dissolved in a lipid emulsion *Magn. Reson. Med.* 41:1058-1064 (1999)
- [45] Peled S., Jolesz F. A., Tseng C.-H., Nascimben L., Albert M. S. and Walsworth R. L., Determinants of tissue delivery for ^{129}Xe magnetic resonance in humans, *Magn. Reson. Med.* 36:340-344 (1996)
- [46] Albert M. S., Schepkin V. D. and Budinger T. F., Measurement of ^{129}Xe T_1 in blood to explore the feasibility of hyperpolarized ^{129}Xe MRI, *J. Comp. Assist. Tomography* 19(6):975-978 (1995)
- [47] Bifone A., Song Y.-Q., Seydoux R., Taylor R. E., Goodson B. M., Pietrass T., Budinger T. F., Navon G. and Pines A., NMR of laser-polarized xenon in human blood, *Proc. Natl. Acad. Sci. USA* 93:12932-12936 (1996)

- [48] Wolber J., Cherubini A., Dzik-Jurasz A. S. K., Leach M. O. and Bifone A., Spin-lattice relaxation of laser-polarized xenon in human blood, *Proc. Natl. Acad. Sci. USA* 96:3664-3669 (1999)
- [49] Wilson G. J., Santyr G. E., Anderson M. E. and DeLuca P. M., Longitudinal relaxation times of ^{129}Xe in rat tissue homogenates at 9.4 T, *Magn. Reson. Med.* 41:933-938 (1999)
- [50] Swanson S. D., Rosen M. S., Agranoff B. W., Coulter K. P., Welsh R. C., Cupp T. E., Brain MRI with laser-polarized ^{129}Xe , *Magn. Reson. Med.* 38:695-698 (1997)
- [51] Chupp T. E., Coulter K. P., Rosen M. S. and Swanson S. D., Chemical shift imaging of laser-polarized ^{129}Xe magnetization in rats *in vivo*, *Eur. Radiol.* 9:B45 (1999)
- [52] Albert M. S., Venkatesh A. K., Li L.-P., Chin C.-L., Balamore D. and Jolesz F. A., Dynamic uptake of hyperpolarized ^{129}Xe in the rat brain *Eur. Radiol.* 9:B41 (1999)
- [53] Goodson B. M., Song Y.-Q., Taylor R. E., Schepkin V. D., Brennan K. M., Chingas G. C., Budinger T. F., Navon G. and Pines A., *In vivo* NMR and MRI using injection delivery of laser-polarized xenon, *Proc. Natl. Acad. Sci. USA* 94:14725-14729 (1997)
- [54] Albert M. S., Venkatesh A. K., Zhao L., Balamore D. and Jolesz F. A., Using carrier-agents in live rats to deliver hyperpolarized ^{129}Xe , *Eur. Radiol.* 9:B44 (1999)
- [55] Wolber J., Rowland I. J., Leach M. O. and Bifone A., Intravascular delivery of hyperpolarized $^{129}\text{Xenon}$ for *in vivo* MRI, *Appl. Magn. Reson.* 15:343-352 (1998)
- [56] Kety S. S., Measurement of local blood flow by the exchange of an inert, diffusible substance, *Meth. Med. Res.* 8:228-236 (1960)
- [57] Belliveau J. W., Rosen B. R., Kantor H. L., Rzerdzian R. R., Kennedy D. N., McKinstry R. C., Vevea J. M., Cohen M. S., Pykett I. L. and Brady T. J., Functional cerebral imaging by susceptibility-contrast NMR, *Magn. Reson. Med.* 14:538-546 (1990)
- [58] Yonas H., Johnson D. W. and Pindzola R. R., Xenon-enhanced CT of cerebral blood flow, *Sci. Amer., Sc. & Med.* 2:58-67 (1995)

- [59] Wilke N., Simm C., Zhang J., Ellermann J., Ya X., Merkle H., Path G., Lüdemann H., Bache R. J. and Uğurbil K., Contrast-enhanced first pass myocardial perfusion imaging: correlation between myocardial blood flow in dogs at rest and during hyperemia. *Magn. Reson. Med.* 29:485-497 (1993)
- [60] Rosen B. R., Belliveau J. W., Vevea J. M. and Brady T. J., Perfusion imaging with NMR contrast agents. *Magn. Reson. Med.* 14:249-265 (1990)
- [61] Delorme S. and Knopp M. V., Non-invasive vascular imaging: assessing tumour vascularity. *Eur. Radiol.* 8(4):517-27 (1998)
- [62] Tofts P., Berkowitz B. and Schnall M. D., Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model. *Magn. Reson. Med.* 33:564-568 (1995)
- [63] Swanson S. D., Chupp T. E., Coulter K. P. and Rosen M. S., Tissue perfusion using laser-polarized ^{129}Xe . *Eur. Radiol.* 9:B40 (1999)
- [64] Wolber J., Rowland I. J., Leach M. O. and Bifone A., Perfluorocarbon emulsions as intravenous delivery media for hyperpolarized xenon. *Magn. Reson. Med.* 41:442-449 (1999)
- [65] National Cancer Institute's SEER database. Canadian Cancer Statistics. National Cancer Institute of Canada (1997)
- [66] Brenner R. J., Breast MR imaging: an analysis of its role with respect to other imaging and interventional modalities. *MRI Clinics of North America*, 2(4):705-723 (1994)
- [67] Santyr G. E., MR imaging of the breast: imaging and tissue characterization without intravenous contrast, *MRI Clinics of North America*, 2(4):673-690 (1994)
- [68] Heywang S. H., Fenzl G., Hahn D., Krischke I., Edmaier M., Eiermann W. and Bassermann R., MR imaging of the breast: comparison with mammography and ultrasound. *J. Comput. Assist. Tomogr.* 10(4):615-20 (1986)
- [69] Abraham R. J., Fisher J. and Loftus P., *Introduction to NMR spectroscopy* John Wiley & Sons (1988)

- [70] Abragam A., *Principles of nuclear magnetism*, Oxford (1961)
- [71] Look D. C. and Locker D. R., Time saving in measurement of NMR and EPR relaxation times, *Rev. Sci. Instrum.* 41(2):520-251 (1970)
- [72] Zhao L., Mulkern R., Tseng C.-H., Williamson D., Patz S., Kraft R., Walsworth R. L., Jolesz F. A. and Albert M. S., Gradient-echo imaging considerations for hyperpolarized ^{129}Xe , *J. Magn. Reson. B* 113:179-183 (1996)
- [73] Mulkern R. V., Melki P. S., Jakab P., Higuchi N. and Jolesz F. A., Phase-encode order and its effect on contrast and artifact in single-shot RARE sequences, *Med. Phys.* 18(5):1032-1037 (1991)
- [74] Pietrass T. and Gaede H. C., Optically polarized ^{129}Xe in NMR spectroscopy, *Adv. Mat.* 7:826-838 (1995)
- [75] Knize R. J., Wu Z. and Happer W., Optical pumping and spin exchange in gas cells, *Adv. in Atomic and Mol. Phys.* 24:223-267 (1988)
- [76] Raftery D., Long H. W., Shykind D., Grandinetti P. J. and Pines A., Multiple-pulse nuclear magnetic resonance of optically pumped xenon in a low magnetic field, *Phys. Rev. A* 50(1):567-574 (1994)
- [77] Ottinger C., Scheps R., York G. W. and Gallgher A., Broadening of the Rb resonance lines by the noble gases, *Phys. Rev. A* 11(6):1815-1828 (1975)
- [78] Zeng X., Miron E., Van Wijngaarden W. A., Schreiber D and Happer W., Wall relaxation of spin polarized ^{129}Xe nuclei, *Phys. Lett.* 96A(4):191-194 (1983)
- [79] Driehuys B., Cates G. D. and Happer W., Surface relaxation mechanisms of laser-polarized ^{129}Xe , *Phys. Rev. Lett.* 74(24):4943-4946 (1995)
- [80] Breeze S., Lang S., Moudrakovski I., Ratcliffe C. I., Ripmeester J. A., Santyr G., Simard B. and Zuger I., Coatings for optical pumping cells and short term storage of hyperpolarized xenon, *J. Appl. Phys.*, in press
- [81] Reif F., *Fundamentals of statistical and thermal physics*, McGraw-Hill (1965)

- [82] Lawrence J. H., Loomis W. F., Tobias C. A. and Turpin F. H., Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils. *J. Physiol.* 105:197-204 (1946)
- [83] Bronskill M. J. and Sprawls P., *The physics of MRI, 1992 AAPM summer school proceedings*, American Institute of Physics (1993)
- [84] Diehl P. and Jokisaari J., *J. Magn. Reson.* 88:660-665 (1990)
- [85] Ptyal B. R., Gao J.-H., Williams R. F., Roby J., Saam B., Rockwell B. A., Thomas R. J., Stolarski D. J. and Fox P. T., Longitudinal relaxation and diffusion measurements using magnetic resonance signals from laser-polarized ^{129}Xe nuclei. *J. Magn. Reson.* 126:58-65 (1997)
- [86] Press W. H. et al. *Numerical Recipes in C*, 2nd ed., Cambridge (1992)
- [87] Cates G. D., Benton D. R., Gatzke M., Happer W., Hasson K. C. and Newbury N. R., Laser production of large nuclear-spin polarization in frozen xenon. *Phys. Rev. Letters* 65(20):2591-2594 (1990)
- [88] Takezawa J., Miller F. J. and O'Neil J. J., Single-breath diffusing capacity and lung volumes in small laboratory mammals. *J. Appl. Physiol.* 48(6):1052-1059 (1980)
- [89] Jameson C. J., Jameson A. K. and Hwang J. K., Nuclear spin relaxation by intermolecular magnetic dipole coupling in the gas phase. ^{129}Xe in oxygen. *J. Chem. Phys.* 89:4074-4081 (1988)
- [90] Mugler J. P. III, Optimization of gradient-echo sequences for hyperpolarized noble-gas MRI. *Proc. ISMRM. 6th Annual Meeting* #1904 (1998) *MR. J. Magn. Res. Series B* 113:179-183 (1996)
- [91] Crawley A. P. and Henkelman R. M., A stimulated echo artifact from slice interference in magnetic resonance imaging, *Med. Phys.* 14:842-848 (1987)
- [92] Morris P. G., *Nuclear magnetic resonance imaging in medicine and biology*, Oxford (1986)

- [93] Saam B., Yablonskiy D. A., Gierada D. S. and Conradi M. S., Rapid Imaging of hyperpolarized gas using EPI. submitted for publication
- [94] Pollack G. L., Kennan R. P. and Holm G. T., Solubility of inert gases in PFC blood substitute, blood plasma, and mixtures, *Biomat., Art. Cells and Immob. Biotech.*, 20(2-4):1101-1104 (1992)
- [95] Smith R. A., Porter E. G. and Miller K. W., The solubility of anesthetic gases in lipid bilayers, *Bioch. Biophys. Acta.* 645:327-338 (1981)
- [96] Miller K. W., Reo N. V., Schoot Uiterkamp A. J., Stengle D. P., Stengle T. R. and Williamson K. L., Xenon NMR: Chemical shifts of a general anesthetic in common solvents, proteins, and membranes, *Proc. Natl. Acad. Sci USA* 78:4946-4949 (1981)
- [97] Venkatesh A. K., personal communication
- [98] Wilson G. J., Santyr G., Anderson M. and DeLuca P., Transverse relaxation times of ^{129}Xe in rat tissue homogenates and blood, private communication
- [99] Battino R., *Solubility Data Series, Oxygen and Ozone*, vol. 7, Pergamon (1981)
- [100] Cheetham J. J., Nir S., Johnson E., Flanagan T. D. and Epand R. M., The effects of membrane physical properties on the fusion of sendai virus with human erythrocyte ghosts and liposomes: analysis of the kinetics and extent of fusion, *J. Biol. Chem.* 269:5467-5472 (1994)
- [101] Riess J. G., Overview of progress in the fluorocarbon approach to *in vivo* oxygen delivery, *Biomat., Art. Cells and Immob. Biotech.*, 20(2-4):183-202 (1992)
- [102] Zhao L. et al. *Proc. ISMRM, 6th Annual Meeting #1908* (1998)
- [103] Ratner A. V., Muller H. H., Bradley-Simpson B., Johnson D. E., Hurd R. E., Sotak C. and Young S. W., Detection of tumors with ^{19}F magnetic resonance imaging, *Invest. Radiol.* 23:361-364 (1988)
- [104] Rowan J. O., *Physics and the circulation*, Adam Hilger (1981)
- [105] Farhi L. E., Elimination of inert gas by the lung, *Respir. Physiol.* 3:1-11 (1967)

- [106] Edelstein W. A., Glover G. H., Hardy C. J. and Redington R. W., The intrinsic signal-to-noise ratio in NMR imaging, *Magn. Reson. Med.* 3:604-618 (1986)
- [107] Allen T. M., Liposomal drug formulations: Rationale for development and what we can expect for the future, *Drugs* 56(5):747-56 (1998)
- [108] Alexander A. L., McCreery T. T., Barrette T. R., Gmitro A. F. and Unger E. C., Microbubbles as novel pressure-sensitive MR contrast agents, *Magn. Reson. Med.* 35:801-806 (1996)
- [109] Kaplan J. I. and Fraenkel G., *NMR of chemically exchanging systems*, Academic Press (1980)
- [110] Allerhand E. and Gutowsky H. S., Spin-echo studies of chemical exchange. II. Closed formulas for two sites, *J. Chem. Phys.* 42(5):1587-1599 (1965)