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PVA-Fricke Hydrogels for Radiotherapy Dosimetry using Magnetic Resonance Imaging

By

Kenneth Nkongchu, B.Sc.

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, Canada

August 2001

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PVA-Fricke Hydrogels for Radiotherapy Dosimetry Using Magnetic Resonance Imaging

Submitted by Kenneth Nkongchu, B.Sc.

in partial fulfillment of the requirements for

the degree of Master Of Science

Chair, Department of Physics

Thesis Supervisor

Carleton University

Date 12 Sept 2001

Abstract

Fricke-gel dosimetry using Nuclear Magnetic Resonance (NMR) imaging may be useful for the purpose of verification of complex spatial dose distributions in conformal radiotherapy. Unfortunately, currently existing Fricke gels (agarose, gelatin) are plagued by the problem of diffusion of ferric ions ($[\text{Fe}^{2+}]$) which blurs the spatial dose distribution thereby limiting its clinical application. A newly developed gel, polyvinyl alcohol (PVA) Fricke-hydrogel appears to significantly reduce diffusion.

The NMR proton spin-lattice relaxation rate ($1/T_1$) and the optical density (OD) dose response of PVA Fricke-hydrogel was studied in the range 0 – 10 Gy for different $[\text{Fe}^{2+}]$ and PVA concentrations. A Look-Locker imaging pulse sequence calibrated against an inversion recovery sequence was employed for the quantification of $1/T_1$. A concentration of 20% PVA and 0.3 mM $[\text{Fe}^{2+}]$ was judged as optimal for gel dosimetry with a $1/T_1$ dose response of $0.0321 \pm 0.0003 \text{ s}^{-1} \text{ Gy}^{-1}$. This PVA Fricke-hydrogel formulation appears to show potential for its eventual application in radiotherapy treatment planning verification.

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List of Abbreviations

IMRT	Intensity modulated radiation therapy
PVA	Polyvinyl alcohol
PAG	Polyacrylamide gelatin
NMR	Nuclear magnetic resonance
MR	Magnetic resonance
CT	Computed tomography
RF	Radiofrequency
T_1	Longitudinal (or spin lattice) relaxation time
$1/T_1$	Spin-lattice Relaxation rate
T_2	Transverse (or spin-spin) relaxation time
TE	Echo time
TR	Repetition time
FOV	Field of view
IR	Inversion recovery
LL	Look-Locker
FX	Ferrous ion-xyleneol
TI	Inversion time
OD	Optical density
SNR	Signal-to-noise ratio

Chapter 1

Introduction

The primary objective in radiotherapy is to deliver a prescribed dose of radiation to the tumour as precisely as possible while minimizing the dose to the surrounding healthy tissues. Conformal radiotherapy, a technique for delivery of radiation dose in which the high dose regions of the dose distribution corresponds closely to the tumour volume, was developed with this idea in mind. In external beam therapy, imaging and computational advances have enabled the development of powerful three-dimensional (3D) treatment planning software systems with visualization capabilities to enable beam management. This dose conformation is achieved in external beam therapy by the precise management of the radiation beams and their geometry during treatment. In brachytherapy this is done by using remote afterloaders which provide complex dose distributions by using variable source position and dwell times. The clinical implementation of external beam conformal therapy has been limited by difficulties in verifying both the complex dose distributions calculated by the treatment planning system, and the movements of the machines as in intensity modulated radiation therapy (IMRT) [1]. The ICRU (International Commission of Radiation Units and

Measurements) [2] recommends a 5% accuracy in delivery of dose for successful conformal radiotherapy. To ensure this accuracy there is a need for 3D dosimeters for dose verification and measuring methods with high accuracy.

The verification of dose distributions in conformal therapy is complicated principally by two aspects [3]. Firstly, high dose spatial gradients arise in the target volume in an attempt to conform the dose distribution to the tumour (which is inherently 3-dimensional) since current dosimeters have a limited resolution. Secondly, the treatment modes used are typically dynamic with the movement of the radiation source or patient or both. Thus the total dose at a given location is the integration of the dose contributions over time. This indicates that for dosimetric techniques to be practical, they must be able to integrate the dose distributions over time and have the ability to measure the 3D distribution with good spatial resolution. Acquisition of dose in a 3D volume during a dynamic set up is difficult using traditional dosimetric techniques (for example ion chambers) since it is difficult to conform these dosimeters to the volume of interest. Intensive labour is required for 3D dosimetry using traditional methods such as ion chambers and thermoluminescent dosimeters (TLDs) even when the dose distributions have to be monitored at a few points using simple beam arrangements [4]. Gel dosimeters come closest to fulfilling these requirements, since they can be moulded to desired 3D shapes and the eventual spatial dose distribution after irradiation probed by imaging methods such as MR (magnetic resonance) imaging and CT (computed tomography). A gel dosimeter is a 3D matrix mostly made up of crosslinked polymer molecules into which are incorporated chemical substances which are sensitive to radiation. Currently, the most popular dosimeters are: (i) the Fricke-based gel dosimeters with either agarose,

gelatin, sephadex or polyvinyl alcohol (PVA) as the matrix and ferrous ammonium sulphate as the radiation sensitive chemical, (ii) polyacrylamide-gelatin (PAG) polymer-based gel dosimeter with gelatin as the matrix and acrylamide and bisacrylamide as the radiation sensitive chemicals. Of interest to this work is the radiation-induced change in Fricke-based gel dosimeter which can be measured by spectrophotometry and/or NMR (nuclear magnetic resonance).

1.1 Fricke Gel Dosimetry

Conventionally, spectrophotometry was used to probe radiation changes in the Fricke solution dosimeter [5], but in 1984 *Gore et al* [6] proposed that these changes could be measured by NMR relaxation measurements, this change being the conversion of ferrous (Fe^{2+}) ions to ferric (Fe^{3+}) ions due to radiation. This was based on the theory of paramagnetic relaxation developed by *Solomon* (1955) [7] accurately predicting that the NMR relaxation rates, specifically the spin lattice relaxation rates of the water protons in the vicinity of these two species would be different. This was in agreement with the explanation of changing magnetic relaxation rates resulting from fluctuating local time-dependent fields (*Abragam* 1961) [8] described further in chapter 2.

Gore and his group [6] realized that the spin-lattice relaxation rate could be used to quantify the relative abundance of these ions in solution using magnetic resonance (MR) imaging since these parameters govern contrast in MR images. Since MR imaging provides a 3D imaging capability, this indicated a possibility for 3D dosimetry based on NMR and Fricke gels [5]. This initial proposal culminated in the development and extensive investigation of various gel matrices such as agarose, gelatin and sephadex [9-

16] into which are incorporated ferrous ions. These gels act to “stabilize” (or spatially localize) the chemical change (Fe^{2+} ions to Fe^{3+} ions) which takes place upon irradiation. The main requirements [17,18] for a 3D dosimeter, which happen to correspond to some advantages of gel dosimeters compared with the conventional dosimeters are radiation tissue equivalence, dose integration, tissue inhomogeneities and dose rate independence. These are described below. It was due to these desired properties for 3D dosimeters that gave rise to the interest in the development of gel dosimetry.

1.1.1 Radiation Tissue Equivalence

A tissue equivalent material is either a liquid or solid whose absorbing and scattering properties for a given radiation simulate as closely as possible those of a given biological material such as fat, bone or muscle [19]. For muscle or tissue, water is usually the best tissue equivalent material and since a hydrogel is mostly water it should be therefore be tissue equivalent. The tissue (or water) equivalence of dosimeters can be verified using different methods which use the mass and electron density, mass absorption coefficient $\frac{\mu_{en}}{\rho}$ and the mass stopping power $\frac{L}{\rho}$ calculated at various energies making use of the sum of elemental values of $\frac{\mu_{en}}{\rho}$ and $\frac{L}{\rho}$ for different materials weighted by the atomic weight fractions. These values are then compared to the corresponding values of water. Tissue equivalence can also be measured in terms of Hounsfield units or CT (computed tomography) numbers which compare the linear attenuation of x -rays through the material to that through water and Monte Carlo simulation to calculate the photon and electron dose distributions in the phantom. A problem faced by dosimetric techniques

such as film radiography), diode detectors and TLDs is their high effective atomic numbers compared to tissue. This may cause a high dose response at low photon energies due to the Z -dependence of the photoelectric effect. Also the response of the film may vary with photon energy [20], requiring further corrections if the photon spectrum changes in the phantom. Most of the gel dosimeters currently in use are highly tissue equivalent. *Ayyangar and Chan* [21] used Monte Carlo to investigate the tissue equivalence of gelatin Fricke gels. The mass density, central axis percentage depth dose (PDD), energy deposition and isodose distribution for both x-rays and electrons used in radiotherapy were found to be very close to that of water. The calculated differences between the gel and water were found to be consistently less than 1 %. In studies done at low energies by *Kron et al* [22] for the agarose gel dosimeter, the effective atomic number and the CT number (in Hounsfield units) were very close to that of water. Polymer gels are considered essentially tissue equivalent in terms of density and elemental composition. *Keall and Baldock* [23] studied the tissue equivalence of Fricke gels and two different formulations of PAG gels. The linear attenuation, linear absorption coefficient, linear stopping power, radiative stopping power and scattering power of these gels were compared to that of water. Fricke gels were determined to have the best radiological water equivalence, except at low energies <100 keV due to the iron photoelectric cross section. But in terms of radiative and scattering power water equivalence, the polymer gels were the more tissue equivalent. For the photon and electron depth dose distributions, the photon depth dose curves were all within 1 % of those in water and the electron depth dose within 1 mm of those in water. Another study done by *Rousselle et al* [24] for agarose, gelatin and polymer gels in relation to brain

tissues found the difference between these gels and the whole brain tissues within 1 %. *Chu et al* [25,26] reported the tissue equivalence of a 20 % PVA-Fricke hydrogel (the gel studied in this work) measured using x-rays to be 44 Hounsfield units (HU) which can be considered to be tissue equivalent.

1.1.2 Dose integration

To obtain dose conformation to a tumour, complex dose distributions are usually obtained using dynamic treatment schemes with dose delivery done over the treatment time. This requires that the dose be integrated over this period by a dosimeter. Gel dosimeters have an edge over the conventional methods such as ion chambers or TLDs in that these conventional methods cannot be used to probe the 3D distribution effectively during radiation treatment verification while simultaneously doing the dose integration.

1.1.3 Tissue inhomogeneities

Gel dosimeters can easily be used in the design of anthropomorphic phantoms with the variations in absorbed dose arising due to body shape and tissue inhomogeneities investigated by inserting materials into the phantoms. Of particular interest would be inhomogeneities like bones and air spaces (lungs) having density and effective atomic number different from soft tissue. In clinics, the application of standard isodose charts and depth dose tables assume homogeneous unit density medium, whereas in a patient the beam may traverse layers of fat, bone, muscle, lung and tissue. The presence of these inhomogeneities will distort the dose distribution, depending on the amount and type of material present as well as the quality of radiation. For example on the entrance side of a

photon beam where there is soft tissue surrounding bone, there is dose enhancement in the soft tissue adjacent to the bone (predominantly due to electron backscattering for megavoltage energies) while on the transmission side, the forward scatter of electrons from bone and the buildup of electrons in soft tissue give rise to a dose perturbation effect depending on the energy (dose enhancement for high energies > 10 MV at the interface and less dose for energies < 10 MV initially before building up) [27].

1.1.4 Spatial Resolution in 3-D

To measure the high dose spatial gradients associated with conformal therapy, the ability to measure the dose distribution with high spatial resolution becomes important. Dosimetric techniques (methods) such as TLDs and ion chambers are limited by their size and also by the difficulty in mapping the radiation distribution in 3D. Film possessing a very high spatial resolution in 2-D ($\sim 1 \mu\text{m}$) is limited by the fact that these films are not tissue equivalent and can't be present in large quantities. Gel dosimeters can be used to detect integrated dose in 3-D with high spatial resolution ($\sim 1 \text{ mm}$) in all 3 dimensions using imaging modalities such as nuclear magnetic resonance (NMR) or computed tomography-CT (optical or x-ray).

1.1.5 Independence of dose rate and radiation direction

Treatment modalities such as IMRT, where the radiation intensity distribution for each beam is controlled, require that the dosimeter response be independent of dose rate (or intensity). Also this response has to be independent of the radiation direction since the gantry (and/or patient) might have to be rotated to deliver the radiation dose to the

tumour. A dosimeter like an ion chamber can have the problem of its response changing with the orientation of the dosimeter. A number of investigations for various gel dosimeters have been done. *Olsson et al* [9] investigated the dose rate dependence of agarose and gelatin Fricke gels and found their response to be independent of the mean absorbed dose rate up to 12.4 Gy/min. A maximum deviation of 1.5% was observed from the normalized relaxation rate (normalized to mean value of gel). *Appleby et al* [10] used a Cs-137 source to investigate the response for a 1 % agarose gel for dose rates between 0.434 to 3.74 Gy/min and found no dose rate dependence. Using 250 kV highly filtered x-rays and 25 MV x-rays *Schulz et al* [28] found agarose gels had no dose rate dependence between 4.7 and 24.2 Gy/min.

Since the gel dosimeter acts as both phantom and detector, it permits the evaluation of the complete volume of phantom since there is no need to insert probes such as ion chambers to obtain the desired dose information.

1.2 Previous Studies of Fricke Gel Dosimetry

There have been a number of publications of investigations of clinical setups using Fricke gel dosimetry. For example the possibility of use in conformal therapy has been demonstrated [29] by using ferrous sulfate gels to map a conformal radiation treatment comprising five non-coplanar beams. Gel dosimeters also have applicability in the area of brachytherapy where ferrous gels have been used for investigations with cervix applicators positioned in the gel [30] and isodose plots of the dose distribution in 3D obtained using MR imaging. There have also been other fundamental investigations done [31,32] using ferrous gels as well as investigations in treatment planning with

external beams, such as head and neck treatment utilizing compensators, making use of adjoining beams of different qualities [33], dynamic wedge measurements [10], and bladder cancer treatment [33] using multiple beams involving superimposed photon and electron beams for treatment of breast cancer. Implementations to study the dose distribution effects due to inhomogeneities have also been done. For instance, *Thomas et al* [34] studied the effect of lung inhomogeneities on isodose distribution using Fricke-based agarose gels irradiated using a ^{60}Co source. They found discrepancies of 3 % below the lung inhomogeneity between the MR isodose curves and curves determined with a treatment planning system. This discrepancy was attributed to MR artifacts.

Other investigations have been in the area of radiosurgery dose verification [35-38]. For instance, *Coffey et al* [35] using a tissue equivalent phantom (filled with agarose-Fricke gels) for stereotactic localization and dose verification, found the experimental dose verification results agreed within $\pm 4\%$. In another implementation using Fricke-gels, *Guo et al* [36], using ferrous sulphate gel phantom and MR to determine the frame center for the evaluation of the accuracy of MR guided gamma knife surgery, found that the distances between the frame center and the target point defined by MR images were all within the mechanical accuracy of the gamma knife. Despite some of these promising application studies, there still exists a need for the development of a suitable 3D dosimeter with good reproducibility, stability and devoid of the problems faced by the current dosimeters. For the Fricke-based gels, this amounts to developing and investigating a gel with good reproducibility and little or no diffusion of ferric ions.

1.3 Diffusion and Fricke gel dosimetry

Fricke-gels closely fulfill the requirements of a 3D dosimeter but can have some disadvantages associated with them principally due to diffusion of Fe^{3+} ions from the site of radiation chemical change thereby resulting in the loss of spatial information. There have been attempts using different methods to quantify the diffusion coefficients of various Fricke-based gel dosimeters[28, 39-42]. Most of these studies have been done in order to be able to determine the time limit for these gels to be imaged after irradiation such that there won't be any significant degradation in the dose. The problem of diffusion limits the time between irradiation and imaging of the gel to obtain the dose information. Agarose gels [12,13] have a higher sensitivity than gelatin gels and have diffusion rate lower by a factor of 0.7 [42] and require heating to higher temperatures (90-95°C) to melt. Heating the water to such high temperatures results in significant loss of dissolved oxygen and the gels have to be purged with oxygen subsequently to provide electron acceptors for the radiation conversion of Fe^{2+} to Fe^{3+} . Failure to purge with oxygen results in a non-linear response with dose. *Appleby et al* [43] investigated these oxygen effects and showed that by pre-bubbling the solution with nitrogen the onset of non-linearity is only 4 Gy but when bubbled with oxygen the linearity is extended to 10 Gy. *Olsson et al* [11] reported a linearity in the dose range 0 – 40 Gy for oxygen-purged agarose gels, but these gels lost this linearity when not purged with oxygen. These gels also face a lesser problem of auto-oxidation of the ferrous ions to ferric ions (matter of days), where the rate of auto-oxidation increases as the square of the concentration of the ferrous ions and to a first order with the oxygen concentration [44].

These concerns have motivated the search for new gels with improved qualities. *Maryanski et al* [45,46] introduced a different family of gel called PAG gels [47-51], which are based on radiation-induced polymerization and cross-linking of acrylic monomers infused in a gel matrix. The extent of formation of these cross-linked polymers is dose dependent and results in increased NMR relaxation rates mostly spin-spin relaxation rates ($1/T_2$) of neighboring water protons having a higher sensitivity than spin-lattice relaxation rates $1/T_1$. Radiation makes the gels more solid reducing the water motion and therefore the spin-spin relaxation time (T_2). The relative dose distribution for these gels can be obtained by making use of spin-spin relaxation rate $1/T_2$ having a higher sensitivity than $1/T_1$. These gels are able to maintain their spatial distribution of information for a long time (days) and diffusion is less of a problem compared to Fricke gels. Polymer-based gels can also be analyzed using optical methods with image reconstruction in 2 and 3 dimensions since the radiation effect is visible [40,52]. Also there have been suggestions that the dose distributions can be calculated from MR images based on signal intensities and calibration curves[53], a method similar to the H&D (Hurter and Driffield) curves in film dosimetry which requires calibration for every set of film.

Despite the advantage of less diffusion provided by these polymer gels over Fricke-based gels, they still have some undesirable properties. The materials or monomers and their derivatives used in these polymer-based gels are known to be neurotoxins and carcinogens, thereby requiring careful design of the equipment for proper manufacturing and handling of the chemicals. They also face the problem of oxygen poisoning since the radiation-induced chain can only proceed in the absence of

molecular oxygen. Even trace amounts of oxygen can terminate the growing polymer chains and/or result in the lack of reproducibility and linearity [54]. Due to these concerns *Chu et al* [25,26] developed the Fricke-based PVA cryogels (stored at -20°C) and hydrogels (stored at 5°C) in which he reported a significantly lower diffusion coefficient ($0.14\text{ mm}^2\text{hr}^{-1}$ for hydrogels) and auto-oxidation rate of Fe^{2+} ions to Fe^{3+} ions compared to other Fricke-based gels. The gel matrix for the PVA-Fricke gel is based on PVA, a common water soluble polymer that is used in the film industry and as adhesives and is obtainable with tight manufacturing tolerances and with low impurity levels, which is an advantage over organically based gel materials. The PVA-Fricke dosimeter was chosen for this study principally because of its non-toxicity and the fact that it can be easily prepared in the presence of oxygen, unlike the other polymer gel formulations. To date, no complete comprehensive study of PVA-Fricke hydrogels has been carried out.

1.4 Thesis Overview

The purpose of this thesis was to investigate the PVA-Fricke hydrogel dosimeter in two ways: (i) as a precision dosimeter and (ii) as a 3D dosimeter. Spectrophotometric and T_1 relaxation measurements were studied in order to assess the precision of the PVA-Fricke gels. Also the gel and ferrous ion concentrations were optimized in order to give the best sensitivity. A fast imaging technique was employed for the measurement of the relative increase in $1/T_1$ due to the effects of radiation on the dosimeter in order to speed up measurements and reduce the problem of ferric ion diffusing from their site of formation with time.

Chapter one has presented an introduction to this thesis project, stating some of the basic requirements for 3D dosimetry which are fulfilled by gel dosimeters. In chapter two, the basic theory underlying nuclear magnetic resonance (NMR), relaxation (spin-lattice) of protons and enhancement effects due to paramagnetic agents on proton relaxation are presented. The theory of the Look-Locker method for the estimation of T_1 as well as the radiation-chemistry taking place in Fricke-gel dosimeters is also discussed in this chapter. Chapter three describes the methodology involved in the preparation and irradiation of the hydrogels used in this study, as well as the optical (absorbance) and relaxation measurement method employed. The results and discussion of experiments carried out are presented in chapter four. In chapter four, the sensitivity and precision given by the slope and errors on the slope respectively of either $1/T_1$ or absorbance dose response is reported for the various concentrations of PVA and Fe^{2+} investigated. The reproducibility of the sensitivity and precision of this hydrogel is also reported as a function of the period of storage before irradiation. The conclusion is provided in chapter five with a suggestion to an optimized concentration for this hydrogel and directions for future work.

Chapter 2

Theory

Ever since the discovery of the nuclear magnetic resonance (NMR) phenomenon by Bloch and Purcell in 1946, the popularity of the NMR technique has increased [58,59]. Following this discovery, NMR has been used to analyze the structure of materials, including the study of the dynamics of various molecules. Of relevance to this work, are NMR relaxation times that can be used to study protons of hydrogen atoms in water molecules hydrating the solutes produced by radiation in chemical dosimeters such as Fricke-based dosimeters. In this chapter, the basic theory underlying NMR relaxation, a phenomenon which has been extensively studied, is presented in the first section with attention focused on the spin-lattice relaxation mechanism. This is the mechanism mainly used in the quantification of relative changes taking place in Fricke-based gel dosimeters. The second section gives the underlying mechanism of these chemical dosimeters with reference to Fricke-gel dosimeters together with the chemical changes taking place.

2.1 Nuclear Magnetic Resonance

2.1.1 Basic Theory

The Magnetic Resonance (MR) imaging signal originates from nuclei with an odd number of protons and/or an odd number of neutrons, and of most interest in MR is the hydrogen nuclei (protons). A proton has a property of intrinsic angular momentum referred to as spin $\vec{I}$, with an associated magnetic moment $\vec{\mu}$:

$$\vec{\mu} = \gamma \vec{I} \quad 2.1$$

where γ is the gyromagnetic ratio, a known constant unique for each type of atom. For proton, $\gamma/2\pi = 4258$ MHz/Tesla. In a material containing a collection of protons (or spins) in abundance, a net magnetization ($\vec{M}$) results from the ensemble average of the individual dipole moments contained therein. This magnetization will be zero in the absence of a magnetic field. From the quantum mechanical point of view, an applied static magnetic field, $\vec{B}_0$, oriented by convention along the z-axis, causes a splitting of the energy levels between those spins aligned with and against field (Zeeman splitting). For a system with spin of value $1/2$, and specifying the number in the higher energy state by N_- and N_+ the number in the lower state, the energy separation ΔE between the levels is given by:

$$\Delta E = \gamma \hbar B_0 \quad 2.2$$

and $\hbar$ is Planck's constant (divided by 2π). From (Eqn. 2.2) the photon frequency necessary to cause transitions between these levels is known as the Larmor frequency ω_o , where:

$$\omega_o = \gamma B_o \quad 2.3$$

The lower energy state corresponds to an orientation along $\bar{B}_o$ while the higher state corresponds to an orientation against $\bar{B}_o$. Although the N_+ population is of lower energy and the tendency is to occupy the minimum energy state, thermal energy is sufficient to exceed the energy separation. Hence the ratio of the two populations is dependent on the Boltzmann distribution[57]:

$$\frac{N_-}{N_+} = \exp(-\Delta E/kT) \quad 2.4$$

where k is the Boltzmann's constant and T is the absolute temperature. At room temperature and typical field strength (for example 1 T) the ratio $\Delta E/kT$ ($\sim 10^{-6}$) is a very small number, thus it is possible to make a linear approximation of the Boltzmann exponential and thus obtain the magnetization per unit volume [10]:

$$M_o = \left(\frac{N\gamma^2 \hbar^2}{4kT} \right) B_o \quad 2.5$$

where N is the number of nuclear spins per unit volume.

2.1.2 Excitation and Relaxation

In a typical MR experiment, the equilibrium magnetization oriented along $\bar{B}_o$ is disturbed through a resonant radio-frequency (RF) pulse of magnitude B_1 at or near

Larmor frequency, ω_o . Resonant energy absorption by the spin system occurs with the angular frequency ω_o and the net magnetization $\vec{M}$ becomes time dependent such that the longitudinal magnetization $M_z \neq M_o$ and the transverse magnetization $M_{xy} \neq 0$. After excitation, the magnetization tends to relax back to its equilibrium state (with $\vec{M} = \vec{M}_0$).

Fig. 2.1: Rotating frame behaviour of magnetization showing rotation towards the transverse plane induced by $\vec{B}_1$.

The excitation and relaxation are described by the phenomenological Bloch equations [55] which describe the motion of $\vec{M}$ in a frame (Fig. 2.1) rotating with angular velocity ω with respect to the laboratory frame:

$$\frac{dM_{x,y}}{dt} = \gamma (\vec{M} \times \vec{B}_{eff})_{x,y} - \frac{M_{x,y}}{T_2} \quad 2.6$$

$$\frac{dM_z}{dt} = \gamma (\vec{M} \times \vec{B}_{eff})_z + \frac{M_o - M_z}{T_1} \quad 2.7$$

where T_1 and T_2 are the relaxation time constants which characterize the recovery of the magnetization along the $\vec{B}_o$ field and its decay perpendicular to the $\vec{B}_o$ field respectively.

In this rotating frame representation, the magnetic field experienced during MR experiments includes both a static (B_o) term as well as a rotating radiofrequency (RF) term, B_1 provided by an RF coil and can be expressed as:

$$\vec{B} = B_1 \cos(\omega_o t) \hat{i} - B_1 \sin(\omega_o t) \hat{j} + B_o \hat{k} \quad 2.8$$

where B_1 denotes the magnitude of the magnetic field associated with the RF pulse, conventionally directed along the x-axis. The magnetization in this rotating frame precesses about an effective field given by [58]:

$$\vec{B}_{eff} = \vec{B} + \vec{\omega} / \gamma \quad 2.9$$

where $\vec{\omega}$ is the frequency of the rotating frame about the laboratory frame. For the case where $\omega = \omega_o$ on resonance the last term in Eqn.2.8 cancels with the last term in Eqn.2.9, the magnetization only feels the effect of the RF terms resulting in the nutation or tipping of $\vec{M}$ away from its equilibrium position. The amount of tipping depends on both the magnitude of the RF pulse B_1 and the RF pulse length or duration t_p such that the angular increment by which $\vec{M}$ is nutated, θ is given by

$$\theta = \gamma \int_0^{t_p} B_1(t) dt \quad 2.10$$

Thus, B_1 and/or t_p can be set such that $\vec{M}$ is rotated and left in the transverse plane (90° pulse) or $\vec{M}$ is completely rotated and left on the negative $\hat{z}'$ axis (180° pulse). On removing the RF energy, the leftmost terms of the right hand side of Eqns. 2.6 and 2.7 disappear such that only the relaxation terms remain. Solution of these differential equations results in the magnetization relaxing according to:

$$M_{x,y} = M_{x,y}(0) \exp(-t/T_2) \quad 2.11$$

$$M_z = M_0(1 - \exp(-t/T_1)) + M_z(0)\exp(-t/T_1) \quad 2.12$$

From Faraday's law of induction, the rotating transverse magnetization $M_{x,y}$ induces an electromotive force (EMF) in the RF coil oriented to detect changes of magnetization in the xy plane. The same RF coil that nutates or excites the magnetization can also be used to detect the resulting MR signal.

2.1.3 MR Imaging

To be able to obtain an MR image, physical hardware is needed to encode the spatial information, and a mathematical tool is needed to decode the measured signal. This encoding of spatial information is done through the application of slice selection, frequency encoding, and/or phase encoding magnetic field gradients (typically 1 Gauss/cm) as shown by the pulse timing sequence diagram in Fig. 2.2a. During the period these gradients are on, the frequencies at which the spins are precessing in a voxel become dependent on their spatial coordinates $\vec{r}$:

$$\omega(\vec{r}) = \gamma(B_0 + \vec{G} \cdot \vec{r}) \quad 2.13$$

where $\vec{G}$ is the magnetic field gradient vector. The signal from all voxel magnetizations excited by the RF pulse is given by (where the precession due to the B_0 is ignored)

$$S(t) = \iiint \beta(\vec{r}) \exp(i\gamma\vec{G} \cdot \vec{r}) d\vec{r} \quad 2.14$$

where $d\vec{r}$ represents volume integration and the coefficient $\beta(\vec{r})$, represents the spin density, $\rho(\vec{r})$ weighted by for example the longitudinal relaxation time T_1 and the

transverse relaxation time T_2 . For example, in a conventional inversion recovery imaging technique involving a 180° - TI - 90° sequence of pulses, $\beta(\vec{r})$ can be approximated to

$$\beta(\vec{r}) = \rho(\vec{r})(1 - 2\exp(-TI/T_1))\exp(-TE/T_2) \quad 2.15$$

Fig. 2.2: A pulse sequence timing diagram for a 2D gradient echo imaging sequence. The phase encoding y-gradient is pictured as series of horizontal lines to denote that it is being stepped regularly through increasing values ΔG_y during different repetition periods. T_y is the duration the phase encoding gradient is on; G_x , the readout gradient amplitude, G_z , the slice gradient amplitude and Δt , the interval between data samples with a total readout time of T_x .

where TI denotes the inversion time, which is the time between the 180° pulse and the successive 90° “readout” pulse, and TE denotes the echo time. To decode the acquired MR signal, an inverse Fourier transform is used. Fortunately, Eqn. 2.14 already has the form of the Fourier transformation, where the notion of a reciprocal vector or “k” vector is useful:

$$\bar{k} = \frac{1}{2\pi} \gamma \tilde{G} t \quad 2.16$$

Fig. 2.3: The k -space coverage for a 2D image.

Thus, the Fourier space in which MR signal acquisition is done is usually referred to as the k -space (Fig. 2.3). Using Fourier reconstruction, a final complex valued image is obtained:

$$\beta(\bar{r}) = \iiint S(\bar{k}) \exp(-i\bar{k} \cdot \bar{r}) d\bar{k} \quad 2.17$$

Hence, MR imaging amounts to mapping of k -space for the imaging object with the inverse Fourier transform providing the reconstructed image or the spatial representation of the magnetization distribution.

2.1.3.1 Slice Selective Excitation

The use of a magnetic field in conjunction with limited bandwidth RF can excite MR signals only in a single slice of the imaging volume. This is achieved by applying the B_1 field (RF pulse) in the presence a linear gradient field G_z conventionally in the z -direction. With G_z on and because B_1 must be tuned to the Larmor frequency for excitation to occur, B_1 is now only effective over a frequency bandwidth that matches the bandwidth of the resonance frequencies of spins in the slice of interest. This gradient is applied on an axis perpendicular to the chosen slice plane. This bandwidth is given by $\gamma G_z \Delta z$ and is centered about ω_0 for excitation of the plane at $z = 0$ where Δz is the slice thickness. The extent by which the magnetization is nutated when an RF pulse of duration τ applied is given by Eqn. 2.10.

2.1.3.2 Frequency Encoding

This is a method of obtaining spatial information in one direction, whereby a gradient is on at the same time that the MR signal is being received. Thus, having selected a specific plane using the localization in the z -axis (as described above), the transverse magnetization for every point along the x -axis is achieved using a second gradient G_x with all the other orthogonal gradients turned off. The bandwidth of the received signal is given by:

$$\Delta\omega(x) = \gamma G_x FOV_x \quad 2.18$$

where FOV_x is the field of view in the x -direction and the sampling interval Δt given by:

$$\Delta t = 2\pi / \Delta\omega(x) \quad 2.19$$

is related to the total sampling time by:

$$T_x = N_x \Delta t \quad 2.20$$

where N_x is the number of samples. Of particular interest is the generation of echoes for signal acquisition, where phase variant phase shifts are removed momentarily, thereby improving the coherence and strength of the signal. These echoes are of two types: spin echoes (undoing of phase shifts from field inhomogeneities and chemical shifts) and gradient echoes (undoing of phase shifts from gradient fields). In this project only the latter has been used.

In a reference frame rotating at the central (Larmor) frequency ω_o , phase accrues from off-resonance sources due to magnetic field inhomogeneity, chemical shifts and

applied gradient fields. Assuming perfect main-field inhomogeneity and no chemical shift, the effect on the signal phase from the gradient field is:

$$\phi(\vec{r}, t) = \gamma \int_0^t \vec{G}(\vec{r}, \tau) \cdot \vec{r} d\tau \quad 2.21$$

A gradient echo is said to occur when $\phi(\vec{r}, t) = 0$, that is when two gradient lobes of opposite polarity are sequentially imposed along one gradient axis. To achieve this, a gradient lobe of negative polarity is turned on for duration τ_{deph} , which creates a systematic dephasing by warping the spin phases over space, thus the received signal decays faster than the intrinsic T_2 of the material. At this point the polarity of the gradient field is reversed and phase warping accrued from the time period the dephasing gradient field was initiated is then “unwound” because spins that were precessing at a lower frequency are now precessing at a corresponding higher frequency. An echo begins to form as the spins gain coherence and at time τ_{deph} , equal to the duration the negative lobe is applied, an echo is formed.

2.1.3.3 Phase Encoding

The final step in order to produce a 2D image of the slice, involves application of a positionally dependent phase change to the transverse magnetization along the one remaining principal axis of the image plane. This is achieved by applying a gradient field in the y-direction G_y . This phase change is incremented from view-to-view by changing G_y by the amount ΔG_y for N_y phase encode steps (Fig.2.2). Hence, for each phase encode step, G_y is held constant and the projection along the x-direction measured and

the 2D MR image acquisition matrix is usually given by $N_x \times N_y$. The scan time T_{aq} is determined by the number of excitations N_{ex} , N_y and the repetition time TR of the imaging sequence such that:

$$T_{aq} = N_y N_{ex} TR \quad 2.22$$

2.1.4 Spin-Lattice Relaxation

Relaxation occurs because of interactions between spins and other types of magnetic moments such that spins experience time-dependent magnetic or electric fields. These types of interactions could be spin-rotational, anisotropic chemical shift, scalar, quadrupolar but are primarily dipole-dipole interactions for aqueous Fricke gels. In gel dosimeters, the spin system are protons with the dipole-dipole interaction taking place between either the spins themselves or the spins and the ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions. These ions are paramagnetic since they have a net magnetic dipole moment due to the unpaired electrons orbiting in the outer shell of the ions. As indicated in section 2.1.2, T_1 describes the rate at which a non-equilibrium spin distribution exponentially approaches equilibrium following absorption of RF energy. This spin-lattice relaxation is a type of stimulated recovery in which spins that have been excited by the transmitted RF pulse are encouraged to lose energy by action of an alternating magnetic field of appropriate frequency. This stimulated recovery is very efficient when there is a local fluctuating field that can provide a magnetic perturbation at the Larmor frequency, so that there is available a quantum of energy exactly equal to the difference in levels of nuclear spin states.

The theory of NMR relaxation phenomena in liquids was formulated shortly after World War II [9,59-61]. The theory which follows considers only spins of value $I = \frac{1}{2}$ (for example protons) and follows that given in [7]. For a particle of spin $\vec{I}$ interacting with another particle of spin $\vec{S}$, the Hamiltonian of such an interacting pair in a magnetic field B_o along the z-axis is:

$$H = -\hbar\gamma_I B_o I_z - \hbar\gamma_S B_o S_z + H' \quad 2.23$$

where the first two terms are the Zeeman Hamiltonian term and H' is the time dependent perturbation Hamiltonian for either the spin-spin interaction or interaction between the spin and the RF field. Considering only the dipole-dipole interaction (predominant interaction in a Fricke-gel dosimeter) with Hamiltonian:

$$H' = -\left(\frac{\hbar\gamma_I\gamma_S}{r^3}\right)\left[\frac{3(\vec{I} \cdot \vec{r})(\vec{S} \cdot \vec{r})}{r^2} - \vec{I} \cdot \vec{S}\right] \quad 2.24$$

where $\vec{r}$ is the vector between the two spins, the transition probability per unit time (to the first order) between the two eigenstates $|m_i\rangle$ and $|m_j\rangle$ of the unperturbed Hamiltonian with energies E_i and E_j respectively is given by:

$$W_{ij} = \frac{1}{t} \frac{1}{\hbar^2} \left| \int_0^t \langle m_j | H'(t') | m_i \rangle \exp(-i\omega_{ij}t') dt' \right|^2 \quad 2.25$$

with $\omega_{ij} = (E_j - E_i)/\hbar$. For spin values of $\frac{1}{2}$, four eigenstates can be defined so that there exist four unperturbed eigenstates of a pair given by $|+\rangle|+\rangle$, $|+\rangle|-\rangle$, $|-\rangle|+\rangle$, and $|-\rangle|-\rangle$ with occupation numbers N_{++} , N_{+-} , N_{-+} and N_{--} respectively. The transition probabilities per unit time between these 4 states are denoted by W_0 , W_1 , W_1' , and W_2 for transitions between the states $|+\rangle|-\rangle$ and $|+\rangle|+\rangle$, $|+\rangle|+\rangle$ and $|-\rangle|+\rangle$, $|-\rangle|+\rangle$ and

$| \uparrow \rangle | \uparrow \rangle$, and $| \uparrow \rangle | \downarrow \rangle$ and $| \downarrow \rangle | \uparrow \rangle$ respectively. Considering only the longitudinal component of the magnetic moment (I_z, S_z), the equations of motion can be shown to be:

$$\frac{d\bar{I}_z}{dt} = -(W_0 + 2W_1 + W_2)(\bar{I}_z - I_0) - (W_2 - W_0)(\bar{S}_z - S_0) \quad 2.26$$

$$\frac{d\bar{S}_z}{dt} = -(W_2 - W_0)(\bar{I}_z - I_0) - (W_0 + 2W_1 + W_2)(\bar{S}_z - S_0) \quad 2.27$$

where I_0 and S_0 are the equilibrium values of the magnetic moments of spins $\bar{I}$ and $\bar{S}$, and $\bar{I}_z$ or $\bar{S}_z$ denote the average values of the longitudinal component of these magnetic moments.

For a system where the spins are identical $\gamma_I = \gamma_S$ (gyromagnetic ratios for the moments $\bar{I}$ and $\bar{S}$), the observable quantities become $\bar{I}_z + \bar{S}_z$ and it follows that $W_1 = W_1'$, giving the equation of motion as

$$\frac{d(\bar{I}_z + \bar{S}_z)}{dt} = -(W_1 + W_2)(\bar{I}_z + \bar{S}_z - I_0 - S_0) \quad 2.28$$

having an exponential solution with the relaxation time:

$$\frac{1}{T_1} = 2(W_1 + W_2) \quad 2.29$$

From the computed values of transition probabilities [64] in a homogeneous system ($\omega_I = \omega_S = \omega$):

$$\frac{1}{T_1} = \frac{6}{20} \frac{\hbar^2 \gamma^4}{r^6} \left[\frac{\tau_c}{1 + \omega^2 \tau_c^2} + \frac{4\tau_c}{1 + 4\omega^2 \tau_c^2} \right] \quad 2.30$$

where τ_c is the correlation time and ω the Larmor frequency of the spin. The expression in Eqn. 2.30 is for rotational motion, which is all that is necessary to consider for intra molecular dipole-dipole interactions.

A further source of interaction on the spin are fluctuations in the local field arising from the protons on neighboring molecules and is mainly caused by translational motion such that [59]:

$$\left(\frac{1}{T_1} \right)_{transl} = \frac{9\pi^2 \gamma^4 \hbar^2 \eta N_0}{5kT} \quad 2.31$$

where η is the viscosity of the liquid and N_0 the number of molecules per cm^3 . Combining Eqns. 2.30 and 2.31, the observed relaxation rate is the sum of the intra-molecular (rotational) and intermolecular (translation) terms:

$$\frac{1}{T_1} = \left(\frac{1}{T_1} \right)_{rot.} + \left(\frac{1}{T_1} \right)_{transl.} \quad 2.32$$

2.1.5 Relaxation of Nuclei in Paramagnetic Solution

The relaxation of a nuclei spin $\vec{I}$ in a paramagnetic solution is almost entirely the result of the dipole-dipole interaction H between $\vec{I}$ and the electronic spin $\vec{S}$ of a paramagnetic ion. Since the perturbation for the electronic spin $\vec{S}$ relaxation can be considered negligible in the time scale of observations of the nuclear magnetic moment, $\vec{S} = S_0$. Thus from Eqns. 2.24 and 2.25 the nuclear spins $\vec{I} = \frac{1}{2}$ have simple relaxation times [7]:

$$\frac{1}{T_1} = W_0 + 2W_1 + W_2 \quad 2.33$$

After inserting the transition probabilities, the spin lattice relaxation rate becomes:

$$\frac{1}{T_1} = \frac{1}{10} \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{r^6} \left[\frac{\tau_c}{1 + (\omega_I - \omega_S)^2 \tau_c^2} + \frac{\tau_c}{1 + \omega_I^2 \tau_c^2} + \frac{\tau_c}{1 + (\omega_I + \omega_S)^2 \tau_c^2} \right] \quad 2.34$$

Paramagnetic agents on the atomic scale generate extremely strong local magnetic fields experienced by water protons ($\gamma_s = 658\gamma_I$), because the electrons have a smaller mass but have the same charge as the protons, so that any water molecule approaching an unpaired electron will experience an interaction which can promote relaxation.

The correlation time, τ_c characteristic of this interaction is determined by the combined effects of three independent processes: τ_r , rotation (alters the orientation of the proton relative to the magnetic field of the electrons and doesn't vary much from one ionic species to the next); τ_s , electron spin relaxation (refers to the time which elapses on average before the electron spin itself alters its orientation) and; τ_m , proton exchange (denotes process whereby the water molecules enter and depart the hydration sphere of the paramagnetic center, τ_m). Thus,

$$\frac{1}{\tau_c} = \frac{1}{\tau_r} + \frac{1}{\tau_s} + \frac{1}{\tau_m} \quad 2.35$$

Since the above relation indicates that τ_c is dominated by the fastest process, $1/\tau_m$ can be neglected since the exchange process is very slow. Though the spin states and ionic radii are different for Fe^{2+} and Fe^{3+} ions, the dominant correlation time is τ_s ($\sim 10^{-12}\text{s}$), which is approximately thirty times larger in Fe^{3+} than in Fe^{2+} ions [6]. The increased relaxation

rate of Fe^{3+} ions relative to the Fe^{2+} ions is principally due to the difference in correlation time for each ion with the ratio [62] $\tau_c^{3+}/\tau_c^{2+} \approx 34$.

2.2 T_1 Measurement

Pulse methods provide the most versatile method for measuring T_1 's over a wide range of values. The conventional method to estimate T_1 is the inversion recovery (IR) pulse sequence illustrated in Fig. 2.4. It consists of a 180° pulse which inverts the equilibrium longitudinal magnetization $\bar{M}_0$. This places the magnetization along the negative z-axis at which point $\bar{M}_0$ relaxes back to equilibrium along $\hat{z}'$. If at a time TI (known as the inversion time), a 90° pulse is applied, the longitudinal magnetization will be tipped into the transverse plane, at which point a free induction decay (FID) forms and signal acquisition takes place. If the system is allowed to return to equilibrium by waiting at least $5T_1$ intervals, the sequence can be repeated at time TR (the repetition time) to collect a signal corresponding to a new TI value. Thus, each point on the recovery curve (Fig. 2.4c) results from a separate $180^\circ, \text{TI}, 90^\circ$ sequence and can be used to extract T_1 by fitting using Eqn. 2.15.

The main drawback of this technique is the long TR required for the longitudinal recovery which, when coupled with the need for acquisition of multiple data points to characterize the recovery curve, makes the measuring process time consuming (hours). This draw back can be overcome by using a “one shot” method proposed by Look and Locker [63]. In the Look-Locker method, all the TI points required are collected in a single shot and hence results in time saving especially for T_1 imaging. This Look-Locker

(LL) imaging sequence can have an efficiency, accuracy and precision approaching the inversion recovery method [64]. The behaviour of the MR signal in the Look-Locker imaging sequence has been completely characterized [65] as discussed below.

Figure 2.4. Determination of T_1 by IR sequence. (a) $\vec{M}$ is inverted by 180° pulse. (b) After time TI a 90° pulse rotates $\vec{M}$ to the y' axis. (c) The signal amplitude which is proportional to the value of $\vec{M}$ as a function of time TI . Each point results from a separate 180° - TI - 90° sequence.

2.2.1 Look-Locker Method for T_1 imaging

The basic idea behind this method is that following an inversion pulse (for optimal dynamic range), the recovery of longitudinal magnetization is repeatedly sampled during its approach to steady state ($\neq M_0$) by a series of small flip-angle RF pulses (α) separated by a small time interval τ (see Fig.2.5). The magnetization recovery is modulated by the α pulses, and therefore the magnetization is driven to a steady state with the modified relaxation time T_1^* :

$$T_1^* = \frac{T_1}{1 - \frac{T_1}{\tau} \ln(\cos(\alpha))} \quad 2.36$$

After the inversion (180°) RF pulse, which sets the longitudinal magnetization

Fig. 2.5: A schematic diagram of a Look-Locker pulse method (the phase and read encoding gradients omitted in this diagram follow the gradient echo representation in Fig. 2.2). In the implementation of the method, the 180° pulse is adiabatic and non-slice selective. G_z indicates the slice select gradients with S representing the spoilers.

$M(t=0) = M_0$ to a defined starting value $-M_0$, the train of readout α pulses are followed by a set of gradient echoes in order to form an image. Sufficient data (128 X 64) can be collected at each sample point to produce a complete image. Unlike the inversion recovery method, all the points (Fig.2.4c) required to characterize the recovery curve are collected following a single 180° and train of α pulses. The τ is chosen to be constant. After each gradient echo acquisition, the remaining transverse magnetization is destroyed by a spoiler gradient. This is to avoid the preceding residual transverse magnetization affecting signal due the next α pulse. The theoretical signal equation also includes the effect of a non-zero time t_d between the first inversion pulse and first α pulse, and a waiting time t_r at the end of the train of α pulses. From Brix *et al* [65], longitudinal magnetization just before the n-th ($1 \leq n \leq N$) pulse is given by:

$$M_n = M_0 [F + (\cos(\alpha)E_\tau)^{n-1}(Q - F)] \quad 2.37$$

where

$$F = (1 - E_\tau) / (1 - \cos(\alpha)E_\tau)$$

$$Q = \frac{-F \cos(\alpha)E_r E_d [1 - (\cos(\alpha)E_\tau)^{N-1}] - 2E_d + E_r + 1}{1 + \cos(\alpha)E_r E_d (\cos(\alpha)E_\tau)^{N-1}}$$

$$E_\tau = \exp(-\tau/T_1),$$

$$E_r = \exp(-tr/T_1),$$

$$E_d = \exp(-td/T_1),$$

M_0 is the equilibrium magnetization, and N is the total number of read-out pulses (and also corresponds to the number of images). The signal amplitude of the n -th gradient-echo image at a pixel (i, j) is given by:

$$S_n(i, j) = |\sin(\alpha)(i, j) M_n(i, j) \exp(-TE/T_2^*(i, j))| \quad 2.38$$

where TE is the echo time (time between the read out pulse and the middle of the gradient echo) and T_2^* is the decay constant characterizing the decay of the transverse magnetization. The above equations can be arranged into an IR relation with the relaxation constant given by Eqn.2.36 [66].

2.3 Fricke dosimetry

Water forms the bulk of most chemical dosimeters, thus the action of radiation on water and the products of water radiolysis become very important in the subsequent reactions taking place in these dosimeters. For instance in the standard Fricke dosimeter (consisting of 1 mM ferrous sulphate (FeSO_4) or ferrous ammonium sulphate $\text{Fe}(\text{NH}_4)_2(\text{SO}_4)_2$, 1 mM NaCl (sodium chloride), 0.4 M sulphuric acid (H_2SO_4) air saturated and prepared from triply distilled water), the dosimeter solution is usually at least 96 % water[73]. The radicals $^{\circ}\text{H}$, $^{\circ}\text{OH}$, e_{aq}^- , H_2O_2 (e_{aq}^- is an aqueous ion) produced from the radiolysis of water [5,67-71] (Appendix A) are mainly responsible for the subsequent reactions taking place in the standard Fricke dosimeters and Fricke-gel dosimeters.

2.3.1 Fricke-Gel Dosimetry

The Fricke-dosimeter is very useful in determining the average dose to an irradiated volume since there is constant diffusion of the ferric ions within the solution. To be able to apply it in 3D dosimetry, the solution has to be incorporated into a gel matrix for spatial localization of chemical changes (Appendix B). Fricke gel dosimeters have a higher sensitivity than the traditional Fricke dosimeter. This is not unexpected, since it is well known that organic impurities can increase the ferric yield [5,68] and it is organic substances that are used in gelling. To explain the much improved sensitivity of Fricke-based polymer gel dosimeters, a chain reaction within the gel has been proposed [72,73], with the reaction scheme being adapted from Hart (1952) [74] for ferrous sulfate solutions containing formic acid. The products from the radiolysis of water ($^{\circ}\text{H}$, e_{aq}^{-} , $^{\circ}\text{OH}$, and H_2O_2) initiate this chain reaction. Using RH to represent the gel molecule, and RX and ROH to represent the reduced and oxidized forms of the gel molecule respectively, the following reaction scheme broken into three stages was postulated:

Initiation

By exposing the gel to radiation, the radicals $^{\circ}\text{H}$, $^{\circ}\text{OH}$, e_{aq}^- and H_2O_2 are generated from water radiolysis. These products react with the gel molecule, RH and induce the radical, $^{\circ}\text{R}$ (reactions 2.40 and 2.41), which starts the chain reaction.

Propagation

Steps 2.42 and 2.47 are the most important steps for the chain reaction. In step 2.42 a radical $^{\circ}\text{RO}_2$ is formed which both oxidizes both Fe^{2+} ions, (2.43), (2.45), and (2.46), and results in a new radical, $^{\circ}\text{RO}$. This radical can react again with the gel molecule (2.47), resulting in a new $^{\circ}\text{R}$ radical and the reaction can then start from the beginning again. This process is dependent on the gel being well oxygenated. Reactions (2.50) –(2.54) could terminate the chain and will dominate at high doses as Fe^{3+} builds up.

Termination

The reaction products from reactions 2.50 to 2.54 will not contribute further to continual chain reactions. There is a finite possibility that ferric ions will be reduced, 2.50 and 2.54. This possibility is normally small, but would increase when the fraction of ferric ions grows. Reactions 2.51 and 2.53, though producing ferric ions, will terminate the chain reaction

2.5.2 NMR Fricke Dosimetry

Each of the different spin groups in gel dosimeters have an inherent relaxation properties determined by the molecular dynamics and interactions experienced by the spins. If the spin groups are not isolated, an exchange of magnetization information occurs between the spin groups so that the overall observed relaxation rate differs from the inherent relaxation of the individual spin groups. The simple Bloch equations no longer express the magnetization evolution of the heterogeneous spin system wherein some form of exchange occurs. When exchange occurs there are additional terms in the Bloch equation to account for the loss or gain of spins between the different groups. For instance, the diffusion of water molecules from the hydration sphere of ferric ions to the bulk water region. This exchange can be broken down into 3 categories namely slow, intermediate and fast regimes [75,76]: (i) In the slow regime the exchange rates are slow compared to the inherent relaxation rates, and the relaxation is the weighted average of effects taking place in each group, (ii) for the intermediate exchange, the observed rates and magnetization fractions of the spin groups remain complicated functions of the

inherent relaxation rates and exchange rates, (iii) for the fast exchange, the rates of magnetization exchange between the groups are much faster than the inherent rates and the relaxation is described by a single relaxation rate, a weighted average of the various relaxation rates.

In Fricke gel dosimeters, there are four water proton groups (hydrogen nuclei on water molecule): the bulk water protons, the water proton hydrating the ferrous and ferric ions, and the water protons hydrating the gel. The exchange of water protons between all four groups determine the overall relaxation rate observed. Each proton group has associated with it an inherent relaxation rate with the size determined by the water proton fraction p^i . $p^i = k^i [i]$ gives the relation of the water proton to the actual concentration of the hydrated solute, where k^i is the fraction of water protons hydrating the solute of concentration $[i]$. Rapid exchange has been observed for the overall relaxation rate R_1 ($1/T_1$) of water in Fricke gels [76]. This rate is simply the sum of the inherent rates, each weighted by the fraction of water protons p^i , in their respective groups, as follows [81]:

$$R_1 = p^{3+} R_1^{3+} + p^{2+} R_1^{2+} + p^{gel} R_1^{gel} + (1 - p^{3+} - p^{2+} - p^{gel}) R_1^{water} \quad 2.55$$

which can be rearranged to have

$$R_1 = r_1^{2+} [Fe^{2+}] + r_1^{3+} [Fe^{3+}] + r_1^{gel} [gel] + R_1^{water} \quad 2.56$$

where the r_1^i are the relaxivities of the respective groups and specify the ability to enhance the spin-lattice relaxation of water protons. Eqn.2.56, indicates that in the fast exchange regime, R_1 varies linearly with the concentration of ions. By noting that $[Fe^{2+}] + [Fe^{3+}] = [Fe^{2+}]_0$, where $[Fe^{2+}]_0$ is the initial ferrous ion concentration Eqn. 2.56 may be rewritten as [81]

$$R_{1Gy} = (r_{eff}^{3+} - r^{2+})[Fe^{3+}] + r^{2+}[Fe^{2+}] + R_1(0Gy) \quad 2.57$$

where $R_1(0Gy) = (r^{2+}[Fe^{2+}]_0 + r^{gel}[gel]_0 + R_1^{water})$. Thus, the ability of NMR to measure the relaxation time of an irradiated Fricke-gel comes from the difference in the relaxivity of the two paramagnetic ions. Also of note is the ratio of the inherent spin lattice relaxation rates for protons in the coordination shell of the two ions (Fe^{2+} and Fe^{3+}) which can be calculated from Eqn.2.34, and at 1.5 T, $R_1^{Fe^{3+}} / R_1^{Fe^{2+}} = 16.6(r_{2+}/r_{3+})^6$ [41]. This relation has also been suggested [73] as an explanation of the potential of the NMR method to measure the relative concentrations of Fe^{2+} and Fe^{3+} ions in irradiated Fricke solutions. The term r_{2+}/r_{3+} is the ratio of the distances between the coordination of water protons and the centers of the ferrous ions and ferric ions.

Chapter 3

Materials and Methods

In this chapter, a description of the materials used for the preparation of the gel samples, their preparation procedure and irradiation procedure is presented. The instruments and methods used for quantification of the radiation change both spectrophotometry and MR are presented in the latter part of the chapter.

3.1 Sample Preparation

PVA (polyvinyl alcohol) gels consisting of 50 mM sulfuric acid (UNI 1830 Cas no 7664-93-9, J.T.Baker, USA), 98 % hydrolysed PVA (13000-23000 mw. 34,840-6 Aldrich Milwaukee WI), ferrous ammonium sulfate (20,350-5, Aldrich, Milwaukee WI) and xlenol orange (22,785-4, Aldrich Milwaukee WI) were prepared. Sample preparation [25,26] consisted of dissolving PVA crystals in a pre-made 50 mM sulfuric acid solution (which was made using DI water) to obtain PVA concentrations of 20% . 24% or 27.6% by mass (w/w). The PVA concentrates were then boiled under continuous stirring in a flask with a reflux condenser to eliminate loss of water. Due to the fact that the viscosity increases during the first 30 minutes and stirring is not very effective at this

stage, the boiling was done in two phases. In the first phase, heating was done at a temperature of 85°C for 1 hour in order to prevent burning and to permit the PVA to go into solution with a reduction in viscosity. The second phase involved heating at a temperature of 100°C for 2 hours in order to obtain complete dissolution (This is a consequence of PVA's appreciable crystalline content, thus reducing dissolution in water at room temperatures. This requires heating to a fairly high dissolution temperature and then keeping at that temperature for full molecular dispersion to take place[77]). The requirement of high dissolution temperature (100°C or above) is crucial, and failure to do so subsequently leads to automatic oxidation of ferrous (Fe^{2+}) ions to (Fe^{3+}) ions upon mixing the ferrous ion solution with the boiled PVA concentrate. Ferrous ion and xylenol (FX) concentrations of 4.2 mM, 3.0 mM, 1.8 mM, and 1.2 mM were then prepared in a molar ratio of 1:1 between the Fe^{2+} ions and xylenol orange. The xylenol orange permits spectrophotometry to be done in the visible region of the electromagnetic spectrum. The xylenol orange used in the gel preparation is a metal indicating dye which complexes with ferric ions and this complex has a maximum light absorption at the green wavelength. The degree of complexing increases with the dose and is observed as a colour change with a darker brownish coloration for higher doses due to the increased presence of Fe^{3+} ions. The xylenol orange though permitting colour change for optical dosimetry, also has the advantage of reducing the diffusion rate of ferric ions. In the complex formation, the metal ion is the central atom. This resultant increment in size reduces the average path each metal ion travels per unit time [78].

After letting the PVA-water mixture cool down to 40°C. it was then mixed with the FX solution in a mass ratio of 5:1. The gel mixture was then poured into centrifuging

tubes and centrifuged for 10 minutes so as to remove any air bubbles. The air bubbles have to be eliminated to perform optical density or MR measurements. After centrifuging, the gel mixture was then poured into 1 cm x 1 cm x 4 cm polystyrene spectrophotometer cuvettes. This gave a final of twelve combinations of PVA/FX with concentrations of 15%, 20 % and 23 % w/w for the PVA each with 0.7 mM , 0.5mM, 0.3mM and 0.2mM FX. The gels were then refrigerated for two weeks at a temperature of about 5 °C in order to obtain proper gelation. The range of Fe^{2+} concentration was chosen based on the fact that too small a concentration of Fe^{2+} ions will limit the dynamic range (linear portion of a dose response curve) as shown in Fig 3.1 and Fig. 3.2 for a

Fig. 3.1: $1/T_1$ versus dose plot for a 20% w/w PVA and 0.1 mM Fe^{2+} concentration. The curve is non-linear in the 0 – 10 Gy range.

20% w/w PVA and 0.1 mM $[\text{Fe}^{2+}]$ hydrogel that was made and irradiated in order to define the minimum $[\text{Fe}^{2+}]$. This is due to the fact that the amount of Fe^{2+} ions available for oxidation will become exhausted for higher doses. On the other hand, using too high an Fe^{2+} ion concentration, will result in a very short initial T_1 with less effective shortening of the T_1 upon irradiation, making the quantification of the relative increase between dose levels less efficient.

Fig. 3.2: OD versus dose plot for a 20% w/w PVA and 0.1 mM Fe^{2+} ion concentration. The curve is non-linear in the 0 – 10 Gy range

3.2 Irradiations

Irradiations were performed at the Institute for National Measurement Standards (INMS) NRC using a ^{60}Co Eldorado 6 (Atomic Energy of Canada) therapy unit. The

samples (or cuvettes) were allowed to stand for 2 hours following removal from the refrigerator in order for the gels to equilibrate to room temperature and then irradiated in groups of 5 at each dose level. This was done in order to avoid condensation on the surface of the cuvettes affecting the optical density (or absorbance) readings. The samples (cuvettes) were placed in groups of fives at 100 cm from the source with the aid of a holder providing full build-up and a phantom to provide full back scatter with the field size of 17 cm x 17 cm set at the middle of the cuvettes. The field size of 17 cm x 17 cm was chosen so as to minimize any dose gradient across the five samples, since for a given field size, only the central third of it is uniform. In order to reproducibly set the field size, a mechanical template was employed. This template has holes at either ends that can slip over a pair of machined pins, one pair for each of the vertical and horizontal collimators.

By varying the exposure time, dose of values of approximately 0, 2, 4, 6, 8 and 10 Gy were delivered with samples irradiated in groups of 5 at each dose level. The following relation was used to calculate the dose rate, $\frac{D}{t}$ from the exposure rate, $\frac{X}{t}$:

$$\frac{D}{t} = \frac{X}{t} K_{FS} f_{med} K_{BS} K_{\%dd} \quad 3.1$$

where K_{FS} (= 1.040) and K_{BS} (= 1.056) are the 17 cm x 17 cm field size and backscatter correction factors respectively. $K_{\%dd}$ (= 0.9790) is the percentage depth dose correction factor correcting for the dose fall-off due to the offset of the cuvettes midpoint from the depth of maximum dose while f_{med} (in rad/R) is the rad-to-roentgen conversion factor for water to air.

3.3 MR Measurements

For Fricke-based gels, it is crucial to use a fast imaging method in order to minimize the blurring effects due to diffusion of the ferric (Fe^{3+}) ions. In this project a Look-Locker imaging method was implemented for the quantification of the relative increase in spin lattice relaxation time T_1 due to the increase in the concentration of ferric ions from radiation. The Look-Locker imaging sequence used in this project was based on a modification (as described below) of an already existing gradient echo imaging sequence in the MR computer console (MRRS, Guildford, England, Model #5000) of the Carleton Magnetic Resonance Facility (CMRF). This sequence was implemented on a 1.89 T (Magnex Scientific, Abingdon, Oxon, England) magnet with all measurements done at room temperature.

3.3.1 Imaging Pulse Sequence

Fig. 2.4 shows the Look-Locker imaging sequence employed in this study. The following parameters were used: $t_d = 20\text{ms}$, slice thickness of 7 mm, a total of 24 (N) 5° flip angles (RF pulses) spaced with an inter-pulsing time τ of 150 ms, a field of view (FOV) of 140 mm with an acquisition matrix ($N_x \times N_y$) of 128 x 64, an echo time TE of 6 ms, a TR of 4000 ms with two averages taken. The choice of 150 ms for τ allows sufficient time for the various encoding gradients.

The flip angle α was varied from 5° to 40° and the choice of 5° was to minimize the effect of tip angle accuracy on the fitted T_1 due to the coupling between T_1 and α .

Arranging Eqn.2.36 to give T_1 in terms of α and calculate to first order the error propagated into T_1 due to error in α :

$$\frac{\partial T_1}{\partial \alpha} = \frac{\tau}{(\tau/T_1^* + \log_e(\cos(\alpha)))^2} \tan(\alpha) \quad 3.2$$

Thus the error in T_1 due to propagation of error in α is quite severe as α increases. The choice of TR of 4000 ms provides sufficient time for complete recovery of magnetization before the next inversion/ α train. It took approximately 9 minutes to acquire a complete data set.

In imaging a given batch of gels all the samples were imaged at once. It was important that a good population inversion of spins in a given slice across the whole image (FOV) was achieved in order to minimize the effects of residual transverse magnetization at the slice edges. An adiabatic inversion pulse fairly insensitive to RF and static field non-uniformities was employed for this purpose (see Appendix C). This was in order to reduce deviation in the estimated T_1 for samples with the same dose, since caution was taken to spread out samples with the same concentration (or gels irradiated to same dose). No position dependence on the extracted T_1 was observed. The adiabatic pulse implemented is based on the method suggested by *Hardy et al* [79]:

$$\omega(t) - \omega_0 = \omega_1 \tan(\varepsilon \omega_1 t) \quad 3.3$$

where $-T_0/2 \leq t \leq T_0/2$, T_0 being the total sweep time and the constant ε is determined by $\omega_1 = \gamma B_1$, T_0 , and the angular frequency sweep range $2\Omega_1$:

$$\varepsilon = \left(\frac{2}{\omega_1 T_0} \right) \arctan \left(\frac{\Omega_1}{\omega_1} \right) \quad 3.4$$

The wave editor available on the MR image console was used to implement this adiabatic pulse based on Eqn. 3.3 with $B_1 = 0.2 \text{ G}$, $\Omega = \pm 20 \text{ kHz}$ and $T_0 = 10 \text{ ms}$.

3.3.2 Data Fitting

To extract T_1 , a three parameter fit of Eqn.2.38 to the image signal intensity was done. The three parameters T_1 , α and $A I = M_0 \exp(-TE/T_2^*)$ were computed based on regions of interest drawn by hand over cuvettes in the Look-Locker images by minimizing the weighted sum χ^2 of square deviations (non-linear least square) where the quantity χ^2 is defined as

$$\chi^2 = \sum_{n=1}^N [(S_n - L_n) / \sigma_n]^2 \quad 3.5$$

where L_n is the measured signal and σ_n the standard deviation of the n-th gradient echo. As described above, variations in α were expected due to positional variations in the flip angle across the image. The least squares fitting assumed a Gaussian noise distribution and used a Levenberg-Marquardt algorithm, with the errors on the fitted parameters calculated from the inverse covariance matrix. Although the MR magnitude data has a Rician distribution for low signal to noise ratio (SNR), this distribution approaches a Gaussian distribution as the SNR increases. The SNR in the acquired images was high enough to justify a least-squares fit. Due to the non-linear nature of the signal equation, the fitting efficiency was found to be sensitive to the starting values. Therefore a starting value $T_{1(0)}$ for the fit was estimated from the relation

$$T_{1(0)} = \tau \left[\ln \left\{ \cos(\alpha) \frac{L_{i-1} - L_{i-2}}{L_i - L_{i-1}} \right\} \right]^{-1} \quad 3.6$$

where the points i were chosen on the steeply ascending part of the recovery curve. $\alpha_{(0)}$ was set to the prescribed value used in the sequence. $A_{I(0)}$ was set to the maximum signal value.

To validate the performance of the Look-Locker sequence, aqueous gadolinium (Gd) samples were prepared with concentrations varying between 0.13 mM and 0.67 mM and imaged both with a conventional inversion recovery technique and the Look-Locker imaging method. The fitted T_1 's using both methods were then compared. The inversion recovery imaging sequence used a FOV of 140 mm, a 128 x 128 acquisition matrix, TIs of 7, 42, 78, 117, 158, 202, 250, 301, 357, 418, 485, 561, 646, 745, 861, 1004, 1188, 1448, 1891, 1960 ms, a slice thickness of 7 mm, with a TR of 9060 ms. The IR T_1 was calculated using a 3-parameter (T_1 , A, B) least square fit of the inversion recovery signal equation:

$$S_{IR} = A(1 - B \exp(-TI / T_1)) \quad 3.7$$

to the image intensity measurements. All the fittings were done using Matlab software package (Matlab 5.3, The Matworks Inc. USA).

3.4 Spectrophotometry

The spectrophotometric absorbance or optical density (OD) of the samples was also investigated as a function of dose using a Cary 400 Spectrometer (Varian Optical Inst., Australia) to measure the optical density. Broad band radiation from a quartz halogen lamp is collected, focused and directed through a monochromator which can be adjusted to isolate selected wavelengths. With the spectrophotometer radiation of the selected wavelength from the monochromator exits and strikes a rotating mirror, which

alternately directs the beam through a “sample” space and then through a “reference” space. The two light beam paths are then redirected to converge onto a phototube. The relative intensities of the two beams alternately strike this phototube, providing a measure of the amount of radiation absorbed (or of the amount transmitted) by the sample. The instrument readout may be selected to be linear in percent transmission or absorbance. All measurements were done in the absorbance or OD mode. The absorbance of a substance at a particular wavelength is the negative base 10 log of the transmittance

$$Abs = \log_{10} \left(\frac{\text{radiation_transmitted_by_sample}}{\text{radiation_transmitted_by_reference_sample}} \right) \quad 3.8$$

An absorption spectrum from 400 nm to 700 nm shown in Fig. 3.3 was obtained for a sample irradiated up to 5 Gy with an un-irradiated sample used as the reference sample. The absorbance maximum was centered at 545 nm with a bandwidth of 3.5 nm. These values were used in all subsequent readouts. The samples were allowed to equilibrate to room temperature upon removal from the refrigerator, after which the sample optical densities were read before irradiations. The samples were then read again after irradiation at 20.0 ± 0.1 °C. The readings of each cuvette’s OD, pre and post-irradiation was done to minimize the differences in optical density values due to differences in thickness between cuvettes given the same dose.

Fig.3.3: Absorption spectrum of an irradiated PVA-Fricke hydrogel sample over the wavelength range of 400 nm to 700 nm with a 3.5 nm bandwidth. The absorbance peak is at 545 nm.

3.5 Reproducibility

The dose response ($1/T_1$ and absorbance) was investigated as a function time between making the gels and irradiation. This was done by making three batches of gel all having a final concentration of 20 % w/w PVA/0.3 mM Fe^{2+} . These three batches were broken down into four different groups and irradiated after different periods of storage varying from 1 week to 4 weeks.

Chapter 4

Results and Discussion

In this chapter, the results of the experiments are presented. In the first section, results of the performance of the Look-Locker sequence validated against an inversion recovery sequence are shown. In this section, the effect of tip angle on the estimated T_1 is also presented. In the second section, the dose response or the sensitivity (MR relaxation and optical density) defined as the slope of the relaxation rate $1/T_1$ or the change in optical density (or absorbance) versus dose is given. The precision results are presented as the errors on the slopes. The reproducibility studies for three different batches broken into five different groups is presented in the third section.

4.1 MR Measurements

4.1.1 Effect of Tip angle on T_1

Fig 4.1 shows the effect of increasing the tip angle in an attempt to increase signal intensity with the other parameters held constant for a group of 4 samples with the same T_1 values. As the tip angle is increased beyond approximately 20° , the estimated T_1 increases drastically. This can be explained from the fact that as the tip angle is increased, the recovery is being driven to the steady state faster with increasing tip angle values

(reducing the dynamic range). This is because, normally after tipping the spins to the transverse plane for signal acquisition, sufficient time must be allowed for the spin longitudinal magnetization to recover to its recovery path before the next tipping takes place. This condition becomes increasingly violated as the tip angle increases, since the amount of $M_z(0)$ tipped into the transverse plane increases with the tip angle, and thus more time would have to be allowed between nutations as well. If one decides to use larger tip angles (for large signal intensities) and to increase the inter-pulse timing, one would be faced with the problem of not enough points being sampled before complete relaxation recovery takes place. Thus, only the steady state part of the curve (especially for samples with shorter T_1 values) would be sampled. This would therefore limit the combined range of T_1 s one can properly estimate. Also for a smaller number of tip angles, N (for optimal estimation, if one desires very large tip angles), the number of degrees of freedom becomes too poor for a good estimate of T_1 using a three-parameter fit. Thus there is some sort of inverse relationship between the optimal tip angle used and the number of data points N collected along a T_1 relaxation curve using the Look-Locker method of image acquisition. For the range of T_1 s encountered here (300 ms to 1100 ms) a tip angle of 5° was found to be optimal due to smaller error (as indicated in Fig. 4.1) and as shown in the next section.

Fig. 4.1: Flip angle dependence on the estimated T_1 using the Look-Locker method.

4.1.2 T_1 Calibration

Fig. 4.2 shows a plot of the T_1 determined by the Look-Locker (LL) imaging sequence against the IR sequence. Overall the accuracy and precision of the 2D imaging Look-Locker sequence was high. The LL determined T_1 measurements were accurate and precise (2 % for the worst case) for gadolinium samples having T_1 s ranging from 300 ms to 1100 ms. For T_1 s shorter than 300 ms not enough data points are sampled before the steady part of the curve is reached and the extracted T_1 is not very reliable using the parameters in section 3.3.1. This also corresponds to the lower range of the PVA-Fricke

hydrogel T_1 s which was encountered in the project. In an attempt to reduce the effect of the error on tip angle propagating into the estimated T_1 , the 5° tip angle was preferred over values such as 10° and 15° (Fig. 4.1). For higher doses making use of this method to estimate the T_1 's, the parameters would have to be re-adjusted. The SNR was high enough to produce reliable fits. Also for the higher angles, the positional variations in the amount the spins (magnetization) would be tipped will be greater than for $\alpha = 5^\circ$, thus introducing more FOV variations. The slope of the Look-Locker determined T_1 versus that of the IR T_1 was closer to identity (1.003 ± 0.017) for 5° compared to 15° with slope 1.164 ± 0.049 . The 15° or 10° flip angle tended to underestimate the T_1 s. For example an intercept of -106 ± 35 ms was observed for 15° and -6 ± 11 ms for the 5° tip angle. The data collected with LL imaging sequence took approximately 9 minutes compared to a matter of about 6 hours for the IR sequence which had to be run overnight. Thus, one is looking at time saving in MR data acquisition while trying to maintain a high accuracy and precision. This can be very crucial for imaging Fricke-based gel dosimeters when one is faced with the problem of diffusion of ferric ions particularly in obtaining 3D qualitative images for treatment planning and/or therapy methods such as conformal therapy. The total time for data acquisition could have been shortened further by reducing the repetition time, TR because of the dead time put at the end after the last data point. This dead time (optional [64]) of 380 ms was to permit the magnetization to completely recover and have enough magnetization (equilibrium) for the next sequence of 180° /train of α flip pulses.

Fig. 4.2: Look-Locker estimated T_1 compared with inversion recovery determined T_1 s. The dotted line is the line of identity. The error bars ($< 2\%$) on the Look-Locker estimated T_1 s are too small to show.

4.2 Dose Response

Figs. 4.3 to 4.8 show the linear least square weighted fits of the relaxation rate $1/T_1$ and the absorbance OD dose response curves for the various combinations of PVA (15 %, 20 % and 23 %) and Fe^{2+} concentrations (0.2 mM and 0.7 mM). They all show an increase in $1/T_1$ and OD with dose. The increase in T_1 with dose is due to the increase in the concentration of the more paramagnetic Fe^{3+} due to the radiation-induced oxidation of Fe^{3+} and associated enhancement of the proton relaxation rate. As for the increase in

absorbance with dose, there is more darkening (optical density) as the dose delivered increases. The horizontal curves in Figs. 4.3 to 4.6 are the dose response curves for samples made devoid of Fe^{2+} ions. They don't indicate any significant increase in $1/T_1$ or increase in absorbance with dose. This is an indication that the effects being measured were solely due to the Fricke mechanism (conversion of Fe^{2+} to Fe^{3+}). Visually, no darkening was observed with dose of these samples.

Fig. 4.3: The $1/T_1$ dose response for 15 % PVA concentration showing the effect of decreasing dose response with increase in Fe^{2+} ion concentration. The measurement error bars are smaller than the symbol used to represent the points but were typically $< 2\%$ based on the standard deviation of the mean of 5 samples at each dose.

Fig. 4.4: The OD dose response for 15 % PVA concentration showing the effect of decreasing dose response with increase in Fe^{2+} ion concentration. The measurement error bars are smaller than the symbol used to represent the points but were typically $< 1\%$ based on the standard deviation of the mean of 5 samples at each dose.

Fig. 4.5: The $1/T_1$ dose response for a 20 % PVA concentration showing the effect of decreasing dose response with increase in Fe^{2+} ion concentration. The measurement error bars are smaller than the symbol used to represent the points but were typically < 2 % based on the standard deviation of the mean of 5 samples at each dose.

Fig. 4.6: The OD dose response for 20 % PVA concentration showing the effect of decreasing dose response with increase in Fe^{2+} ion concentration. The measurement error bars are smaller than the symbol used to represent the points but were typically < 1 % based on the standard deviation of the mean of 5 samples at each dose.

Fig. 4.7: The $1/T_1$ dose response plot for a 23 % PVA concentration. The measurement error bars are smaller than the symbol used to represent the points but were typically $< 2\%$ based on the standard deviation of the mean of 5 samples at each dose. Irradiations were done 2 days after preparation.

Fig. 4.8: The OD dose response plot for 23 % PVA concentration showing the effect of decreasing dose response with increase in Fe^{2+} ion concentration. The measurement error bars are smaller than the symbol used to represent the points but were typically $< 1\%$ based on the standard deviation of the mean of 5 samples at each dose. Irradiations were done 2 days after preparation.

4.2.1 Effect of change in Fe^{2+} ion concentration

Table 4.1 shows the various dose response slopes (or sensitivity) with the error on the slope (precision) given by the error from the linear least square weighted fit of the data points. The higher intercept for 0.2 mM Fe^{2+} compared to the 0.3 mM concentration shown in Figs. 4.3 and 4.5 is probably due to the fact they were not from the same batch. The Fe^{2+} ion concentration significantly influences the sensitivity or dose response of the gel given by the slope of the linear portion of the $1/T_1$ or the change in optical density plot against the dose. The sensitivity as shown in Table 4.1 (and later in Fig. 4.9) increases with a decrease in the initial Fe^{2+} ion concentration. This effect was observed for both the MR and the optical density dose response as also shown in Figs. 4.3 to 4.8 for all the three PVA concentrations. This is because at high Fe^{2+} ion concentrations, the probability of the radicals reacting with the PVA gels decreases. Thus the ferric yield will decrease, since fewer radicals will be formed that eventually can oxidize the ferrous ions. This is consistent with the proposed reaction mechanism governing Fricke-gels, since reactions 2.40 and 2.53 (section 2.2.1) represent competition for the OH radicals between the Fe^{2+} and the gel molecule. For smaller Fe^{2+} ion concentration reaction 2.40 takes place more readily resulting in the propagation stage (reactions 2.42-2.49) where more polymer radicals required for the Fe^{2+} oxidation (reactions 2.43, 2.45 and 2.46) are continuously being produced by reaction 2.47 needed for reaction 2.42. This is also due to the fact that for a given dose, the dosimeter with the smaller Fe^{2+} ions has the largest response mainly because the PVA-Fricke hydrogels prepared with the lower Fe^{2+} ion concentration have longer relaxation times prior to irradiation. This suggests a PVA-

Fricke hydrogel with low initial Fe^{2+} ion concentration, due to their larger dose response.

However, the problem with too a low a concentration is that saturation of the ferric ion

PVA (% w/w)	$[\text{Fe}^{2+}]$ (mM)				Units	
	0.2	0.3	0.5	0.7	mM	
15	0.0315 ± 0.0006	0.0289 ± 0.0004	0.0276 ± 0.0006	0.0251 ± 0.0006	$(\text{s}^{-1} \text{Gy}^{-1})$	$1/T_1$
	0.0773 ± 0.0010	0.0729 ± 0.0005	0.0600 ± 0.0005	0.0553 ± 0.0002	(Gy^{-1})	OD
	0.0333 ± 0.0006	0.0321 ± 0.0003	0.0287 ± 0.0009	0.0235 ± 0.0006	$(\text{s}^{-1} \text{Gy}^{-1})$	$1/T_1$
20	0.0694 ± 0.0005	0.0604 ± 0.0003	0.0484 ± 0.0003	0.0450 ± 0.0006	(Gy^{-1})	OD
	0.0322 ± 0.0007	0.0303 ± 0.0006	0.0254 ± 0.0008	0.0235 ± 0.0007	$(\text{s}^{-1} \text{Gy}^{-1})$	$1/T_1$
	0.0624 ± 0.0005	0.0531 ± 0.0003	0.0430 ± 0.0001	0.0366 ± 0.0001	(Gy^{-1})	OD
23	0.0322 ± 0.0007	0.0303 ± 0.0006	0.0254 ± 0.0008	0.0235 ± 0.0007	$(\text{s}^{-1} \text{Gy}^{-1})$	$1/T_1$
	0.0624 ± 0.0005	0.0531 ± 0.0003	0.0430 ± 0.0001	0.0366 ± 0.0001	(Gy^{-1})	OD
	0.0322 ± 0.0007	0.0303 ± 0.0006	0.0254 ± 0.0008	0.0235 ± 0.0007	$(\text{s}^{-1} \text{Gy}^{-1})$	$1/T_1$

Table 4.1: Sensitivity of 20 % PVA and 15 % PVA for different ferrous ion concentrations $[\text{Fe}^{2+}]$. The units different are the $1/T_1$ dose response ($\text{s}^{-1} \text{Gy}^{-1}$) from the optical OD response (Gy^{-1}). The errors are from a linear least square weighted fit of the data points.

concentration will occur at a much lower dose (Fig. 3.1 and Fig. 3.2) and the system may then become unreliable. This observed increase in dose response as the Fe^{2+} ion concentration decreases has been observed for other Fricke-gel dosimeters such as gelatin and agarose. Appleby *et al* [72], Olsson *et al* [12], Kron and Pope [80] have all reported

an increase in the dose response (and chemical yield) with a reduction in the Fe^{2+} ion concentration. The Fe^{2+} ion concentrations investigated varied between 0.1 mM and 2 mM. However, despite this trend, there have been some contradictory reports. *Hazle et al* [81] reported an increase in sensitivity with Fe^{2+} ion concentration for gelatin gels with the NMR sensitivity reaching a plateau value of $0.423 \text{ s}^{-1}\text{Gy}^{-1}$ for concentrations of 0.5 mM, 1 mM and 2 mM. In another study by *Schulz et al* [13] on agarose gels he also reported a constant sensitivity for Fe^{2+} ion concentrations greater than 0.5 mM but reported a higher sensitivity for 0.25 mM concentration by a factor of 0.7.

4.2.2 Effect of change in PVA concentration

Table 4.1, and Figs 4.4, 4.6, 4.8 and 4.9 indicate that 15% w/w PVA has the highest optical dose response between the three PVA concentrations for a given Fe^{2+} ion concentration. This is consistent with the proposed mechanism (section 2.2.1) with reactions 2.50 and 2.54. With increasing PVA concentrations more of reactions 2.50 and 2.54, the backward reactions, are taking place thereby reducing the ferric ion yield. One would expect the same tendency for the MR $1/T_1$ relaxation dose response to be consistent with the reaction mechanism and the effect of reduction in the spin lattice relaxation time T_1 with increase in viscosity for relaxation values of the gel prior to irradiation, but this wasn't observed for the three concentrations. Instead, the 20 % PVA seems to show a higher sensitivity over the 15 and 20% w/w PVA. From similar studies by *Chu et al* [26,27] of the PVA concentration on the $1/T_1$ dose response, they didn't observe any clear trend of decreasing dose response with increase in PVA concentration as is seen with the optical measurements. For example, for a 20 % w/w PVA and 0.4 mM

Fe^{2+} ion concentration they [27] observed an MR dose response of $0.017 \text{ s}^{-1}\text{Gy}^{-1}$, while for the same Fe^{2+} ion concentration with a 15 % w/w PVA concentration they observed a $0.019 \text{ s}^{-1}\text{Gy}^{-1}$ dose response. For the other Fe^{2+} concentrations between 15% and 20% PVA concentrations they observed that the higher concentration showed either a higher dose response or remained constant. All the gel batches in this project showed good linearity, with the linearity measured by the correlation coefficient r^2 of 0.9975 or better for the MR dose response and for the optical dose response, an r^2 of 0.9992 or better. In other Fricke-formulations reported for the gel concentration effects on the dosimeter NMR sensitivity, the sensitivity has been found to decrease with increase in the gel concentration. For agarose studies, the concentration has been mostly between 1 % and 2 % w/w (*Olsson et al* [9]), and for gelatin dosimeters a range as wide as 2 % to 10 % (*Olsson et al* [9], *Duzenli et al* [82], *Zahmatkesh et al* [83]). There have still been contradictory reports on the gel concentration effect on the dose response. *Schulz et al* [14], reported that the dose response remained constant with change in the agarose concentration, while *Zahmatkesh et al* [83] reported an increase in sensitivity for studies on agarose gels with concentration varied between 0.5 % and 2 % by weight.

The PVA-Fricke hydrogel MR $1/T_1$ sensitivity observed in this project varied between $0.0215 \text{ s}^{-1}\text{Gy}^{-1}$ and $0.033 \text{ s}^{-1}\text{Gy}^{-1}$ for 23 % w/w PVA and 0.7 mM Fe^{2+} ion concentration, and 20 % w/w PVA and 0.2 mM Fe^{2+} ion concentration respectively, compared with the aqueous Fricke dosimeter with a sensitivity of $0.0182 \text{ s}^{-1}\text{Gy}^{-1}$ [84] at 25 MHz. This comes as no surprise, since it is well known that addition of organic substances to the aqueous Fricke solution has the effect of increasing the sensitivity of the aqueous Fricke dosimeter. The values observed for the dose response both MR and

optical response didn't agree with the only previous investigations [26] using PVA-Fricke hydrogel, where the OD dose response varying from 0.036 Gy^{-1} for 20 % PVA and 0.8 mM Fe^{2+} to 0.060 Gy^{-1} for 15 % PVA and 0.2 mM Fe^{2+} concentration was measured. As for the MR $1/T_1$ response, the reported [26] measured values ranging from $0.015 \text{ s}^{-1}\text{Gy}^{-1}$ for 20% PVA and 0.8 mM Fe^{2+} to $0.021 \text{ s}^{-1}\text{Gy}^{-1}$ for 15 % PVA and 0.2 mM Fe^{2+} concentrations. A higher dose response was measured in this project within this range than previously reported [26]. This discrepancy might probably come from the method of preparation. For instance in the preparations by *Chu et al* [26], the PVA mixture was heated to 120°C while the maximum heating temperature used in the gel preparation for this project was 100°C and the heating had to be broken down into two phases. Another probable source of difference might come from the stock or brand of PVA chemicals used.

Fig. 4.9: Slopes of (a) $1/T_1$ and (b) OD dose response as a function of Fe^{2+} concentration for the various PVA concentrations showing decrease in sensitivity with increase in the initial Fe^{2+} concentration. The curves are not fits to the data points but are added only for visual guidance.

4.3 Optimized PVA-Fricke Hydrogel

Figs. 4.10 and 4.11 show the $1/T_1$ sensitivity-PVA concentration curves for the four different ferrous ion concentrations and the error on the $1/T_1$ sensitivity for the various PVA concentrations as a function of the Fe^{2+} ion concentration respectively. Fig. 4.10 shows 20% w/w and 0.2 mM Fe^{2+} as having the highest $1/T_1$ dose response and 20% PVA and 0.3 mM Fe^{2+} the best precision (Fig. 4.11). But to avoid a limited dose range for the 0.2 mM Fe^{2+} since the 20% PVA and 0.1 mM (Fig. 3.1) dose response is already non-linear, the 20% PVA and 0.3 mM Fe^{2+} could be optimal for NMR relaxation gel dosimetry.

Fig. 4.10: $1/T_1$ sensitivity as a function of the PVA concentration for the 0.2 mM, 0.3mM, 0.5mM and 0.7 mM Fe^{2+} concentrations. The curves are not fits but are only for visual guidance.

Fig. 4.11: $1/T_1$ precision (error on the slope of $1/T_1$ versus dose response curves) as a function of PVA concentration for the various Fe^{2+} ion concentrations. The 0.7 mM curve lies on the 0.2 mM curve. The curves are not fits but are meant to serve only as visual guidance.

4.4 Reproducibility

Table 4.2 shows the sensitivity and error (precision) for the three batches of PVA-Fricke hydrogel (20% w/w PVA/0.3 mM Fe^{2+}) irradiated at different periods after preparation. The sensitivities of the different dosimeter groups are quite close despite the

prolonged period of storage (refrigeration). In an earlier batch of gels prepared, an optical dose response of $0.0595 \pm 0.0009 \text{ Gy}^{-1}$ ($r^2 = 0.9997$) was determined for a 20 % PVA and 0.3 mM Fe^{2+} concentration. This batch didn't have a corresponding relaxation rate response because by the time it was made, the imaging sequence and the MR scanner wasn't available. Table 4.2 indicates that even after this prolonged period of storage, the

Dose Response			
Storage Time (weeks)	$1/T_1 \text{ (s}^{-1}\text{Gy}^{-1}\text{)}$	OD (Gy^{-1})	Batch No.
1	N/A	0.0595 ± 0.0009	1
1	0.0330 ± 0.0005	0.0630 ± 0.0001	2
2	0.0321 ± 0.0003	0.0604 ± 0.0001	
3	0.0298 ± 0.0006	0.0606 ± 0.0003	3
4	0.0310 ± 0.0006	0.0594 ± 0.0003	

Table 4.2: Sensitivity ($1/T_1$ and OD) of 20 % PVA and 0.3 mM $[\text{Fe}^{2+}]$ for 3 different preparations with the storage time varied between 1 to 4 weeks.

Fricke mechanism can still be detected without much change in the sensitivity. The sensitivity is fairly stable, with the one standard deviation on the mean of approximately 3% and 1% for the $1/T_1$ sensitivity ($n = 4$) and OD sensitivity ($n = 5$) respectively. The linearity of these four different irradiated groups was still retained varying from an r^2 of 0.9974 to 0.9990 for the MR $1/T_1$ relaxation dose response while the optical response r^2

varied from 0.9990 to 1.000. Thus, the PVA-Fricke gel can be made and stored (refrigerated) until required to use especially in cases where NMR instruments are not readily available. This is also an indication of a low rate of ferrous ion auto-oxidation.

Fig. 4.12 shows the response of a 20 % PVA and 0.3 mM Fe^{2+} ion concentration for a

Fig.4.12: Linear fits for a 20 % PVA and 0.3 mM concentrations for two different $1/T_1$ readings. The lower curve indicates reading taken after irradiation and the upper for readings taken 48 hours later.

PVA gel obtained on the same day after irradiation with a response of $0.0321 \pm 0.0003 \text{ s}^{-1} \text{Gy}^{-1}$ compared to that obtained 2 days after irradiation with a response of $0.0321 \pm 0.0004 \text{ s}^{-1} \text{Gy}^{-1}$ which is the same as the previous value. The different intercepts are due to Fe^{2+} ion auto-oxidation during the period of storage. This implies that a possible usage of these gels would be to have vials that are made and stored under the same conditions as the irradiated vials to act as the control. A possible combined usage of the spectrophotometry OD dose response and the $1/T_1$ dose response would be to use the OD dose response to normalize the $1/T_1$ dose response and these ratios should be fairly constant in so far as both methods are measuring the same effect.

Chapter 5

Conclusion/Future Work

5.1 Conclusion

The PVA-Fricke hydrogel in this study was found to have promising properties in terms of its linear response with dose in the dose range of 0 – 10 Gy. The effect of the PVA gel concentration and the initial ferrous ion concentrations on the PVA-Fricke hydrogel sensitivity was investigated making use of spectrophotometry to determine its absorbance and MR to determine the spin-lattice relaxation time T_1 . In the determination of the T_1 of these samples, a fast imaging method was implemented. It was validated against an inversion recovery sequence using gadolinium samples and was shown to be quite accurate and precise. To reduce the problem of RF absorption and magnetic field inhomogeneities an adiabatic inversion was incorporated into the sequence.

The concentration of ferrous ions was varied from 0.2 mM to 0.7 mM for a given PVA concentration. This corresponded with an NMR relaxation rate ($1/T_1$) dose response varying from $0.0315 \pm 0.0006 \text{ s}^{-1}\text{Gy}^{-1}$ to $0.0251 \pm 0.0006 \text{ s}^{-1}\text{Gy}^{-1}$, and an optical (OD) dose response varying from $0.0773 \pm 0.0010 \text{ Gy}^{-1}$ to $0.0553 \pm 0.0002 \text{ Gy}^{-1}$ for a 15 % PVA concentration. As for the 23 % PVA concentration, the $1/T_1$ dose response varied

between $0.0322 \pm 0.0007 \text{ s}^{-1}\text{Gy}^{-1}$ and $0.0215 \pm 0.0007 \text{ s}^{-1}\text{Gy}^{-1}$ while the OD response varied between $0.0624 \pm 0.0005 \text{ Gy}^{-1}$ and $0.0366 \pm 0.0366 \text{ Gy}^{-1}$. In all the studies, both NMR and spectrophotometry, a trend of decreasing sensitivity was observed with increase in the Fe^{2+} ion concentration.

For the PVA gel matrix concentration, a trend was observed in the OD response between the three concentrations studied in this project. The 15% w/w PVA concentration showed a much higher sensitivity than the 20% w/w PVA concentration which in turn had a higher sensitivity than the 23% w/w PVA concentration for the various Fe^{2+} ion concentrations. This wasn't the case for the $1/T_1$ dose response which had neither an increasing nor decreasing trend for the three PVA concentrations but had a maximum response at 20% w/w PVA. In all the investigated concentrations, the measured radiation effect was determined to be due mainly to the radiolytic conversion of ferrous ions to ferric ions. The correlation between the measured radiation effects and the dose delivered was very good with an R^2 of 0.9974 or better for the $1/T_1$ response and 0.9992 or better for the OD response.

Based on these results, a PVA-Fricke hydrogel of 20% w/w PVA concentration and 0.3 mM Fe^{2+} could be recommended for gel dosimetry. This is because of the following: (i) its high dose response and lower background when compared to the higher Fe^{2+} ion concentrations, (ii) preferable over 0.2 mM Fe^{2+} concentration because of its better $1/T_1$ dose response and precision, (iii) of the need to avoid a possible limited dose range, (iv) the 20 % w/w PVA is preferred over 15 % because of its higher viscosity which would be a factor in reducing the diffusion of Fe^{3+} ions, and over 23 % because of its higher sensitivity. Also two factors that might limit the use of such a high

concentration (23%) or even a much higher gel concentration are: (i) possible loss of tissue equivalence and (ii) difficulty in stirring the PVA-acid solution mixture.

5.2 Future Work

The main factor limiting the application of Fricke-gel dosimeters is the diffusion of ferric ions. This diffusion has been assessed in other Fricke-gel formulations [22,40,41,78] and this limits the time between irradiation to complete MR scanning to within two hours [85] for most irradiation set-ups in order to minimize any significant blurring of images. Thus, before these PVA-Fricke hydrogels can be used in any application, the diffusion coefficient of the ferric ions should be measured in order to establish a time frame between irradiation and completion of scanning without any blurring effects. This would require irradiating one half of a PVA-Fricke hydrogel sample or phantom in order to create an edge which can then be scanned over time. This coefficient can then be estimated from the rate of change of the scanned edge profile.

The function of xylenol orange in Fricke-gels is usually two-fold: (i) to permit a visible colour change with dose and (ii) to act as a chelating agent to the ferric ions and thus reduce the problem of diffusion. The addition of xylenol orange can reduce the diffusion coefficient of ferric ion in Fricke gels by a factor of about 2.5 [22]. However, there is a drawback associated with the addition of xylenol to Fricke gels. It seems to inevitably reduce the relaxation dose response of the dosimeter (a factor of about 7 for gelatin and agarose Fricke gels) [26]. For PVA-hydrogels used in this study, it is not yet clear if xylenol orange plays any role in the reduction of ferric ion diffusion and if it adversely affects the relaxation dose response. Thus, investigating the effect of xylenol

orange concentration would help towards the possible production of a more optimized PVA-Fricke hydrogel in terms of its relaxation dose response.

The Look-Locker T_1 measurement method implemented in this work is a 2D imaging sequence. More work needs to be done on this sequence in order to extend it to three dimensions in order to be able to do volumetric T_1 mapping for clinical dose distribution. With such a 3D sequence, lower and/or higher density objects could then be inserted into a gel phantom in order to mimic the effects of inhomogeneities such as bone on the dose distribution (anthropomorphic phantom).

Given the high OD response, precision and stability there exist the possibility of its eventual use as a precision dosimeter with a much tighter manufacturing procedure. More comprehensive research to completely characterize the Fricke-hydrogel (and/or cryogel) dosimeter is needed to envisage its eventual clinical use for conformal therapy and hopefully this study has helped in laying some of the groundwork for other researchers interested in studying this gel dosimeter.

Appendix A

Water Radiolysis

The overall process of producing chemical changes by the use of ionizing radiation starts with the irradiation of water and aqueous solution and terminates with the establishment of chemical equilibrium. The radiation chemistry of water has been extensively studied and well understood [68-70]. This process can be divided into three stages [69].

The *physical stage* consists of energy transfer to the system, with a duration of the order of 10^{-15} sec or less. The incident radiation produces, directly or indirectly ionization of water,

as well as excitation,

The *physicochemical stage* consists of processes which lead to the establishment of thermal equilibrium in the system. Its duration is usually taken to be of the order of 10^{-11} sec or less. Electrons ejected in the ionization process generally have enough kinetic energy to escape from the attraction sphere of the positive molecular ion and diffuse into the medium. They become thermalized and hydrated:

The H_2O^+ ions undergo a proton transfer with neighboring water molecules,

and the H_3O^+ becomes hydrated; hence, the point of formation and initial spatial distribution of $H_3O_{aq}^+$ and the oOH are essentially the same and different from those for e_{aq}^- . The dissociation of the excited H_2O molecules gives the hydrogen atom and the oOH radical as the main product

It also gives a low yield for hydrated electrons and eventually molecular oxygen.

The *chemical stage* consists of diffusion away from the point of origin and chemical reaction of primary species (e_{aq}^- , oOH , $H_3O_{aq}^+$, oH) and leads to the reestablishment of chemical equilibrium. It begins in the spur about 10^{-11} after the passage of radiation and about 10^{-10} sec in the bulk of the solution.

Appendix B

Fricke Dosimetry

The use of ferrous sulphate as a chemical radiation dosimeter first proposed by Fricke and Hart [5] has as its principal reaction the radiolytic conversion of ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}). This dosimeter solution is usually at least [69] 96 % water and in consequence the radiation interacts with the water, and the primary radicals produced through water radiolysis. These radicals are mainly responsible for the subsequent reactions which take place in Fricke gels. A simplified description of the ensuing reactions is as follows [69].

A ferrous ion is oxidized to a ferric ion by the hydroxyl radical

and the hydrogen atom from A.5 produced by water radiolysis reacts with dissolved oxygen O_2 to give a hydroperoxyl radical

which in turn oxidizes a ferrous ion

and leads to the formation of hydrogen peroxide

which then forms a further ferric ion

Each hydrogen atom forms a hydroperoxyl radical (HO_2) radical and these oxidizes three ferrous ions, one by reaction B.3 and two by reactions B.1 and B.5. Each hydroxyl radical oxidizes one ferrous ion and each hydrogen peroxide oxidizes two ferrous ions, giving a ferric ion yield of

$$G(Fe^{3+}) = 2G_{H_2O_2} + 3G_H + G_{{}^{\circ}OH} \quad 2.50$$

Appendix C

Adiabatic Inversion Pulse

In the implementation of the Look-Locker imaging technique used in this study, an adiabatic inversion pulse was used based on the theory given below.

In the rotating frame of reference, the net magnetization, $\vec{M}$ precesses about the effective field $\vec{B}_{eff}$ at a frequency given by

$$\Omega = [(\omega_0 - \omega)^2 + (\gamma B_1)^2]^{1/2} \quad C.1$$

This condition (off resonance $\omega_0 - \omega \neq 0$) can arise due to chemically shifted nuclei or magnetic field inhomogeneities. It has been shown [10,86], that if the rate at which $\vec{B}_{eff}$ is tipped is slow enough, $\vec{M}$ is able to “follow” $\vec{B}_{eff}$, that is, remain continuously aligned with $\vec{B}_{eff}$. $\vec{M}$ will be aligned along the x' -axis if $\vec{B}_1$ is aligned along this axis at resonance and will accompany $\vec{B}_{eff}$ to become aligned eventually along the $-\hat{z}'$ axis. For $\vec{M}$ to keep up to $\vec{B}_{eff}$, the rate of precession ω_{eff} of $\vec{M}$ about $\vec{B}_{eff}$ must be faster than the angular velocity of $\vec{B}_{eff}$, $d\theta_B/dt$, that is:

$$\omega_{eff} = \gamma B_{eff} \gg \frac{d\theta_B}{dt} \quad C.2$$

where θ_B is the angle between the effective field and the z-axis. This is the adiabatic condition. From Eqns. 2.9, C.1 and C.2, and making use of the fact that the minimum value of B_{eff} is B_1 , one can get (the Bloch condition)

$$\frac{d(\omega - \omega_0)}{dt} \ll \omega_1^2 \quad \text{C.3}$$

where $\omega_1 = \gamma B_1$. But adiabatic passage (field sweep corresponding to C.3) requires that not only the above equation is obeyed but also that no relaxation occurs during the sweep and therefore yields

$$\frac{\omega_1}{T_2} \ll \left| \frac{d(\omega - \omega_0)}{dt} \right| \ll \omega_1^2 \quad \text{C.4}$$

where T_2 is the spin-spin relaxation time.

Linear frequency sweeps determined by C.4 require relatively large amounts of RF power to completely invert the magnetization. This is because by using the fact that the minimum value of B_{eff} is B_1 in the derivation of C.4, the upper limit on the sweep rate is made more restrictive than it needs to be for all points in the sweep. Since ω_{eff} is much larger at the beginning and the end of the sweep than in the middle, $d\theta_B/dt$ can be increased there accordingly. Based on this, *Hardy et al* [79] obtained an even better sweep function as shown Fig. C.1 by formulating the Bloch condition starting from C.2 in a slightly different manner. By requiring that $\vec{M}$ precess about B_{eff} at a faster rate than the change in the z-component of the field, then

$$\varepsilon \omega_{eff}^2 = \left[\frac{d(\omega - \omega_0)}{dt} \right] \quad \text{C.5}$$

where $0 < \varepsilon < 1$. Substituting from equation C.1 and integrating a tangential sweep can be obtained

$$\omega(t) - \omega_0 = \omega_1 \tan(\varepsilon \omega_1 t) \quad \text{C.6}$$

where $-T_0/2 \leq t \leq T_0/2$, T_0 being the total sweep time and the constant α is determined by $\omega_1 = \gamma B_1$, T_0 , and the angular frequency sweep range $2\Omega_1$:

$$\varepsilon = \left(\frac{2}{\omega_1 T_0} \right) \arctan \left(\frac{\Omega_1}{\omega_1} \right) \quad \text{C.7}$$

Fig.C.1: Tangential and linear frequency sweeps. The tangential sweep changes quickly at the beginning and end, and slowly in the middle where B_{eff} is small. Adapted from *Hardy et al* [84].

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