SPATIALLY LOCALIZED NUCLEAR MAGNETIC RESONANCE
by
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The work presented in this thesis has involved the development and experimental implementation of a new method incorporating Nuclear Magnetic Resonance (NMR) methodology, and which enables a volume to be accurately defined and non-invasively interrogated within a larger object, by a sequence of radiofrequency (RF) and linear magnetic field gradient pulses.

The most important feature of the VOISINER (volume of interest by selective inversion, excitation and refocusing) sequence is its flexibility with respect to the location and size of the region of interest. The spatial coordinates and the size of the volume of interest can be directly selected from conventional NMR images and then converted into the VOISINER sequence by an appropriate setting of the radiofrequency carrier frequencies of the frequency-selective RF pulses and an appropriate scaling of the field gradient strengths used during those RF pulses. As part of the experimental protocol, the VOISINER sequence was actually combined with conventional spin echo imaging in order to facilitate the selection of the region of interest and the optimization of the spatial sensitivity profile of the localization process.

The applicability of the VOISINER sequence was then examined under various experimental conditions in order to evaluate the factors that can deteriorate or improve the efficiency of its spatial selectivity and detection sensitivity.

Potential extensions of the VOISINER technique for extracting a variety of high-resolution NMR information have been explored and experimentally demonstrated by combining it with conventional NMR methodology. In particular, it was combined with the inversion recovery method to measure on a model system, spatially localized spin-lattice ($T_1$) relaxation times. With regard to imaging, studies of a model system have been used to evaluate the technical prospects for using the VOISINER sequence as the
basis for high-resolution imaging of small regions within a large object. Finally, to demonstrate that the technique is applicable for studies of living systems, it was tested on a human forearm and spatially localized $^1$H high-resolution spectra were successfully obtained from muscle tissue and bone marrow.
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à mon père et à ma mère
1. INTRODUCTION

1.1 Historical Perspective

In 1946 the research groups of both Bloch (1) and Purcell (2) independently succeeded in detecting by electromagnetic means nuclear magnetic resonance (NMR) transitions in bulk matter. Since then, NMR spectroscopy has evolved to become one of the most powerful techniques for probing structural and dynamical questions at the atomic level. It has found applications in a broad variety of disciplines including solid-state physics, physical and organic chemistry, and more recently, biochemistry, biology and medicine.

This rapid progress can be attributed to a remarkable feature of NMR, that is, "... the close connection between theory and experiment that leaves little room for a theory that could not be tested by a suitable experiment or for an experiment that does not admit of a well-defined theoretical interpretation ..."1. Equally important to this progress were a number of technical and conceptual innovations. The improvements in field homogeneity increased the resolution and hence, new features such as the chemical shift (3-6) and later the spin-spin coupling (7-8) appeared in the NMR spectrum. The introduction in 1966 by Ernst and Anderson (9) of pulse Fourier Transform (FT) methods and the development of high field superconducting magnets in the late sixties considerably enhanced the detection sensitivity and allowed the spectra of many nuclei with small gyromagnetic ratios to be recorded routinely. The advent of FT methods also triggered an unpredicted and intense development of new experimental techniques both in high-resolution NMR (10) and in solid-state NMR (11). However, this would not have been possible without the advances in computer technology and its progressive integration to NMR spectrometers in the early seventies. The enormous flexibility

gained from computer controlled apparatus provided the means to carry out these experiments that were growing in complexity and were involving an ever-increasing demand on data storage and processing capabilities.

More recently, since the seventies, two major new developments in NMR spectroscopy have attracted tremendous interest and been accorded considerable efforts. One has been the introduction of two-dimensional Fourier transformation that was first proposed by Jeener in 1971 \cite{12} and later demonstrated by Ernst and coworkers in 1975 to be of wide generality and versatility in high-resolution NMR \cite{13}, and also in NMR imaging \cite{14}. This concept has led to an avalanche of methods that can now be used to study molecules of extremely high structural complexity \cite{15}.

The other development has been the application of NMR spectroscopy to studies of living systems. Although the idea was not new \cite{16} and the potential of NMR in the biological sciences was recognized, the real emergence of NMR as a tool to probe biological systems came from a number of significant works of which Damadian \cite{17} in 1971, Lauterbur \cite{18} in 1973, Hoult \emph{et al.} \cite{19} in 1974, and Ackerman \emph{et al.} \cite{20} in 1980, are probably the ones that captured most interest from the scientific community. Damadian reported that the spin-lattice relaxation times of water in certain malignant tumours of rats were longer than those in normal tissues and therefore, suggested that NMR could have some diagnostic value. Lauterbur was the first to report an NMR imaging experiment that consisted of mapping the spatial distribution of the macroscopic proton (\textsuperscript{1}H) spin density within an object. This opened the door to a new application area whose goal is to generate a map showing the internal structure of an heterogeneous system by exploiting the spatial variation of the NMR signal intensity when subjected to appropriate spatial encoding. Hoult \emph{et al.} reported that they could obtain \emph{in vitro} \textsuperscript{31}P high-resolution spectra from an intact biological tissue, namely from intact muscle freshly excised from the hind leg of a rat. They demonstrated that valuable metabolic
information could be obtained by working on an isolated but intact living tissue. Although experiments on a variety of organs and improvements in the techniques to oxygenate and perfuse the samples during the experiment soon followed, this technique was destructive in the sense that it had recourse to some form of surgery to extract the tissues or organs from the animal. On the other hand, studies on tissues and organs of intact animals were hindered by the lack of experimental techniques to spatially localize the NMR signal from specific regions within the specimen. To solve that problem, Ackerman et al. proposed the use of a surface coil\(^1\) (single loop of wire) as the NMR transmitter coil. Such a coil produces a very inhomogeneous radiofrequency excitation field that decreases rapidly with the depth of penetration and induces an NMR signal from a disc-shaped region directly beneath the surface of the coil. Consequently, only a specific region confined in the vicinity of the coil is detected and spatially localized spectroscopy is thus achievable. Their technical innovation was first applied on an intact anaesthetized rat, and \(^{31}\)P spectra were subsequently obtained from the leg muscle and the brain.

Those studies demonstrated that both spatial and spectral information could be obtained from within an object or living system and, established the basis for a new field of NMR, known as spatially dependent NMR; this has since progressed along two parallel and probably complementary paths. The first path has been directed to the use of NMR as an imaging technique. Following Lauterbur's contribution, several alternative NMR imaging schemes (21-22) and a wide range of applications have been developed and experimentally demonstrated by other investigators. These early, encouraging results also prompted the construction of magnet systems with a working volume large enough to accommodate a human patient.

\(^1\) Parenthetically, it is worth mentioning that Morse and Singer in 1970 (O. C. MORSE AND J. R. SINGER, Science 170, 440 (1970).) obtained blood flow measurements by NMR, using surface coils.
In a biological context, NMR imaging, unlike X-ray Computed Tomography (23), appears to be non-invasive because of the low-energy radiation employed, and also has the ability to obtain excellent image contrast between tissues of same proton densities by appropriate manipulation of the experimental parameters. This is possible because of the intrinsic sensitivity of the NMR signal to tissue parameters such as the spin-spin ($T_2$) and spin-lattice ($T_1$) relaxation times, diffusion and flow. Today, NMR imaging is a well-established clinical tool that can provide anatomical information and also discriminate between some pathological tissues (24).

Early NMR imaging methods completely ignored the spectroscopic aspect, and the observed spin density reflected essentially the contributions of all chemical species present in the object. Since those early experiments were performed at field strengths smaller than 0.5 Tesla and with a rather poor field homogeneity (1 part in $10^5$), the experimental conditions were anyway insufficient to resolve chemical shifts. However, with the growing interest of obtaining spectroscopic information, the existing imaging techniques were modified, either to selectively image a specific chemical shift (25-30), or to incorporate the chemical shift as an additional dimension (31-35). The former gave rise to the so-called chemical-shift resolved imaging techniques while the latter gave rise to the so-called phase-encoding gradient or spectroscopic imaging techniques. High field superconducting magnets (>1.5 Tesla) with sufficient field homogeneity (1 part in $10^7$), and a bore large enough to image small animals and human limbs and later, human patients, were also being developed.

In the second area of spatially dependent NMR, the focus has been on the use of NMR to interrogate localized regions within an object. There are many circumstances where only specific portions of an object are of particular interest and therefore a different approach more suitable than NMR imaging, which provides spin density information throughout the whole sample, is desirable. Furthermore, the main objective
is often to obtain high-resolution NMR measurements from the selected volume since this offers the possibility of monitoring a diverse range of biochemical processes by suitable detection of key metabolites without disturbing the metabolism to any perceptible level. Although spectral information can be obtained with the so-called spectroscopic imaging techniques, this requires long measurement times and the handling and storage of large data matrices. Moreover, alleviation of these problems is often at the expense of the spatial and spectral resolution.

Despite the early success and the widespread use of surface coil technology, it soon became obvious that the spatial localization achieved in a single pulse experiment was often insufficient. To achieve a better spatial localization, several groups have later proposed different improvements. Some have designed spatially selective radiofrequency pulse sequences that accentuate the radiofrequency field dependence of the detected signal intensity such as phase cycled depth pulse sequences pioneered by Bendall et al. (36-38) and composite pulse schemes pioneered by Shaka and Freeman (39-42), and Tycko and Pines (43). Others have combined the principle of rotating frame zeugmatography (31) with the inherent radiofrequency field gradients produced by a surface coil to yield a one-dimensional chemical shift image (32). Surface coils have also been combined with frequency-selective radiofrequency pulses in the presence of a gradient of the main static field, as in the depth resolved surface coil spectra (DRESS) experiment (44).

However, an inherent drawback of the methods that use surface coil technology is that the excited region is limited to tissues and organs close to the surface of the specimen. The first experiment to successfully select a restricted volume deep inside a specimen and obtain high-resolution NMR measurements was performed by Gordon et al. (45-46) in 1980, at about the same time as the experiments performed by Ackerman et al. using surface coils. The method they used and which they named the topical
magnetic resonance (TMR) method, was conceptually similar to an imaging technique previously developed and known as focused nuclear magnetic resonance (FONAR) (47). Essentially, it consists of spatially profiling the static field $B_0$ with a static non-linear magnetic field gradient in order to restrict the static field $B_0$ homogeneity to a localized volume within a specimen. The signal with narrow lines from the region of interest can then be mathematically separated from the inhomogeneously broadened signal from the rest of the sample. However, this method suffers from a poorly defined volume due to the difficulty of generating a magnetic field which is very uniform across the volume of interest but extremely non-uniform at its periphery. Furthermore, the volume of interest is basically confined to the centre of the coils that produce this field profiling, and thus to excite different locations, the object has to be moved with respect to these coils. Another approach, based on the sensitive point method (48) was also later proposed (49-50). This technique relied upon the use of slowly time-varying static linear field gradients to eliminate signal contributions from regions with a time-dependent $B_0$ field. Although this method allowed the selected volume to be moved easily, it suffered from a poorly defined volume and spectral resolution losses associated with the time-dependent gradients.

In 1984, Aue et al. (51) proposed a new technique based on the use of conventional radiofrequency volume resonator coils and linear magnetic field gradients. Their technique, known as volume-selective excitation (VSE) is based upon the combination of non-selective radiofrequency pulses and frequency-selective radiofrequency pulses in the presence of orthogonal linear magnetic field gradients of the static field $B_0$. The cumulative effect of their pulse sequence gives rise to a signal originating exclusively from the region which is at the intersection of the three orthogonal slices defined by the selective pulses. The main advantage of this technique
is to make selection of the volume of interest very flexible with respect to its location, its size and its shape.

The flexibility gained with the use of frequency-selective radiofrequency pulses in the presence of orthogonal field gradients has prompted the development of alternative techniques, such as the image-selected in vivo spectroscopy (ISIS) (52), the solvent-suppressed spatially resolved spectroscopy (SPARS) (53) and the spatial and chemical-shift-encoded excitation (SPACE) (54) techniques, the last two being variants of the VSE method with improvements to make it less susceptible to experimental limitations.

Although the majority of clinical spectroscopic data to date derives from the surface coil technology and its related techniques, the experimental implementation of some of the techniques using pulsed field gradients such as ISIS and SPARS have already demonstrated their superior definition and control of the selected volume. Furthermore, they can also be combined with an imaging experiment thereby providing a direct means to select the region of interest.

1.2 Scope and Contents of the Thesis

Ideally, the ultimate three-dimensional spatially localized technique would achieve a complete volume localization in a single 90° pulse without exciting the rest of the sample and would enable the location of the volume of interest to be easily varied. Although such a technique does not yet exist and may sound somewhat utopic, the methods which rely upon the use of frequency-selective radiofrequency pulses in the presence of linear field gradients share some of the desired features and have the practical advantage that they can operate with standard technology.

Notwithstanding the utmost objectives of the ideal technique, the work presented in this thesis deals predominantly with a new volume-selective excitation scheme based upon the concepts of frequency-selective irradiation in the presence of field gradients of
the main field. There are three primary reasons which motivated this approach; first, its potential and versatile prospects; second, the need to improve several aspects of the prevalent techniques; and finally, as part of the author's effort to gain a certain expertise in the field and to search for new and alternative avenues for achieving three-dimensional spatial localization.

The remainder of the thesis is divided into six chapters. Chapter 2 reviews the basic concepts of Nuclear Magnetic Resonance and some of its parameters. Chapter 3 discusses the general concepts of NMR imaging, frequency-selective irradiation in the context of slice-selection and reviews some of the techniques currently used for achieving spatially localized NMR. Chapter 4 introduces the reader to a new volume-selective excitation scheme and discusses in detail the experimental implementation and the protocol used for focussing on the volume of interest. Chapter 5 is devoted to the evaluation and optimization of the technique in terms of its volume-selectivity and detection sensitivity. There is a wide variety of NMR information that can be extracted from the volume of interest and thus, Chapter 6 discusses some applications that demonstrate the generality of the technique. Finally, since this work was initiated, several other groups have suggested new experimental techniques based upon the use of slice-selective radiofrequency pulses and therefore, in Chapter 7, a brief review of the work presented in this thesis as well as a qualitative comparison with the existing techniques is made.
2. NMR FUNDAMENTALS

2.1 Nuclear Magnetization

Many atomic nuclei possess a spin angular momentum \( I \). The projection of \( I \) upon any direction is quantized and may take the values, \( mh/2\pi \) where \( h \) is Planck's constant and \( m \) a discrete spin variable whose range consists of the \( 2I+1 \) values: \(-I, -I+1, \ldots, I-1, I\). A nucleus with a non-zero spin angular momentum has associated with it a collinear dipolar magnetic moment, \( \mathbf{u} = \gamma hI/2\pi \). The constant of proportionality \( \gamma \) is called the gyromagnetic ratio and is a characteristic of the nucleus. The magnitude of \( \mathbf{u} \) is approximately three to four orders of magnitude smaller than the Bohr magneton.

When a nuclear spin is placed in an external magnetic field \( B_0 \), say applied along the \( z \)-axis, the Hamiltonian describing the interaction between its nuclear magnetic moment \( \mathbf{u} \) and \( B_0 \) is

\[
H = -\mathbf{u} \cdot \mathbf{B}_0 = -\gamma hB_0 I_z/2\pi
\]  

[2-1]

The eigenvalues of this Hamiltonian or the energies of interaction are quantized into \( 2I+1 \) equally spaced energy levels

\[
E_m = \gamma h B_0 m/2\pi
\]  

[2-2]

with an energy difference between two adjacent levels of

\[
\Delta E = \gamma h B_0/2\pi
\]  

[2-3]

In addition to the appearance of these energy levels, this interaction also produces a clockwise precession of the magnetic moment \( \mathbf{u} \) about \( B_0 \), as shown in Figure 2.1. Formally, this is expressed by the following equation which describes the time evolution of the quantum mechanical expectation value of the nuclear magnetic moment \( \langle \mathbf{u} \rangle \):
\[ \frac{d}{dt} \langle \mathbf{u}(t) \rangle = \langle [\mathbf{u}, \mathbf{H}] \rangle = -\left( \frac{\hbar \gamma}{2\pi} \right)^2 \langle [\mathbf{I}, -\mathbf{I} \cdot \mathbf{B}_0] \rangle \]  

[2-4]

After simplification, we obtain

\[ \frac{d}{dt} \langle \mathbf{u}(t) \rangle = \gamma \langle \mathbf{u}(t) \rangle \times \mathbf{B}_0 \]  

[2-5]

This equation has the same form as the equation predicted by the classical theory of electromagnetism for the case of a magnetic moment \( \mathbf{m} \) subjected to a magnetic field \( \mathbf{B}_0 \)

\[ \frac{d}{dt} \mathbf{m} = \gamma \mathbf{m} \times \mathbf{B}_0 \]  

[2-6]

Eqs. [2-5] and [2-6] describe a gyroscopic precession of the magnetic moment about the magnetic field at an angular frequency, \( \omega_0 = \gamma B_0 \), known as the Larmor frequency.

We now consider a system consisting of a large number \( N \) (per unit volume) of individual identical nuclear spins in thermal equilibrium with the surroundings at temperature \( T \) and subjected to a magnetic field \( \mathbf{B}_0 \). From the Boltzmann law of statistical mechanics the probability of finding the nuclear spin in a state with energy \( E_m \) is proportional to \( \exp(-E_m/kT) \) and thus the lower energy states are slightly favored. This creates a preferential alignment of the nuclear spins along the external magnetic field and consequently, gives rise to a net macroscopic nuclear magnetization \( \mathbf{M} \) collinear with \( \mathbf{B}_0 \). However, for typical values of \( \mathbf{B}_0 \) attainable in the laboratory, the energies \( E_m \) involved are small. Therefore, the excess populations in the lower states remain small and the resulting macroscopic magnetization may be approximated by the well-known Curie's law
\[ M = \frac{N(\gamma h/2\pi)^2I(I+1)}{3kT} B_0 \]  

[2-7]

This nuclear magnetization is typically $10^{-6}$ to $10^{-7}$ smaller than the electronic paramagnetism. It may classically be visualized by imagining an ensemble of identical nuclear magnetic moment vectors precessing at the same frequency about the static magnetic field $B_0$ as shown in Figure 2.2 for the case of nuclei with spin $I=1/2$; there are more magnetic moments aligned in the direction of $B_0$ and since there is no preferential orientation in a plane perpendicular to $B_0$, their phase is random and their vectorial sum leave only a net magnetization along the direction of $B_0$ with no components in the transverse plane.

Fig. 2.1. The Larmor precession of a nuclear magnetic moment about the static magnetic field $B_0$. 
FIG. 2.2. Precession of an ensemble of identical nuclear magnetic moment vectors (spin 1/2) with random phase in the plane perpendicular to $B_0$. Their vectorial sum produces a net magnetization only in the z direction.

2.2 The NMR Experiment: A Classical Description

The strong presence of the electronic magnetization may completely overshadow the nuclear magnetization and therefore, preclude its detection by any magnetostatic means. This leads the way to the use of a so-called "resonant" method that enables transitions to be induced and detected between magnetic energy levels of the nuclear spin system. Such a method permits selection of the nuclear magnetization from the total magnetization because, for typical values of the static field $B_0$, the energy difference between levels lies in the radiofrequency region of the electromagnetic spectrum for nuclear spins or the microwave region for electron spins.

The method most commonly used today is known as the Nuclear Magnetic Resonance (NMR) experiment. Essentially, it consists of irradiating the nuclear spins with a small rotating magnetic field $B_1$ applied perpendicular to the field $B_0$, i.e. in a plane transverse to $B_0$. When the frequency of $B_1$ is chosen to be near the Larmor
frequency of the spins, a detectable non-equilibrium magnetization is created in the transverse plane and its various components correspond to the frequencies and intensities of the magnetic dipole transitions of the nuclear spin system. In energy terms, transitions between adjacent nuclear spin levels can be induced if the energy of $B_1$, $\hbar \omega / 2\pi$, equals the energy difference $\Delta E = \gamma h B_0 / 2\pi$ between adjacent levels. This corresponds to the resonance condition, that is, when the frequency of $B_1$ matches the Larmor frequency of the nuclear spins.

If we now examine more precisely the influence of the fields $B_1$ and $B_0$ on the motion of the magnetization, a convenient way is to use a classical vector model formalism. Although it has severe limitations for describing many new complex pulse NMR techniques, such as multiple quantum experiments, most of the experiments discussed in this thesis can be adequately described by this approach.

Thus, in a classical description, the motion of the macroscopic magnetization from an ensemble of non-interacting, or weakly interacting, nuclear spins embedded in external magnetic fields can be accurately described by the following equation:

$$\frac{dM}{dt} = \gamma (M \times B)$$  \hspace{1cm} [2-8]

where the field $B$ is the resultant of the applied external fields $B_0$ and $B_1$. In practice the field $B_1$ is not rotating, but oscillating along a certain direction $(\cos(\varphi), \sin(\varphi), 0)$ in the transverse plane. However, such a field is equivalent to the sum of two rotating components in the transverse plane with equal but opposite angular frequencies $(\omega, -\omega)$. Since $B_1 \ll B_0$, its effect on the magnetization is negligible unless its angular frequency $\omega$ is in the neighbourhood of the Larmor frequency $\omega_0$ of the nuclear magnetic moments and, therefore, the component rotating in opposite direction $(-\omega)$ to the magnetic moments is ignored. $B$ is thus expressed as
\[ B = i\ 2B_1\cos(\omega t)\cos(\phi) + j\ 2B_1\cos(\omega t)\sin(\phi) + k\ B_0 \]  

This is equation [2-9a]

and if we neglect the \(B_1\) component which rotates at \(-\omega\), the field \(B\) is

\[ B = i\ B_1\cos(\omega t + \phi) + j\ B_1\sin(\omega t + \phi) + k\ B_0 \]  

This is equation [2-9b]

\[ = [ i\ \omega_1\cos(\omega t + \phi) + j\ \omega_1\sin(\omega t + \phi) + k\ \omega_0 ]/\gamma \]

where \(i, j, k\) are the unit vectors in the laboratory frame and \(\omega_1\) is the angular velocity of the precession of the magnetization about the field \(B_1\). At this point, it is useful to transform to a coordinate system rotating about the \(z\)-axis at the same angular frequency as the rotating component of the magnetic field \(B_1\). In this rotating frame, as shown in Figure 2.3, \(B_1\) is fixed and the magnetization \(M\) appears to precess about an effective field \(B_{\text{eff}}\) which is the resultant of \(B_1\) and a resonance offset field, \(\Delta B_0 = k(\omega_0 - \omega)/\gamma\). This resonance offset field accounts for the fact that in the absence of \(B_1\), the magnetization is viewed to precess about the \(z\)-axis at a frequency which corresponds to the difference between its Larmor frequency and the frequency of the rotating frame. In this rotating frame, the field \(B\) has thus transformed into an effective field \(B_{\text{eff}}\) expressed as

\[ B_{\text{eff}} = i'B_1\cos(\phi) + j'B_1\sin(\phi) + k'(\omega_0 - \omega)/\gamma \]

\[ = [ i'\omega_1\cos(\phi) + j'\omega_1\sin(\phi) + k'\Delta\omega_z ]/\gamma \]  

This is equation [2-10]

where \(i', j', k' = k\) are the unit vectors in the rotating frame and \(\Delta\omega_z = (\omega_0 - \omega)\) is the resonance offset frequency. The magnitude of \(B_{\text{eff}}\) is

\[ |B_{\text{eff}}| = [(B_1)^2 + (\Delta B_0)^2]^{1/2} \]

\[ = [((\omega_1)^2 + (\Delta\omega_z)^2)/\gamma = \omega_{\text{eff}}/\gamma \]  

This is equation [2-11]
where \( \omega_{\text{eff}} \) is the angular velocity of the precession of the magnetization about the effective field \( B_{\text{eff}} \). The equation of motion of the magnetization in the rotating frame is thus

\[
\frac{dM}{dt} = \gamma (M \times B_{\text{eff}}) \tag{2-12}
\]

If \( B_{\text{eff}} \) is applied for a time duration \( t \), the magnetization vector will precess through an angle \( \psi = \gamma B_{1} t \) from its initial position \( M_i \) to its final position \( M_f \), as shown by Figure 2.4A; if during this time \( t \), \( B_{\text{eff}} \) is time-independent, eq. \( [2-12] \) yields the solution

\[
M_f = \mathcal{R}(\theta, \varphi, \psi) M_i \tag{2-13}
\]

where \( \mathcal{R} \) is a \( 3 \times 3 \) rotation matrix written as

\[
\mathcal{R} = \begin{bmatrix}
    n_x^2[1 \cdot \cos(\psi)] + \cos(\psi) & n_x n_y [1 \cdot \cos(\psi)] + n_x \sin(\psi) & n_x n_z [1 \cdot \cos(\psi)] - n_y \sin(\psi) \\
    n_x n_y [1 \cdot \cos(\psi)] - n_x \sin(\psi) & n_y^2 [1 \cdot \cos(\psi)] + n_y \sin(\psi) & n_y n_z [1 \cdot \cos(\psi)] + n_x \sin(\psi) \\
    n_x n_z [1 \cdot \cos(\psi)] + n_x \sin(\psi) & n_y n_z [1 \cdot \cos(\psi)] - n_x \sin(\psi) & n_z^2 [1 \cdot \cos(\psi)] + \cos(\psi)
\end{bmatrix} \tag{2-14}
\]

\[
n_x = \sin(\theta) \cos(\phi) \\
n_y = \sin(\theta) \sin(\phi) \\
n_z = \cos(\theta)
\]

The three angles describing this rotation are defined as follows:

\[
\theta = \arctan(\omega_1 / \Delta \omega_2) \\
\varphi : \text{phase of } B_1 \\
\psi = [(\omega_1)^2 + (\Delta \omega_2)^2] t = \omega_{\text{eff}} t
\]
If the resonance condition $\omega = \omega_0$ is attained, then $B_{\text{eff}} = B_1$ and the magnetization vector precesses about $B_1$ at an angular frequency, $\omega_1 = \gamma B_1$. If $B_1$ is arbitrarily chosen to be polarized along the rotating $x$-axis ($i'$) and if it is applied for a time duration such that the precession angle $\psi = \pi/2$, the magnetization vector $M$ that was initially at equilibrium along the $z$-axis will lie along the rotating $y$-axis ($j'$) in the transverse plane of the rotating frame of reference, as shown in Figure 2.4B. Such a rotation is said to be a $90^\circ$ pulse and the notation used to describe such a pulse is $(\pi/2)_x$ or $(90^\circ)_x$. The subscript refers to the direction along which the field $B_1$ is applied in the rotating frame. A non-equilibrium magnetization has thus been created in the transverse plane and seen from the laboratory frame, the components of the transverse magnetization precess at their Larmor frequency and produce a time-varying magnetic flux which can induce a voltage in a receiver coil properly placed in the transverse plane. This induced signal and the spectrum it yields after Fourier analysis is dependent upon several NMR parameters that we now briefly describe.

![Precession of the magnetization vector](image)

**Fig. 2.3.** Precession of the magnetization vector $M$ in the presence of the fields $B_0$ and $B_1$, seen from the rotating frame. In this rotating frame, $B_1$ is fixed and $M$ appears to precess about an effective field $B_{\text{eff}}$. 
Fig. 2.4. Precession of the magnetization vector about the effective field $B_{\text{eff}}$. (A) If $B_{\text{eff}}$ is applied for a time duration $t$, the magnetization precesses through an angle $\psi = \gamma B_1 t$. (B) $B_{\text{eff}} = B_1$, and $t$ is such that $\psi = \pi/2$.

2.3 The NMR Parameters

In a NMR experiment, the nuclear spin is subjected to a variety of interactions which can be classified into two distinct groups. The first one includes the interactions which are produced by "external" means, namely by the application of magnetic fields produced in the laboratory such as $B_1$ and $B_0$. The second group arises when the nuclear spin is embedded in a molecular environment, namely, when it interacts with the local "internal" fields originating from neighbouring nuclear spins and surrounding electrons. The external interactions are, indeed, responsible for the nuclear magnetic resonance phenomenon, whereas the internal interactions are responsible for the structure of the NMR spectrum and provide mechanisms for the establishment of a macroscopic magnetization in thermal equilibrium with the surroundings.

A detailed account of these internal interactions and their effects is beyond the scope of this work. Instead, in what follows, we briefly describe some measurable
quantities through which these interactions exhibit some of their properties. For the purpose of this work, we define these quantities as NMR parameters and restrict our discussion to the ones which are relevant to this work and appear in the NMR of liquids.

2.3.1 Structural Parameters

The various properties of the internal interactions undergo substantial changes in the liquid state. Since their behaviour and consequently, their effects are very sensitive to any motions and rotations, in liquid, the rapid isotropic rotational tumbling and translational motion of individual molecules average to zero the contribution of certain interactions (direct dipolar and quadrupolar interactions) to the structure of the NMR spectrum. Despite these motional averaging in the liquid state, some internal interactions will nevertheless survive. However, they will lose their anisotropic nature and reduce down to sharply well-defined isotropic values.

The first interaction that survives motional averaging in the liquid state is the chemical shift interaction. It is the major mechanism responsible for the structure of NMR spectra of liquids. Essentially, it is caused by the orbital motions of the surrounding electrons which produce at the nuclear site, a small magnetic field that is proportional to \( B_0 \). The local magnetic field at the nucleus can therefore be written

\[
B_{\text{loc}} = (1-\sigma)B_0 \tag{2-15}
\]

where \( \sigma \) is a dimensionless constant and expresses the contribution of the small fields generated by the surrounding electrons. Therefore, in the NMR spectrum, this constant causes a shift of the resonance frequency \( \omega_0 \) by an amount

\[
\Delta \omega_\sigma = \sigma \omega_0 \tag{2-16}
\]
and, since it reflects the chemical environment of the nucleus, nuclei with different chemical environments will resonate at different frequencies. The constant $\sigma$ is thus termed the chemical shift and is usually expressed in units of $10^{-6}$ (ppm). In high-resolution $^1$H spectroscopy, it covers a range of about 10 ppm.

The second interaction that survives motional averaging but also loses its anisotropy, is the indirect dipolar interaction also known as the spin-spin coupling. In this coupling, two nuclear spins interact indirectly through bonding electrons and causes one nuclear spin to experience a field which varies depending upon the orientation of the other. The hamiltonian describing this coupling between two spins can be written in the form

$$H_J = J \mathbf{I}_1 \cdot \mathbf{I}_2 \tag{2-17}$$

This coupling is usually smaller than the chemical shift interaction. It is the second mechanism responsible for the structure of NMR spectra of liquids and causes characteristic splittings of the chemical shift lines observed in a NMR spectrum. The constant $J$ is called the scalar coupling constant and is usually expressed in Hertz (Hz). For protons, it is of the order of several Hertz.

### 2.3.2 Relaxation Parameters

The establishment of the Boltzmann populations when a nuclear spin system is brought into a magnetic field $B_0$ or the return of the spin system to thermal equilibrium with the surroundings (lattice) after radiofrequency irradiation is governed by spin-lattice relaxation phenomena. In energy terms, the trend towards an excess population in the lower energy states created by the presence of $B_0$, involves an energy transfer from the nuclear spin system to the lattice. Such a process is characterized by a time constant, known as the spin-lattice relaxation time $T_1$, which quantifies the rate of transfer of
energy from the nuclear spin system to its surroundings. $T_1$ is also known as the first order time constant for this spin-lattice relaxation process. Essentially, it is caused by the interaction of the nuclear spins with randomly fluctuating magnetic fields or electric gradients (for spins $I > 1/2$) originating from molecular motions. If these local fields have transverse components which fluctuate at frequencies near the Larmor frequency of the individual spins, they can induce transitions between the energy levels and therefore provide mechanisms for relaxation.

There is an additional relaxation process that appears when transverse magnetization is created by NMR. However, in energy terms, this relaxation phenomenon does not involve any energy exchange with the surroundings and therefore there is no change in the relative populations of the energy levels. This process is also known as the spin-spin relaxation and its first order time constant is referred to as the *spin-spin relaxation time* $T_2$. This relaxation process causes the decay of the transverse magnetization towards its equilibrium value ($M_x = 0, M_y = 0$) and essentially, it involves the dephasing of the transverse components of the individual nuclear magnetic moments which arise from a spread in the Larmor frequencies, due to local field fluctuations caused by neighbouring spins.

There are several mechanisms responsible for these relaxation processes, but since they are not needed and too bulky to be described here, the reader is referred to the books written by Abragam (55) or Slichter (56) for a complete description.

In a vectorial representation, the trend of the magnetization $M$ towards its equilibrium value $kM_0$ after a perturbation can, from phenomenological arguments, be accurately described by the Bloch equation (57):

$$\frac{dM}{dt} = \gamma(M \times B) - (i M_x + j M_y)/T_2 + k(M_0 - M_z)/T_1$$  \[2-18\]
where \( i, j, k \) are the unit vectors of the laboratory frame. In the rotating frame, the Bloch equation is expressed as

\[
\frac{dM}{dt} = \gamma (M \times B_{\text{eff}}) - (i'M_x + j'M_y) / T_2 + k'(M_0 - M_z) / T_1 \tag{2-19}
\]

and in a matrix form, it is given by

\[
\begin{bmatrix}
\frac{d}{dt} M_x \\
M_y \\
M_z
\end{bmatrix} =
\begin{bmatrix}
-1 / T_2 & \Delta \omega_z & -\omega_1 \sin(\varphi) \\
-\Delta \omega_z & -1 / T_2 & \omega_1 \cos(\varphi) \\
\omega_1 \sin(\varphi) & -\omega_1 \cos(\varphi) & -1 / T_1
\end{bmatrix}
\begin{bmatrix}
M_x \\
M_y \\
M_z
\end{bmatrix} +
\begin{bmatrix}
0 \\
0 \\
M_0 / T_1
\end{bmatrix}
\]

Solution of the Bloch equation after the equilibrium magnetization has been flipped into the transverse plane along the rotating y-axis by a \((\pi/2)_x\) pulse is given by

\[
\begin{align*}
M_x &= -M_0 \sin(\Delta \omega_z t) \exp(-t / T_2) & [2-20a] \\
M_y &= M_0 \cos(\Delta \omega_z t) \exp(-t / T_2) & [2-20b] \\
M_z &= M_0 \left[ 1 - \exp(-t / T_1) \right] & [2-20c]
\end{align*}
\]

Eqs. [2-20a] and [2-20b] describe an exponential decay of the transverse magnetization components \( M_x \) and \( M_y \) towards their equilibrium value \((M_x = M_y = 0)\) whereas eq. [2-20c] describes the exponential growth of \( M_z \) towards its equilibrium value \( M_0 \), as shown in Figure 2.5 for different times \( t \). Since \( M_x \) and \( M_y \) are necessarily zero when \( M_z = M_0 \), the relationship, \( T_2 \leq T_1 \), holds at all time.
Chapter 2 NMR Fundamentals

2.4 The Pulse Fourier Transform Experiment

In a sample there is likely to be a distribution of Larmor frequencies and the resonance condition will not be fulfilled for all the nuclear spins simultaneously. In Pulse Fourier Transform NMR, the field $B_1$ is chosen to be large enough so that $\omega_1 >> (\omega_0 - \omega)$ for all $\omega_0$ in the sample. Thus in a typical experiment, an intense, but brief, $(\pi/2)$ radiofrequency pulse flips the equilibrium magnetization in the transverse plane. The induced signal, which is commonly referred to as the Free Induction Decay (FID), is initially in the radio-frequency range. It is then demodulated with respect to the frequency of the $B_1$ field by a phase sensitive detector to yield a signal that is typically in the audio-frequency range. This signal demodulation is equivalent to observing the magnetization in the rotating frame. In quadrature detection, both components $M_x$ and $M_y$ are detected and a convenient way to express this signal is to write it in a complex form

$$s(t) = K [M_x(t) + iM_y(t)]$$  [2-21]
and hence

\[ s(t) = K M_0 \exp(-i\Delta\omega_z t) \exp(-t / T_2) \]  \[ 2-22 \]

where \( i = (-1)^{1/2} \) and \( \Delta\omega_z \) is an arbitrary resonance offset frequency typically in the audio-frequency range. \( K \) is a time-independent constant of proportionality between the transverse magnetization and the signal it induces. Fourier Transformation (58) of the time domain signal \( s(t) \) yields a frequency domain spectrum \( S(\omega) \)

\[ S(\omega) = \int_{-\infty}^{\infty} s(t) \exp(i\omega t) \, dt \]  \[ 2-23 \]

\[ = K [A(\omega) + iD(\omega)] \]

that is composed of a real part \( A(\omega) \) known as the Absorption spectrum and of an imaginary part \( D(\omega) \) known as the Dispersion spectrum:

\[ A(\omega) = \frac{M_0 / T_2}{(1/T_2)^2 + (\omega - \Delta\omega_z)^2} \]
\[ D(\omega) = \frac{M_0 (\omega - \Delta\omega_z)}{(1/T_2)^2 + (\omega - \Delta\omega_z)^2} \]  \[ 2-24 \]

\( A(\omega) \) is also known as a Lorenztian absorption line. The Fourier Transformation defined in eq. [2-23] will yield positive frequencies, in the Fourier domain, for magnetization components (with positive gyromagnetic ratios) which are precessing clockwise in the rotating frame.

2.5 The Spin Echo Experiment

In principle, the spin-spin relaxation time \( T_2 \) is obtainable by measuring the linewidth at half-height of the Lorenztian absorption line in the NMR spectrum.
However, the inhomogeneity of the static field $B_0$ created by the magnet causes the spins in different portions of the sample to precess at slightly different Larmor frequencies. Since the signal arises from the whole sample, all these separate portions get out of phase with each other and thus accelerates the decay of the transverse magnetization. This decay is characterized by an effective relaxation time $T_2^* < T_2$ which is roughly defined by

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \gamma \Delta B$$  \hspace{1cm} [2-25]

where $\Delta B$ is the total field inhomogeneity across the sample. In 1950, E.L. Hahn (59) made the experimental discovery that this phenomenon was reversible under appropriate conditions. From the Bloch equation, it can be shown that the application of a $(\pi)$ pulse at a time $\tau$, which can be longer than $(\gamma \Delta B)^{-1}$, following the initial $(\pi/2)$ pulse can restore the full transverse magnetization at a time $2\tau$ by refocusing in phase the spins of all the different parts of the sample. This phenomenon is called a spin echo and the $(\pi)$ pulse is called a refocusing pulse. Although it is not necessary to use a $(\pi)$ pulse for producing a spin echo (Hahn first used a $(\pi/2)$ pulse), it is the easiest to visualize and the rationale of the method is depicted in Figure 2.6.

In (a), the magnetization initially at equilibrium along the $z$-axis is flipped along the $y$-axis of the rotating frame by a $(\pi/2)_x$ pulse. The total magnetization can be thought of being the vectorial sum of individual macroscopic magnetization components arising from different parts of the sample. Since they experience slightly different values of the applied field, they begin to fan out, as some precess faster (A) and some slower (B) than the precession frequency $\omega_0$ chosen as the rotating frequency of the rotating frame, as shown in (b). At a time $\tau$, a $(\pi)_y$ pulse rotates by $180^\circ$ about the $y$-axis the magnetization components, as shown in (c). Right after the refocusing pulse (d), the components are still precessing in the same direction but, because of the action of the $(\pi)_y$ pulse, they now
move toward the y-axis until they all come in phase along the y-axis (e). This corresponds to the peak amplitude of the echo. In fact, the recovered transverse magnetization is proportional to \( \exp(-2\pi T_2) \) if diffusion effects are neglected (60). At a time \( t > 2\tau \), the magnetization components dephase again (f).

The spin echo, since its development, has played a major role in Pulse NMR and is a key concept that will be extensively used throughout the remaining of this work.

Fig. 2.6. The spin echo experiment.
3. SPATIALLY DEPENDENT NMR

The main objective in Spatially Dependent NMR is to obtain NMR measurements as a function of the spatial coordinates. In this chapter, we discuss some of the general concepts involved in the spatial encoding and spatial discrimination of the observed NMR signal. In the first section, we focus on the spatial encoding properties of linear magnetic field gradients of the static field $B_0$. This leads, in the second section, to a basic treatment of NMR imaging methods with a strong emphasis on Fourier methods, due to their particular relevance to this work and ease of implementation. This is followed, in the third section, by a discussion of frequency-selective irradiation experiments in the context of slice-selection. Finally, in the last section, we briefly discuss the two general approaches used for achieving spatially localized NMR which consist of using gradients of the radiofrequency field $B_1$ or gradients of the static field $B_0$.

3.1 Magnetization in a Linear Magnetic Field Gradient

In conventional NMR of liquids, inhomogeneities in the magnetic field $B_0$ throughout the sample cause a spatial variation of the Larmor frequency which broadens the absorption line. In practice, however, they are much smaller than $B_0$ and can therefore be expressed as the non-zeroth order terms of a Taylor’s expansion of $B_0$ about the origin:

$$k B_0(r) = k [B_0 + \Delta B_0(r)]$$

$$= k [B_0(0) + (\nabla B_0(0)) \cdot r + (\nabla \nabla B_0(0)) : rr/2 + ...]$$

[3-1]

Furthermore, these inhomogeneities $\Delta B_0$ are usually minimized by using a set of shim coils which produce additional magnetic fields of carefully controlled geometry and
strength to cancel each term of the expansion in order to keep \( B_0 \) constant throughout a small volume around the origin.

If we now focus our attention to the first order term and neglect the higher order ones, its effect is to produce a linear variation of the field, and consequently, of the resonance frequency \( \omega_0 \), with respect to the spatial coordinates:

\[
B_0(x,y,z) = B_0 + G \cdot r
= B_0 + (G_x x + G_y y + G_z z)
\]

\[
\omega_0(x,y,z) = \omega_0 + \gamma G \cdot r
= \omega_0 + \gamma (G_x x + G_y y + G_z z)
\]

where the vector \( G \) has the components

\[
G_x = \frac{\partial B_0}{\partial x}, \quad G_y = \frac{\partial B_0}{\partial y}, \quad G_z = \frac{\partial B_0}{\partial z}
\]

If \( G \) is independent of the spatial coordinates, then it is referred to as a linear magnetic field gradient and the coils which produce such a field variation are called linear gradient coils. An interesting thing to note is that the field variation within a plane perpendicular to the field gradient vector \( G \) is zero and consequently, the spins within that plane will resonate at the same frequency. From now on, this plane will also be referred to as an isochromatic plane.

The response of the transverse magnetization upon application of a linear magnetic field gradient can easily be described by studying its evolution in the rotating frame. After the application of a \((\pi/2)_x\) pulse, the transverse magnetization is now subjected to a linear field gradient. Under the influence of the latter, the individual macroscopic components of the magnetization which arise from different parts of the sample precess at frequencies corresponding to their position, as expressed by eq. [3-2b].
Fourier Transformation of this transverse magnetization will yield a spectrum that will show a distribution of resonance frequencies with amplitude proportional to the integrated spin density in the isochromatic plane perpendicular to the field gradient vector \( G \). To demonstrate this, we now consider a simple object in the presence of a field gradient \( G \), applied along the \( z \)-axis of the laboratory frame, as illustrated in Figure 3.1A. The total signal arising from the object can be written as

\[
s(t) = \int K \rho(r) \exp[-i\gamma G_z zt - t/T_2(r)] \, dr^3
\]  \[3-4\]

where \( \rho(r) \), \( G_z \) and \( K \) are respectively the nuclear spin density, the \( z \) field gradient and a time-independent constant of proportionality between the magnetization and the signal it induces. Fourier Transformation of \( s(t) \) yields:

\[
S(\omega) = \int s(t) \exp(i\omega t) \, dt
\]

\[
= \int K \rho(r) \exp[i(\omega - \gamma G_z z)t - t/T_2(r)] \, dr^3 dt
\]

\[
= \int K \rho(r) \Gamma(\omega - \gamma G_z z) \, dr^3
\]  \[3-5\]

where \( \Gamma \) is the complex line shape function

\[
\Gamma(\omega) = A(\omega) + iD(\omega)
\]

\[
= \frac{M_0 / T_2}{(1/T_2^2 + \omega^2)} + i \frac{M_0 \omega}{(1/T_2^2 + \omega^2)}
\]  \[3-6\]

Rewriting eq. [3-5],

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\[ S(\omega) = \left[ \int \int K \rho(x,y) \, dx \, dy \right] \Gamma(\omega / \gamma G_z - z) \, dz \]  

[3-7]

this is equivalent to the sum of a series of Lorenztian lines, each centered at \( \omega = \gamma G_z z \), with an amplitude equal to the integrated spin density of a slice of thickness \( dz \), oriented perpendicular to the \( z \)-axis, as illustrated in Figure 3.1B.

Although early workers had realized that linear field gradients cause a dependence of the line shape upon the geometrical shape of an homogeneous sample (60–62), the conceptual step for using them to obtain structural information from an inhomogeneous sample was first taken by Lauterbur (18) and independently by Mansfield and Grannell (63).

Fig. 3.1. Illustration of the integrated spin density projection of an object in a field gradient. (A) The three dimensional object is subjected to a linear field gradient applied along the \( z \) axis of the laboratory frame. (B) Projection of the integrated spin density.
3.2 Imaging

The use of a linear magnetic field gradient to convert spatial variations of the nuclear spin density along one direction into measurable signal variations in the NMR frequency spectrum can be extended to two and three spatial dimensions to obtain the two and three dimensional macroscopic distribution of the nuclear spins.

This extension leads to NMR imaging techniques. The first imaging experiment was performed by Lauterbur in 1973 (18); in his original experiment, the image was constructed by first obtaining several one-dimensional projections of the object at different directions defined by the field gradient. These projections were then subjected to a so-called projection-reconstruction algorithm (64), which also forms the basis of the highly successful X-ray computerized tomographic (CT) scanner pioneered by Hounsfield (23). In the years following Lauterbur's original experiment, several investigators developed and demonstrated alternative imaging schemes and, for a detailed description and a full evaluation of these techniques, the reader is referred to reviews on the subject (21-22).

However, we may briefly describe qualitatively the sensitivity and performance time of these methods by classifying them according to the manner in which a volume element of the object to be imaged, is investigated. This classification is due to Brunner and Ernst (65), and comprises four different groups: these include sequential point, sequential line, sequential plane and simultaneous methods. Consider that the sample volume to be imaged is cubic and consists of \( n^3 \) volume elements. Furthermore, to completely reconstruct the three-dimensional image, all volume elements must be interrogated and, this may be obtained from \( N \) experiments, where \( N \leq n^3 \). We may also arbitrarily equal to 1 the signal-to-noise ratio (S/N) of a single volume element obtained after a single experiment and define \((S/N)_N\) as being the S/N of a single volume element after \( N \) experiments.
In sequential point measurement methods, each volume element is investigated one by one and therefore, \( N = n^3 \) and \( (S/N)_N = 1 \); imaging methods known as the sensitive point technique (48) and the field focusing NMR method (FONAR) (47) belong to this category. In sequential line measurement methods, the volume elements along an entire selected line are simultaneously observed and hence, \( N = n^2 \) and \( (S/N)_N = 1 \); the multiple sensitive point method (66) and the line-scan method (67) fall into this category. In sequential plane measurements, the volume elements of an entire plane are simultaneously observed. This simultaneous observation of all volume elements does not necessarily imply that each volume element is spatially resolved in a single experiment. Although it can be achieved by the planar spin imaging method (68) or echo-planar imaging method (69), for which \( (S/N)_N = 1 \) and \( N = n \), most sequential plane imaging methods require \( n \) experiments to resolve all the volume elements of the plane while observing the signal of the entire plane and thus, \( N = n^2 \) and \( (S/N)_N = n^{1/2} \). The two-dimensional Projection-Reconstruction Zeugmatography imaging technique (18) and all two-dimensional Fourier imaging methods including the original Fourier Zeugmatography (14), Rotating Frame Zeugmatography (70), Spin Warp (71), and more recently the Stimulated Echo (STE) imaging method (72), fall into this class. Finally, in simultaneous measurement methods, the volume elements of the entire object are simultaneously observed. These methods are an extension of the sequential plane methods into three dimensions. The three-dimensional version of the echo-planar method, which to our knowledge has not been implemented yet, would only require a single experiment to completely resolve the three-dimensional image of the object and therefore, \( N = 1 \) and \( (S/N)_N = 1 \). Three-dimensional versions of the projection-reconstruction method and Fourier Imaging methods have been implemented (73-74) and require \( n^2 \) experiments, while observing the signal from the entire object and thus, \( N = n^2 \) and \( (S/N)_N = n \).
This simple treatment has not taken into account several other factors which are important in selecting an imaging method. Briefly, these include the sensitivity to experimental parameters such as the relaxation times and diffusion, the ease of implementation, and the instrumentation and computational requirements.

Since the Fourier Imaging procedure has proven to be very versatile (75), can be adapted in a variety of ways and rely upon straightforward multi-dimensional Fourier Transformation for image reconstruction, it is consequently the method that will be used in this work. It was first proposed by Kumar et al. (14) and is strongly related to two-dimensional NMR spectroscopy (13). The general scheme for a two-dimensional NMR experiment requires the measurement of the signal as a function of two independent time variables. The pulse sequence for such a class of experiments can be divided into three periods, commonly referred to as the preparation, evolution and detection periods. The basic experimental sequence proposed by Kumar et al. for a two-dimensional imaging experiment is illustrated in Figure 3.2A. The transverse magnetization which is created by a (90°)x (preparation period), evolves for a time t1 in the presence of a Gx field gradient (evolution period). At the end of this period, the Gx field gradient is switched off and the free induction signal is observed during a time t2 in the presence of a Gy field gradient (detection period). The observed signal is thus a function of both time periods and if the experiment is repeated for a series of t1 values by incrementing t1 by a constant value, a two-dimensional data matrix s(t1,t2) is generated. Two-dimensional Fourier Transformation of this data matrix will yield a frequency domain data matrix S(ω1,ω2) which under these circumstances, corresponds to the spatial distribution of the spins within the plane.

To get a better understanding of the above process, it may be appropriate to consider in more detail the signal arising from the plane to be imaged. During the
evolution period, the transverse magnetization of a single volume element at coordinates \( x, y \) in the plane, is given by

\[ m(t_1, 0) = \rho(x, y) \exp[-i(\Delta \omega_z + \gamma G_x x) t_1] \exp[-t_1 / T_2(x, y)] \]  

where \( \rho(x, y) \), \( \Delta \omega_z \) and \( T_2(x, y) \) are, respectively, the nuclear spin density, a resonance offset arising from a chemical shift or a \( B_0 \) inhomogeneity, and the spin-spin relaxation time of the volume element. Upon completion of the evolution period, \( m \) has accumulated a phase \( \phi_x \)

\[ \phi_x = (\Delta \omega_z + \gamma G_x x) t_1 \]  

which reflects the position of the volume along the \( x \) axis, as shown in Figure 3.2B. Immediately following the evolution period, \( m \) evolves during a time \( t_2 \) in the presence of another field gradient, namely \( G_y \), and therefore during the detection period, its precessional frequency will reflect its position along the \( y \) axis (Fig. 3.2C). \( m \) is now expressed as

\[ m(t_1, t_2) = \rho(x, y) \exp[-i \phi_x] \exp[-i(\Delta \omega_z + \gamma G_y y) t_2] \exp[-(t_1 + t_2) / T_2(x, y)] \]  

and the signal from the entire plane is

\[ s(t_1, t_2) = \iint K m(t_1, t_2) \, dx \, dy \]  

The spatial coordinates \( x \) and \( y \) are thus encoded into \( m(t_1, t_2) \) by making its phase and frequency, during observation, to be spatially dependent upon their respective coordinates.
Fig. 3.2. The basic two-dimensional Fourier imaging method. (A) The basic pulse sequence. (B) State of the transverse magnetization at coordinates \((x,y)\) upon completion of the phase-encoding period (evolution period). (C) State of the transverse magnetization at coordinates \((x,y)\) at an arbitrary time \(t\) during the frequency-encoding period (detection period).
Therefore, the evolution and detection period and their corresponding gradients, will be referred to as the phase- and frequency-encoding periods and the phase- and frequency-encoding gradients.

A convenient and elegant way to describe the spatial encoding (76) embedded in \( m \) is to make a change of variables defined as follows:

\[
\begin{align*}
  k_x &= \int_0^{t_1} \gamma G_x(t) \, dt = \gamma G_x t_1 \quad \text{(if } G_x \text{ constant)} \\
  k_y &= \int_0^{t_2} \gamma G_y(t) \, dt = \gamma G_y t_2 \quad \text{(if } G_y \text{ constant)}
\end{align*}
\]

The vector \( k = (k_x, k_y) \) belongs to the so-called reciprocal space and may be interpreted as a vector of spatial frequency coordinates. With this formulation, the spatial encoding process is equivalent to mapping the spatial frequency domain content of the object directly into the signal. The spatial frequency vector \( k \) and the spatial vector \( r \) are in fact Fourier transform pairs. For instance, low spatial frequency components represent the coarse features of an image, whereas the high frequency components have a direct influence upon the fine details of an image. In this notation, the transverse magnetization of a volume element is thus expressed as

\[
m(k) = \rho(x,y) \exp[-i(\Delta \omega_x/G_x + x)k_x] \exp[-i(\Delta \omega_y/G_y + y)k_y] \\
\cdot \exp[-(k_x/G_x + k_y/G_y) / T_2(x,y)]
\]

and Fourier Transformation of the signal from the entire plane, \( s(k) \), gives
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\[ S(r) = \int s(k) \exp[ik \cdot r] \, dk^3 \]  \hspace{1cm} [3.14a]

\[ = \int \int \int m(k) \exp[ik \cdot r] \, dx \, dy \, dk^3 \]  \hspace{1cm} [3.14b]

\[ = \int \int \rho(x,y) L\left(r_x - (x + \Delta\omega_x/\gamma G_x), r_y - (y + \Delta\omega_y/\gamma G_y)\right) \, dx \, dy \]  \hspace{1cm} [3.14c]

where \( L \) is a complex line shape function expressed as

\[ L(\omega_1, \omega_2) = \Gamma(\omega_1) \Gamma(\omega_2) \]  \hspace{1cm} [3.15]

with \( \Gamma \) defined in eq. [3-6]. This integral represents a "filtered" spin density \( S(r) \) obtained from the two-dimensional convolution of the original spin density function \( \rho(x,y) \) with a complex lineshape function \( L \). If this line shape function was infinitely narrow (infinitely long \( T_2 \) relaxation time), it could be approximated by a Dirac delta function \( \delta^3 \) and evaluation of the integral would yield

\[ S(r) = \rho(r_x - \Delta\omega_x/\gamma G_x, r_y - \Delta\omega_y/\gamma G_y) \]  \hspace{1cm} [3.16]

From eq. [3-14c] or eq. [3-16], it is clear that the image created is directly related to the spatial coordinates and the spin density of the object.

An interesting point to note here is the spatial dependence of the final image upon the resonance offsets, as expressed by the terms, \( \Delta\omega_x/\gamma G_x \) and \( \Delta\omega_y/\gamma G_y \). If the resonance offset corresponds to a chemical shift, this translates into a spatial shifting of the image. Consequently, if there are different chemical shifts, the final image will be the superposition of images spatially shifted with respect to each other. If the resonance offset corresponds to inhomogeneities of the static field \( B_0 \), the resonance frequencies as
well as the frequency dispersion imposed by the encoding gradients will be distorted (77). However, these problems can be minimized if large enough gradients are used in order to keep the ratio $\frac{\Delta \omega_2}{\gamma G}$ as small as possible.

In practice, the pulse sequence of Kumar et al. is rarely used, due to sensitivity losses caused by $T_2$ relaxation during the phase-encoding period and to undesirable effects caused by field gradient rise and fall times at the beginning of the frequency-encoding period. Fortunately, there is a variation of the Kumar et al. imaging procedure which has several improvements and which alleviates the drawbacks mentioned earlier in this paragraph. This method is known as the Spin Warp imaging method (71) and essentially, the phase-encoding is achieved by varying the gradient amplitude instead of the phase-encoding time and the signal is acquired as a spin-echo. The pulse sequence used in this work for two-dimensional imaging derives from the original spin-warp method and is illustrated in Figure 3.3.

The total spin phase accumulation during the phase-encoding period can be written as

$$\phi_x = \int_0^{t_1} \gamma G_x(t) \, dt + \Delta \omega_2 t_1 \quad [3.17]$$

Since the accumulated phase can be represented as an integral, it can be achieved either with the amplitude of the phase-encoding gradient held constant and $t_1$ incremented, or, by holding $t_1$ constant at some convenient value such that $t_1 < T_2$ and, incrementing the amplitude of the phase-encoding gradient. Keeping the phase-encoding time constant has some significant advantages: first, it considerably improves the S/N of the observed signal because it is less susceptible to $T_2$ relaxation time during the phase-encoding period.
Fig. 3.3. A two-dimensional version of the Spin Warp imaging sequence. In the original sequence, the non-selective 90° is a slice-selective pulse and the refocusing of the signal is achieved by inverting the amplitude of the frequency-encoding field gradient.

Second, it partially eliminates the resonance offset effects from the phase-encoding dimension since the resonance offset term will appear as a constant term upon Fourier Transformation in this dimension.

A further improvement is to acquire the signal as a spin-echo: during the phase-encoding period, the frequency-encoding gradient dephases the spins which are refocused during the acquisition by the application of a 180° pulse immediately following the phase-encoding period (Fig. 3.3). This enables the experimentator to position the echo along the time axis away from the gradient stabilization period, and hence avoid the possible signal distortion due to the finite rise time of the field gradient. The symmetry of the echo about the time corresponding to the maximum amplitude of the spin-echo is
usually a good indication of the stability of the amplitude of the frequency-encoding gradient (if we neglect the natural exponential apodization produced by $T_2$). By convention, the time that has elapsed from the initial 90° to the maximum amplitude of the echo is usually referred to as the *echo time* (TE), as shown in Figure 3.3.

In practice, the signal $s(k_x,k_y)$ is sampled at discrete values of $k_x$ and $k_y$ and hence, the signal forms a data matrix. The sampling rates $\Delta k_x$ and $\Delta k_y$ in the spatial-frequency domain are determined according to the desired spatial bandwidth of each dimension which are also known as the *field-of-view* (FOV). In order to prevent fold-over problems (78) due to inadequate sampling, the FOV is usually chosen to be slightly larger than the dimensions of the object. The field-of-view in the phase-encoding (PE) and the frequency-encoding (FE) dimensions are related to the experimental parameters and are defined as follows for the case of constant field gradients

$$\text{FOV}_{PE} = \frac{1}{\gamma \Delta G_x \tau} \quad \text{FOV}_{FE} = \frac{1}{\gamma G_y \Delta t}$$  \[3.18\]

where $\Delta G_x$, $\tau$, $G_y$ and $\Delta t$ are, respectively, the phase-encoding gradient increment, the phase-encoding gradient period, the magnitude of the frequency-encoding gradient and the time sampling period, also known as the *dwell time* (DW), of the digitized signal.

The phase-encoding gradient is incremented in successive experiments and the actual gradient amplitude is given by

$$G_x = n\Delta G_x \quad n = -N/2, -N/2 + 1, ..., 0, ..., N/2 - 1$$  \[3.19\]

where $N$ defines the total number of gradient increments. The value of $N$ is important since it determines the spatial resolution obtained in the phase-encoding dimension given by $\text{FOV}_{PE}/N$, and also, the total imaging time given by $(\text{TR})N$, where TR (repetition time) is the time elapsed between two consecutive individual experiments.
3.3 Slice-Selective Irradiation

The Fourier Transform of the transverse magnetization $m_{xy}$ created upon application of a single 90° RF pulse can be expressed as a function of a resonance offset $\Delta \omega_z$ which reflects the various magnetic dipole transitions of the nuclear spin system. In the context of spatially dependent NMR, this resonance offset may be artificially created by a field gradient of the static field $B_0$ and thus, $\Delta \omega_z$ would be spatially encoded. In conventional NMR, the intensity of the RF pulse is such that it does not affect the shape of the spin absorption spectrum $A(\Delta \omega_z)$. In other words, the excitation spectrum $E(\Delta \omega_z)$ of the RF field $B_1$ is much broader than the spin absorption spectrum width. However, there are various circumstances (79) where it is desirable to selectively irradiate uniformly a narrow frequency band or portions of the spectrum while not perturbing the remaining portions. Such experiments require the use of frequency-selective RF pulses. These pulses, depending on the application, may accomplish different tasks and may be imposed different initial and desired final conditions of the magnetization. Of particular importance to this work are the two following situations: to selectively rotate the magnetization from its equilibrium position parallel to the z-axis to a final position in the transverse (xy) plane over a desired range of resonance offsets (Fig. 3.4); or to selectively invert the transverse magnetization components which are perpendicular to the $B_1$ field over a desired range of resonance offsets (Fig. 3.5) in order to refocus the transverse magnetization, as in a spin echo experiment. The former situation would involve the use of a selective 90° pulse, which could be referred to as a frequency-selective excitation pulse; the latter situation would involve the use of a selective 180° pulse, which could be referred to as a frequency-selective refocusing pulse.
FIG. 3.4. Frequency-selective excitation pulse. Only the magnetization within a range of desired resonance offsets is flipped into the transverse plane.

FIG. 3.5. Frequency-selective refocusing pulse. Only the transverse magnetization within a desired range of resonance offsets is refocused
Whatever may be the task to be accomplished, the effect of those frequency-selective pulses on the magnetization can be described rigorously by the Bloch equation. As we saw in Chapter 2 (Section 2.2), the magnetization, in the rotating frame, precesses about an effective field \( B_{\text{eff}} \) defined as

\[
B_{\text{eff}} = i'B_1 \cos(\varphi) + j'B_1 \sin(\varphi) + k'\Delta B_0
\]

[3-20]

\[
= i'\omega_1 \cos(\varphi)/\gamma + j'\omega_1 \sin(\varphi)/\gamma + k'\Delta \omega_0/\gamma
\]

If the resonance offset field \( \Delta B_0 \) is much larger than \( B_1 \), then \( B_{\text{eff}} = \Delta B_0 \), and the field \( B_1 \) is said to be off-resonance; consequently, the magnetization will not be affected by \( B_1 \). However, if the angular frequency of the RF field is such that \( \omega = \omega_0 \), then resonance is attained and the magnetization will precess about the \( B_1 \) field. Under these conditions, the magnetization interacts strongly with the RF field; this is equivalent to saying that spins with resonance frequencies within the frequency range of the RF field excitation spectrum will be affected by \( B_1 \).

In frequency-selective experiments, the condition \( B_1 \gg \Delta B_0 \), which is usually met in conventional NMR, does not necessarily hold for all resonance offsets present. In practice, these frequency-selective pulses are most conveniently obtained by using a small field \( B_1 \) such that the condition \( B_1 > \Delta B_0 \) is met for only a desired range of resonance offsets. This translates into a long weak RF pulse ("soft" pulse), since for a given flip angle \( \psi = \gamma B_1 t_w \), a decrease in the amplitude of \( B_1 \) must be accompanied by an increase in the pulse width \( t_w \).

In frequency-selective experiments in the context of slice-selection, a frequency-selective pulse is applied in the presence of a magnetic field gradient of the static field \( B_0 \). The resonance offset \( \Delta \omega_z \) is thus artificially created by the presence of the field gradient. To illustrate more clearly what is involved in a slice-selective experiment, and more specifically in a slice-selective excitation experiment, consider a homogeneous spin
Fig. 3.6. Illustration of the effect of a 90° slice-selective excitation pulse. (A) Model system upon which the experiment is performed. (B) Projection of the model system when subjected to a field gradient applied along the z axis. This spectrum was obtained with the pulse sequence shown in Figure 3.3 with no phase-encoding gradient and a z field gradient as the frequency-encoding gradient. (C)-(E) Series of projections showing the effect of a slice-selective pulse applied along the same direction as the projection axis. The pulse sequence of Figure 3.8A with slice-selective pulse widths of, respectively, (C) 1 ms, (D) 2 ms, (E) 4 ms were used. All these spectra are in absolute mode display.
distribution in the form of a cylinder whose axis lies along the z-axis (Fig. 3.6A). We assume that the spins are initially at their equilibrium position parallel to the static field \(B_0\). If a static linear field gradient along the z-axis exists over the sample, the angular frequency for spins which lie in a z-plane is thus \(\omega = \omega_0 + \gamma G_z z\) and Figure 3.6B shows the frequency distribution experienced by the spins in the presence of the z field gradient. We now apply a RF pulse of constant amplitude \(B_1\) with angular velocity \(\omega = \omega_0\). We assume that the amplitude \(B_1\) is adjusted to obtain a 90° flip angle for the spins at resonance. The spins which lie in the isochromatic-plane \(z = 0\) are therefore exactly at resonance and interact strongly with the RF field. Spins either side of this plane will be progressively less affected the further they lie from the isochromatic plane because of their increasing resonance offset \(\Delta\omega_z = \gamma G_z z\). If the pulse width \(t_w\) of the RF field is very short, all the resonance offsets experienced by the spins in the cylinder are small as compared to the amplitude \(B_1\) and consequently, all the spins strongly interact with the RF field. Fourier Transformation of the signal thus yields a spectrum similar to Figure 3.6B. However, if the pulse width \(t_w\) is such that \(B_1 >> \Delta B_0\) does not hold for all the spins, then only the ones which lie closely to the isochromatic plane will be affected by the RF field. This implies that the thickness of the isochromatic plane that will be affected by the RF field will be decreasing if the pulse width is increased, as suggested in Figures 3.6C-E for different pulse widths. An important practical aspect to consider when we use a slice-selective excitation pulse is that it is always accompanied by a large loss in the signal observed from the excited slice. The reason is that within a slice, the magnetization is divided into several magnetization components, each experiencing different resonance offsets; thus each component will acquire a different phase angle in the transverse plane as depicted in Figure 3.7A.
Fig. 3.7. (A) Dephasing of the transverse magnetization upon completion of a slice-selective excitation pulse. (B) The use of a 180° refocusing pulse followed by a field gradient pulse can refocus the transverse magnetization. It will also refocus the dephasing caused by a chemical shift dispersion and magnetic field inhomogeneities. (C) A field gradient reversal may also be used to refocus the transverse magnetization. However, it will not refocus the magnetization dephased by chemical shift dispersion and field inhomogeneities.
However, this dephased magnetization can be refocused (83) either by reversing the field gradient amplitude or by applying a refocusing $180^\circ$ pulse followed by a pulse of the same field gradient whose time duration is approximately equal to half the pulse width of the slice-selective pulse (refer to section 5.3), as illustrated by Figures 3.7B-C.

In practice, such "soft" pulses which have a rectangular shape, are not suitable for slice selection because of the secondary excitation lobes on either side of the primary frequency band as illustrated in Figures 3.6C-E. These side lobes result in excitation of the magnetization in regions other than the desired plane. In analogy to Fourier analysis, the abrupt edge of a rectangular shape function, causes high frequency components on either side of the principal excitation lobe as well as an uneven excitation within the main lobe.

One must therefore seek an RF amplitude modulation function that causes the principal excitation band to be uniform and to eliminate or drastically reduce the sidebands. Tomlinson and Hill (80) were the first to propose a very general method in which the frequency excitation spectrum of the RF pulse is "tailored" to a desired pattern by simply defining the desired excitation pattern in the frequency domain and modulating the amplitude of the RF pulse with the inverse Fourier Transform of this pattern. Such an approach constitutes a linear system approach in solving the Bloch equation; this is equivalent to saying that the induced transverse magnetization $M_{xy}(A\omega_z)$ at a resonance offset $A\omega_z$ is linearly proportional to the RF field amplitude at $A\omega_z$

$$M_{xy}(A\omega_z) = A(A\omega_z) E(A\omega_z) \quad [3-21]$$

where $A$ and $E$ are, respectively, the natural spin absorption spectrum of the spin system and the excitation spectrum of the RF field.
Figure 3.8. Spin frequency response to a 90° slice-selective excitation pulse of various shapes: (A) Pulse sequence used in these experiments. (B) Frequency response to a non-selective pulse. (C) Square pulse of a time duration of 1 ms; (D) $\sin^2(\pi t/T)$ shape, with $0 < t < T$, where $T$ is the time duration of the pulse, $T = 1$ ms; (E) $\sin(3\pi(2t-T)/T)/[3\pi(2t-T)/T]$ shape, with $0 < t < T$, $T = 3$ ms. All these spectra are in absolute mode display.
The linear approximation under certain circumstances has proved to be very helpful and has been used by several authors (81-84) in slice-selective irradiation schemes. Figure 3.8 shows a series of frequency responses experimentally obtained with the use of 90° slice-selective pulses with shapes determined by the inverse Fourier Transform of the desired frequency response of the transverse magnetization. These results clearly indicate the validity of this approach.

Despite its success, the linear system approach for solving the Bloch equation for magnetization initially at thermal equilibrium, constitutes an approximate solution which for large flip angles (180°), is totally inadequate. From a perturbation theory treatment of the magnetization, Hoult (84) showed that if the pulse is sufficiently weak, the induced transverse magnetization will be linearly proportional to the applied field and will be the Fourier transform of the pulse shape with a 90° phase shift. He further showed that for flip angles up to 30°, the linear approximation was valid to within 5%. When the flip angle is 90°, the linear approximation is wrong by 57%. This deviation is caused by a manifestation of the non-linearity of the NMR system to the radiofrequency excitation field and for flip angles more than 180°, the linear response bears little resemblance with the true spin behaviour. This is illustrated in Figure 3.9 for a series of frequency responses of the transverse magnetization to the application of a sin² shaped slice-selective pulse of constant width $t_w$ but of different $B_1$ amplitudes. The magnetization was initially at thermal equilibrium.

Our discussion so far has been directed toward some basic concepts involved in frequency-selective experiments. We have seen that the linear system approach constitutes a good approximation for rather small flip angles and totally fails for large flip angles.
Fig. 3.9. Spin frequency response to a slice-selective excitation pulse of various amplitudes but fixed pulse length. All these spectra are in absolute display mode and a sin² function was used to modulate the amplitude of the slice-selective pulse of a time duration of 1 ms. The amplitude of $B_1$ was varied in order to obtain flip angles of: (A) 15°; (B) 30°; (C) 45°; (D) 90°; (E) 135°; (F) 180°. Strong deviations from the linear behaviour are obvious for flip angles > 90°.
Fig. 3.10. Spin frequency response to a 180° slice-selective refocusing pulse of various shapes. (A) Pulse sequence used in these experiments. (B) Frequency response to a non-selective refocusing pulse. (C) Square pulse of a time duration of 1 ms; (D) $\sin^2(\pi t/T)$ shape, with $0 < t < T$, where $T$ is the time duration of the pulse, $T = 1$ ms; (E) $\sin[3\pi(2t-T)/T]/[3\pi(2t-T)/T]$ shape, with $0 < t < T$, $T = 3$ ms. All these spectra are in absolute mode display.
Recently, several groups have been successful in designing very accurate selective 180° inversion pulses to rotate magnetization from its initial equilibrium position parallel to the field $B_0$ to a position antiparallel to the field over desired ranges of resonance offsets. Some have used a method (85-88) similar to those used to study the phenomenon of self-induced transparency (89) while others have used numerical optimization methods (90-92). However, despite these recent developments, and a new theory for arbitrary pulse shape analysis based on a coherent averaging approach (93), the development of accurate selective 180° pulses used for refocusing purposes remains, in the author’s opinion, elusive. Therefore, we have decided to restrict our brief discussion on some conventional frequency selective 180° refocusing pulse shapes based on a linear system approach. The transverse magnetization frequency response thus obtained is illustrated in Figures 3.10C-E. The experimental implementation is shown in Figure 3.10A. Despite the non-linear behaviour of the spin system, the particular case of a selective 180° pulse applied to magnetization initially in the transverse plane seems nevertheless to bear some resemblance with the linear response. The sin$^2$ shaped refocusing pulse does not produce a very uniform slice profile (Fig. 3.10D), but since it does not practically produce any side lobes, it is the shape that we will use in the next chapters for performing slice-selective refocusing.

3.4 Spatially Localized NMR

All the techniques which have been developed to date for performing spatially localized NMR fall into two general categories: those that achieve localization using field gradients of the radiofrequency field, and those that use field gradients of the main static field $B_0$. The first group includes the techniques that use surface coil technology such as, simple surface coil acquisition (20), depth pulse sequences (36-38) and composite pulse schemes (39-43) which accentuate the degree of spatial localization and push deeper the
sensitive region; and finally, the techniques that are based upon rotating frame
zeugmatography \(31,32,94-96\). The second group comprises the spectroscopic imaging
techniques which produce data sets with two or three spatial dimensions and one
chemical-shift dimension; those that localize by means of static gradients of \(B_0\), such as
the topical magnetic resonance (TMR) approach \(45-46\); and those that use frequency-selective radiofrequency pulses in the presence of pulsed field gradients of the static field
\(B_0\), such as in the volume-selective excitation (VSE) method \(51\) and its variants \(53-54\), the image-selected in vivo spectroscopy (ISIS) method \(52\), and the depth-resolved
surface coil spectroscopy (DRESS) \(44\) method.

A detailed account of all these techniques is beyond the scope of this work. However, concerning the techniques using field gradients of the field \(B_1\), we restrict our
discussion to surface coil technology and present an evaluation of the localization
performance achieved with some depth pulse and composite pulse sequences. That study
was part of some preliminary work done at the beginning of this project and, although it
is not directly related to the new method we describe in the following chapters, the author
has nevertheless decided to include it for pedagogical reasons. Finally, with regard to the
methods using field gradients of the static field \(B_0\), the discussion is limited to the
methods which are the most relevant to this work. Consequently, only the three
dimensional volume-selective techniques which use slice-selective pulses will be
described; these include the VSE method and its variants, and the ISIS methods.

3.4.1 \(B_1\) Discrimination

A unique characteristic of the spatial variation of the radiofrequency field \(B_1\)
throughout a sample is that it creates a spatial variation of the flip angle \(\psi = \gamma B_1(r)t\), and
since the amplitude of the NMR signal is dependent upon it \(\text{amplitude } \propto \sin(\psi)\),
regions of the sample that are experiencing flip angles close to 90° will contribute more
to the observed NMR signal. This concept of spatial encoding through the spatial variation of the flip angle was first exploited by Hoult in 1979 (31) in his Rotating Frame Zeugmatography imaging method. He showed that spatial encoding could be embedded in the amplitude of the signal instead of the phase or the frequency of the signal, as in conventional Fourier imaging methods which use field gradients of the static field. Another factor which must be considered when analyzing the amplitude of the NMR signal, is the efficiency with which it is induced by the transverse magnetization in the NMR receiver coil. Obviously, the further the transverse magnetization lies from the receiver, the smaller the induced signal contribution \( dA \) will be. Hoult demonstrated (97) that this dependence was in fact equivalent to a linear proportionality between the field \( B_1 \) and the signal contribution, as expressed by the following equation which takes into account both, the flip angle dependence and the efficiency of the coupling:

\[
dA \propto B_1 \sin(\gamma B_1 t) \quad \text{[3-22]}
\]

To obtain the full signal, eq. [3-22] must indeed be integrated over the whole sample. Eq. [3-22], whose profile is illustrated in Figure 3.11A, can be advantageously exploited in the context of spatially localized NMR. Such is the case for the use of a surface coil which produces a field that decreases rapidly beneath the surface of the coil. The RF field distribution of a surface coil in the xy plane is illustrated in Figure 3.11B, and as eq. [3-24] implies, the detectable NMR signal will be confined to a region in the vicinity of the coil. This concept was first exploited by Ackerman et al. (20) in 1980 to obtain high resolution spectra from a selected region adjacent to the surface of the sample. The surface coil exhibits another interesting feature that is worth mentioning; since it produces a very inhomogeneous RF field, one can not determine a 90° pulse width but determine the position of the 90° pulse.
Fig. 3.11. (A) Plot of the dependence of the observed NMR signal intensity upon the field strength $B_1$. (B) Contour plot of the field strength $B_1$ produced in the $xy$ plane of the laboratory frame by a single-turn flat circular surface coil positioned in the $xz$ plane of the laboratory frame.
Fig. 3.12. Series of pictures showing the excitation pattern in the xy plane of the laboratory frame by a surface coil positioned in the xz plane. A spin echo imaging sequence similar to Figure 3.3 was used to obtain these images (TE = 10 ms, TR = 2 s, image size: 256 X 256). They also represent the excitation pattern obtained by BendaU's scheme. This was made possible by phase cycling the spin echo imaging sequence with the EXORCYCLE phase cycling routine. The various pulse lengths were: (A) 32 μs; (B) 48 μs; (C) 64 μs; (D) 96 μs; (E) 128 μs. These experiments were performed with a surface coil of 5 cm in diameter, and a plexiglass box (depth, 5 mm; height, 8 cm; width, 10 cm) filled with water.
FIG. 3.12 Continued...
This feature is illustrated in Figures 3.12A-E for various RF pulse lengths and one can in fact excite a deeper region when the pulse length is increased. However, this is at the expense of a serious drawback which is the appearance of responses from other regions: spurious NMR signal will also be excited from sample regions where the flip angle is around 270°, 450°, 630° ... etc. These regions are usually referred to as harmonic responses and are clearly visible in Figures 3.12B-E. Since the determination of a 90° pulse for a surface coil is rather meaningless, we will simply refer to \( \psi \) as an arbitrary flip angle which corresponds to a 90° pulse somewhere beneath the surface.

To further spatially restrict the NMR signal, some workers have designed spatially selective RF pulse sequences that accentuate the RF field dependence of the detected signal intensity. We now present an evaluation of some of these excitation schemes. The first one that we tested was developed by Bendall et al. (36) and consists of the following addition/subtraction scheme:

<table>
<thead>
<tr>
<th>Exp no.</th>
<th>( \psi ) pulse</th>
<th>2( \psi ) pulse</th>
<th>Receiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \psi_x )</td>
<td>2( \psi_x )</td>
<td>add</td>
</tr>
<tr>
<td>2</td>
<td>( \psi_x )</td>
<td>2( \psi_y )</td>
<td>subtract</td>
</tr>
<tr>
<td>3</td>
<td>( \psi_x )</td>
<td>2( \psi_{-x} )</td>
<td>add</td>
</tr>
<tr>
<td>4</td>
<td>( \psi_x )</td>
<td>2( \psi_{-y} )</td>
<td>subtract</td>
</tr>
</tbody>
</table>

The basic sequence starts with a single \( \psi \) pulse, as in simple surface coil acquisition, and is followed by a 2\( \psi \) pulse whose phase after each scan is incremented in 90° steps while the receiver phase is alternated. The resulting signal is thus the combination of four FIDs which were created in a prescribed manner. Essentially, the effect of applying a refocusing pulse (2\( \psi \)) after the initial \( \psi \) pulse is to spatially restrict even further the observed signal. The phase cycling procedure employed in this scheme is also known as the EXORCYCLE phase-cycling routine (98) and was originally designed to reject magnetization components not properly inverted by an imperfect 180° pulse. Bendall et
al. demonstrated that the resulting signal is found to be proportional to \( \sin^3(\psi) \) instead of \( \sin(\psi) \) as for a single \( \psi \) pulse. Since the shape of \( \sin^3(\psi) \) with respect to \( \psi \) is narrower than the shape of \( \sin(\psi) \), a better spatial localization is thus achieved. To image the excitation pattern of this scheme, it was implemented in this thesis as a spin echo imaging sequence (Fig. 3.3) whereby the \( 90^\circ \) and \( 180^\circ \) pulses were replaced by the \( \psi \) and \( 2\psi \) pulses. The images that resulted for different pulse lengths of \( \psi \) are illustrated in Figure 3.12. To compare the excitation profile obtained experimentally with that expected from theory, a cross-section of the image of Figure 3.12C was drawn in Figure 3.13A and compared with the theoretical excitation profile.

The second class of pulse sequences that we have briefly evaluated are called composite pulses and were developed by Shaka and Freeman (39-42), and by Tycko and Pines (43). These pulses are sequences of phase-shifted RF pulses intended to excite nuclear spins over a narrower range of \( B_1 \) amplitudes; this results in a higher degree of spatial localization. They actually originate from a more global effort, which began with the original work of Levitt and Freeman (99), in developing composite pulses which excite nuclear spins over larger ranges of experimental parameters such as resonance offsets, RF amplitudes and spin coupling constants (100). Four composite pulses originating from two design schemes were tested. In fact these pulses are narrowband inversion pulses: they invert nuclear spins over a narrow range of \( B_1 \) amplitudes. The first two composite pulses that we tested were generated by the so-called retrograde compensation expansion developed by Shaka and Freeman (39) and which is expressed as

\[
\Psi_0 = (2\psi)_0 \cdot (2\psi)_{270} \cdot (2\psi)_{180}
\]

\[
\Psi_{n+1} = (\Psi_n)_0 \cdot [(\Psi_n)_{60}]^{-1} \cdot (\Psi_n)_{120}
\]

Only the \( \Psi_0 \) composite pulse and the first iteration \( \Psi_1 \) corresponding to \( n=0 \) were tested,
\[ \Psi_0 = (2\psi)_0 (2\psi)_{270} (2\psi)_{180} \]
\[ \Psi_1 = (2\psi)_0 (2\psi)_{270} (2\psi)_{180} (2\psi)_{60} (2\psi)_{150} (2\psi)_{240} (2\psi)_{120} (2\psi)_{30} (2\psi)_{300} \]

The first composite pulse contains 3 pulses whereas the second composite pulse contains 9 pulses each of which corresponds to a nominal 180° (2\psi) pulse length. Their inversion performance is illustrated in Figure 3.14 and their experimental implementation into a localization scheme is described as follows:

<table>
<thead>
<tr>
<th>Exp no.</th>
<th>(\psi) pulse</th>
<th>Comp. pulse</th>
<th>Receiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\psi_x)</td>
<td>(\psi_x)</td>
<td>add</td>
</tr>
<tr>
<td>2</td>
<td>(\psi_x)</td>
<td>(\psi_y)</td>
<td>subtract</td>
</tr>
<tr>
<td>3</td>
<td>(\psi_x)</td>
<td>(\psi_x)</td>
<td>add</td>
</tr>
<tr>
<td>4</td>
<td>(\psi_x)</td>
<td>(\psi_y)</td>
<td>subtract</td>
</tr>
</tbody>
</table>

This scheme is similar to the scheme proposed by Bendall with the exception that the 2\psi pulse in Bendall's scheme is replaced by a \(\Psi\) narrowband inversion composite pulse. To evaluate the excitation pattern of that scheme, a similar approach as described previously for Bendall's scheme was performed during this thesis work for the two composite pulses. They are illustrated in Figures 3.13B-C.

The other two composite pulses that we tested were derived from an iterative scheme developed by Tycko and Pines and which is expressed as follows:

\[ \Psi_1 = (2\psi)_0 (2\psi)_{120} (2\psi)_{240} \]
\[ \Psi_{n+1} = (\Psi_n)_0 (\Psi_n)_{120} (\Psi_n)_{240} \]

Only the \(\Psi_1\) composite pulse and the third iteration \(\Psi_3\) corresponding to \(n=2\) were tested
\[
\Psi_1 = (2\psi)_0 (2\psi)_{120} (2\psi)_{240} \\
\Psi_3 = (2\psi)_0 (2\psi)_{120} (2\psi)_{240} (2\psi)_{120} (2\psi)_{240} (2\psi)_0 (2\psi)_{240} (2\psi)_0 (2\psi)_{120} (2\psi)_{240} (2\psi)_{120} (2\psi)_{240}
\]

The first composite pulse contains 3 pulses whereas the second one contains 27 pulses.

Their inversion performance is illustrated in Figure 3.15 and their implementation into a localization method, known as narrowband for localization of excitation (NOBLE), is described as follows:

<table>
<thead>
<tr>
<th>Exp no.</th>
<th>Comp. pulse</th>
<th>(\psi) pulse</th>
<th>Receiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\psi_x)</td>
<td>(\psi_x)</td>
<td>add</td>
</tr>
<tr>
<td>2</td>
<td>(\Psi_x)</td>
<td>(\Psi_x)</td>
<td>subtract</td>
</tr>
</tbody>
</table>

With this scheme, only the spins in a narrow range of \(B_1\) amplitudes in the sample will contribute to the signal while the signal contribution from the spins which were unaffected by the inversion pulse will cancel. However, no experimental evaluation of NOBLE was performed in this preliminary work.

The resonance offset effects have not been addressed in this evaluation, but does nevertheless remain an important practical problem that one must consider in real applications. Only the \(B_1\) dependence of the observed signal has been evaluated and from Figure 3.13, it is clear that the composite pulses that were evaluated can obtain a better degree of spatial localization than the depth-pulse method.
FIG. 3.13. Cross sections of the excitation pattern obtained with: (A) depth-pulse sequence, extracted from (D); (B) Shaka and Freeman $\Psi_0$ composite pulse, extracted from (E); (C) Shaka and Freeman $\Psi_1$ composite pulse, extracted from (F). The images of (D)-(F) were obtained under identical experimental conditions as the images shown in Figure 3.12. However, a nominal $\Psi$ pulse of 64 $\mu$s was used for these experiments. The theoretical predictions were obtained with the program listed in Appendix D.
Fig. 3.13 Continued...
Narrowband Inversion (Shaka & al.)

"3 pulse" Composite Pulse

"9 pulse" Composite Pulse

Fig. 3.14. Narrowband inversion pulses; Shaka and Freeman. The theoretical predictions were obtained with the program listed in Appendix D.
Narrowband Inversion (Tycko & al.)

"3 pulse" Composite Pulse

- Amplitude vs. Flip Angle (deg)
- Theoretical
- Experimental
- Single pulse

"27 pulse" Composite Pulse

- Amplitude vs. Flip Angle (deg)
- Theoretical
- Experimental
- Single pulse

Fig. 3.15. Narrowband inversion pulses; Tycko and Pines. The theoretical predictions were obtained with the program listed in Appendix D.
3.4.2 $B_0$ Discrimination

Among the three-dimensional volume-selective techniques that use gradients of the static field $B_0$, the ones which use frequency-selective irradiation in the presence of field gradients of the static field $B_0$ have demonstrated the greatest flexibility in the context of the location, size and shape of the volume of interest. These methods, despite their differences, share the same design philosophy: the volume of interest corresponds to the intersection of three orthogonal slices which are spatially discriminated by the use of slice-selective RF pulses applied in three orthogonal directions, as illustrated in Figure 3.16. The *volume-selective excitation* (VSE) method (51) was the first to use such an approach; soon after its first experimental demonstration, other alternative methods were also proposed and experimentally demonstrated. At the beginning of this work, four methods were in use: the VSE method and two derivatives, the *solvent-suppressed spatially resolved spectroscopy* (SPARS) method (53) and the *spatial and chemical-shift-encoded excitation* (SPACE) method (54), and the *image-selected in vivo spectroscopy* (ISIS) method (52).

The first distinction that one can make when we compare those techniques, is that some of them, such as the VSE-like methods, rely upon *suppression* of the unwanted signal whereas the remaining one, ISIS, relies upon *subtraction* of the unwanted signal. The consequence of these two different approaches is that the VSE-like methods can in principle produce an NMR signal from the region of interest in a single scan, while the ISIS relies upon a subtraction/addition scheme of FIDs which are produced by appropriate combination of slice-selective pulses.

The VSE-like methods consist of three modules each of which discriminates along one of the three orthogonal directions.
Fig. 3.16. Volume of interest defined by the intersection of three orthogonal slices.

To spatially localize the NMR signal in a single acquisition, these modules must be applied consecutively within the same pulse sequence. The effect of a module is to preserve the $z$ magnetization in the plane of interest and generate elsewhere, transverse magnetization incoherently dephased. After application of the three modules, $z$ magnetization remains only in the sensitive volume. A non-selective 90° pulse is thus applied to create a coherent tranverse magnetization exclusively from that region. Since outside the volume of interest, the magnetization is incoherently dephased in the transverse plane, it will not contribute any observable signal. A schematic illustration of the VSE-like pulse sequence and the cumulative localization obtained at different stages of the pulse sequence is shown in Figure 3.17. Although the VSE, SPARS and SPACE methods use the same general approach, they nevertheless have distinct modules which are illustrated in Figure 3.18A-C.
Fig. 3.17. Schematic representation of the VSE-like methods with a pictorial representation of the different stages involved in the spatial localization of the volume of interest. The effect of each module is to preserve longitudinal magnetization in the selected slice and to destroy transverse magnetization created elsewhere.
Fig. 3.18. Pulse sequences of the pulsed field gradient methods described in this section: (A) VSE module. (B) SPARS module. (C) SPACE module. (D) ISIS basic sequence.
The development of SPARS and SPACE was prompted by the very high radiofrequency power requirements needed by the VSE module in order to minimize the off-resonance precessional effects caused by the presence of the field gradient during application of the non-selective 90° pulse found in the 45°(sel.) - 90° - 45°(sel.) pulse cluster. A critical point about the VSE-like methods is that during the selection process and the field stabilization delay between the last selection module and the hard 90° read pulse, magnetization from outside the volume of interest may recover through $T_1$ relaxation and therefore contribute to the observed NMR signal.

The ISIS method, unlike VSE and its variants, necessitates the application of an eight-cycle sequence and the addition and subtraction of FIDs. The method relies upon the use of slice-selective inversion pulses and can be regarded as a three dimensional version of the NOBLE method presented in the preceding section. Therefore, we will not discuss any further the details of the spin manipulation involved for producing a spatially localized signal. The basic pulse sequence is illustrated in Figure 3.18D and the eight experiments are listed as follows:

<table>
<thead>
<tr>
<th>Exp no.</th>
<th>x-slice pulse</th>
<th>y-slice pulse</th>
<th>z-slice pulse</th>
<th>Receiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OFF</td>
<td>OFF</td>
<td>OFF</td>
<td>add</td>
</tr>
<tr>
<td>2</td>
<td>ON</td>
<td>OFF</td>
<td>OFF</td>
<td>subtract</td>
</tr>
<tr>
<td>3</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
<td>subtract</td>
</tr>
<tr>
<td>4</td>
<td>ON</td>
<td>ON</td>
<td>OFF</td>
<td>add</td>
</tr>
<tr>
<td>5</td>
<td>OFF</td>
<td>OFF</td>
<td>ON</td>
<td>subtract</td>
</tr>
<tr>
<td>6</td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>add</td>
</tr>
<tr>
<td>7</td>
<td>OFF</td>
<td>ON</td>
<td>ON</td>
<td>add</td>
</tr>
<tr>
<td>8</td>
<td>ON</td>
<td>ON</td>
<td>ON</td>
<td>subtract</td>
</tr>
</tbody>
</table>

A critical point about the ISIS method is the subtraction/addition of signal contributions which are potentially orders of magnitude larger than those emanating from the volume of interest. It is thus more susceptible to dynamic range problems and to artifacts produced by irregular motions of the sample that may occur during the sequence.
4. THE VOISINER METHOD

In this chapter, a novel method for achieving spatial localization of the NMR signal is introduced, and an analysis of the different aspects involved in its experimental implementation is presented. In the first section, the technique is schematically described and some preliminary results are presented to illustrate its experimental feasibility. The second section describes the apparatus that was used for the experimental implementation of the VOISINER method and examines the various user-controllable parameters which are necessary for optimizing the observed NMR signal intensity and for selecting the location and size of the volume of interest. Finally, in the third section, an experimental protocol is suggested for a systematic adjustment of those parameters involved in the localization process.

4.1 Basic Description and Preliminary Results

The development of the new volume-selective excitation scheme that we introduce in this section was guided primarily by three design objectives: (1) the location of the volume of interest, its size, and to a certain extent, its shape, should be easily varied without necessitating retuning the magnet system; (2) the method should basically be able to provide a spatially localized signal in a single acquisition, thus avoiding dynamic range problems caused by any need to differentiate strong unwanted signals, and also to reduce the time it takes to optimize the magnetic field homogeneity for the volume of interest; (3) the number of RF pulses in the sequence should be minimized in order to reduce the amount of RF power deposition and the loss in resolution and signal intensity that could result from the cumulative effects of imperfections arising from the RF pulses.
The field gradient and radiofrequency pulse sequence which we have called VOISINER\(^1\) (volume of interest by selective inversion, excitation, and refocusing), falls into the same category as the methods relying upon the use of frequency-selective pulses in the presence of pulsed field gradients. Such an approach has the significant advantage of enabling a gradient-controlled localization in all three dimensions by simply varying the carrier frequencies of the slice-selective pulses.

To meet the second design objective, the VOISINER sequence, in common with the VSE-like methods (51,53-54), comprises three distinct modules which are applied consecutively within the same pulse sequence. Each of these modules contains a slice-selective pulse which spatially discriminates a plane perpendicular to one of three orthogonal directions; the cumulative effect of those three modules gives rise to an NMR signal which originates exclusively from the region corresponding to the intersection of the three orthogonal planes. VOISINER can thus induce a coherent signal from the VOI in a single scan. In return, this implies that the unwanted signal must be suppressed, instead of being subtracted from various FIDs, like in the ISIS method (52).

For a more detailed description of the VOISINER method, it is appropriate now to visualize each step by studying the evolution of the magnetization in the rotating frame. Figure 4.1 is a schematic diagram of the VOISINER sequence along with the magnetization state from different portions of the sample at intermediate stages throughout the time sequence of VOISINER.

The first module is conceptually similar to the 45°(sel.)–90°–45°(sel.) pulse sandwich found in the VSE technique (51). The initial slice-selective \((90°)_x\) excitation pulse flips in the transverse plane the longitudinal magnetization from a selected slice perpendicular to the first orthogonal direction, as shown in (a).

\(^1\)In the Petit Robert French Dictionary, VOISINER: 1. to visit one's neighbour. 2. to be placed side by side.
Fig. 4.1. Schematic illustration of the VOISINER sequence which consists of a set of three distinct modules, each of which contains a slice-selective RF pulse. (a)-(e) Magnetization state from different portions of the sample at intermediate stages throughout the time sequence.
Fig. 4.1 Continued...
FIG. 4.1 Continued...
This transverse magnetization whose components are partially dephased by the slice-selective pulse is then refocused by a non-selective (180°)_y followed by a field gradient pulse of a time duration necessary to rephase the transverse magnetization components, as shown in (b). At this point, a non-selective (90°)_x is applied, which flips from the transverse plane to the longitudinal axis, along the –z direction, the refocused magnetization from the slice previously defined. The effect of this pulse is also to rotate in the transverse plane, the longitudinal magnetization from outside the slice. A strong field gradient pulse is then applied to destroy that transverse magnetization. The total effect of the first module, which is named the inversion module, is thus to preserve the longitudinal magnetization of the selected slice (Region 2) and to dephase incoherently the transverse magnetization created elsewhere (Region 1), as illustrated in (c).

At this point, VOISINER diverges from the VSE method, and instead of applying similar modules in the two remaining orthogonal directions, it follows a different approach, as we now examine. The second module consists of only a slice-selective (90°)_x excitation pulse which selects a slice perpendicular to the second orthogonal direction. This module has been named the excitation module since its action is to flip in the transverse plane, the longitudinal magnetization which is at the intersection of the two orthogonal slices defined so far. Upon application of the second module, four different regions with a specific magnetization state can be distinguished. These regions are depicted in (d). Region 1 is not affected by the slice-selective pulse of the second module. However, it is further dephased incoherently by the second orthogonal field gradient pulse applied during the slice-selective pulse. Region 2 is the remaining portion of the slice that was discriminated by the first module, but since it is not affected by the second module, its magnetization state remains the same. Region 3 corresponds to the portion of the sample that was incoherently dephased by the first module and which is now also affected by the second module. The effect of the second module on the
magnetization of this region is to rotate the previously dephased spins in the xy plane into the xz plane. Furthermore, each magnetization component is also dephased into subcomponents about the z-axis. Finally, Region 4 corresponds to the two intersecting slices. However, the slice-selective pulse of the second module has partially dephased the magnetization with respect to the second orthogonal field gradient.

If a segment of Region 4 is now selectively refocused with respect to the second orthogonal field gradient by applying a frequency-selective 180° pulse in the presence of a third orthogonal field gradient followed by a second orthogonal field gradient pulse of appropriate time duration, the transverse magnetization from that segment can be restored; this segment constitutes the selected volume of interest. This selective refocusing sequence, which we have named the refocusing module, constitutes the third module of VOISINER. It thus selects a slice orthogonal to the two previously defined slices, and refocuses that magnetization which is at the intersection of the three orthogonal slices. The magnetization states from the different portions of the slice that were affected by the third module are depicted in (e). Region 5 corresponds to the portion of Region 1 in (d) that is partially refocused with respect to the second orthogonal field gradient. However, since it was also previously dephased with respect to the first orthogonal field gradient, the transverse magnetization remains incoherently dephased and thus, it does not induce any coherent signal during the detection period. The magnetization of Region 6, which corresponds to a portion of Region 2 in (d), remains along the longitudinal axis since the effect of the third module is simply to reinvert the longitudinal magnetization. Consequently, since it does not have any coherent transverse magnetization components, it does not produce any detectable signal. Region 7 corresponds to a portion of Region 3 in (d) whereby the action of the third module is to refocus the magnetization sub-components into the xz plane with respect to the second orthogonal field gradient. Since all the magnetization components are phased out in the
xz plane, there is no net transverse magnetization and if no refocusing mechanisms occur during the detection period, it will not produce any signal. Finally, Region 8 corresponds to the volume of interest (VOI), and since the transverse magnetization is refocused with respect to the second orthogonal field gradient, it gives rise to a detectable signal.

Experimental verification of VOISINER, which in its first experimental form is illustrated in Figure 4.2, was performed on a model system which consisted of a set of three bulbs immersed in a cylindrical bath filled with water which was doped with manganese chloride to give a $T_1$ of approximately 160 ms. The three bulbs were aligned along an axis making a 45° angle with the three orthogonal axes (Figs. 4.3A-4.3B) and were filled respectively with cyclohexane, ethanol, and benzene. Figure 4.4A shows the $^1$H spectrum of the whole phantom obtained with a hard 90° pulse. The broad spectrum of the water resonance (bath) is approximately 400 times larger than the signal originating from each bulb. Figures 4.4B-4.4D show the very good spatial discrimination of the volume of interest from the large background signal obtained with VOISINER; each spectrum was produced in a single acquisition. The spectra of cyclohexane (Fig. 4.4B) and benzene (Fig. 4.4D) are somewhat broader than the spectrum of ethanol (Fig. 4.4C). This is partly due to the absolute mode display used to suppress the effects of J modulation (101), with additional contributions from the poorer homogeneity of $B_0$ away from the centre of the magnet, and possibly to a slightly poorer refocused signal.

Details concerning the apparatus used for performing the experiments described above are discussed in the following section. However, we may mention that a homebuilt elongated saddle coil of 8.9 cm in diameter was used as the RF transmitter and receiver. The slice-selective pulses were achieved using 90° pulse widths of 500 µs and 180° refocusing pulse widths of 1 ms in the presence of field gradients of approximately 0.9 Gauss/cm. The hard 90° pulse had a width of 67 µs.
FIG. 4.2. Illustration of the VOISINER sequence in its first experimental version. The frequency-selective RF pulses of the last two modules have a sin^2 shape. The delay between the intense z gradient pulse, and the selective 90° pulse along y, is included to eliminate gradient overlapping caused by the fall time of the z gradient.

FIG. 4.3. Two orthogonal cross sections ((A) z plane; (B) x plane) of the phantom used in the experimental verification of VOISINER. The three bulbs (internal diameter, 0.9 cm; volume, 0.4 ml) are immersed in a cylindrical bath (length, 7 cm; internal diameter, 5.8 cm; volume, 185 ml) filled with 1 mM aqueous solution of manganese chloride tetrahydrate. Bulb 1 contains cyclohexane and is positioned at (-1, -1, -1) cm with respect to the centre of the magnetic field. Bulb 2 contains ethanol with traces of hydrochloric acid and is positioned at (0, 0, 0) cm. Bulb 3 contains benzene and is positioned at (1, 1, 1) cm.
Fig 4.4. (A) Proton spectrum of the phantom obtained with a single 90° hard pulse. The broad spectrum overshadows contributions from the three bulbs. (B-D) Series of high-resolution spectra showing the volume localization obtained with VOISINER. The three spectra were processed under identical conditions and are plotted with the same scaling factor. The location of the volume of interest was varied so as to consecutively excite (B) bulb 1, (C) bulb 2, and (D) bulb 3. All these spectra are magnitude spectra.
These preliminary results demonstrate the experimental feasibility of VOISINER and indicate three important advantages; these include its capability to obtain NMR spectra from the volume of interest in a single scan, its simple control of the size and location of the volume of interest and the small number of RF pulses applied to the sample. However, the first module of the VOISINER sequence in its original form, as shown in Figure 4.2, requires the use of a short, non-selective 90° pulse (to minimize the acquired phase in the transverse plane of chemical shifts with large resonance offsets) and a field gradient with a short rise time. For apparatus which has limited RF power and field gradients with relatively long rise times, a more appropriate first module which is less susceptible to those limitations is thus desirable. With further experimental evaluations of the first module, we have found that its excitation profile is not very good and in retrospect, we have also found that the apparent good spatial discrimination obtained from those results was greatly helped by the fast T₂ decay of the background signal during the application of the third module. An evaluation of that original first module and of alternative solutions is postponed to Chapter 5.

4.2 Experimental Implementation

4.2.1 Apparatus

All the experiments described in this thesis were performed on a Oxford instruments magnet with a 310 mm diameter horizontal room temperature bore operating at a field strength of 1.89 T (80.3 MHz for ¹H), using a Nicolet NT-300 NMR console equipped with a Nicolet 1280 computer and a 293C pulse programmer. As part of this laboratory’s interest in the field of spatially dependent NMR, shortly after its acquisition, but prior to the beginning of this work, the console was converted into an imaging spectrometer. As part of the conversion, the following components were incorporated to the spectrometer: a homebuilt field gradient control unit with appropriate software to
operate it; three field gradient drivers each of which consisted of a pre-emphasis stage and of an AMCRON model M-600 power audio-amplifier; a broadband (10-86 MHz) ENI linear RF power amplifier; and an experimental setup to generate amplitude modulated RF pulses (102). However at the time of commencement of this work, in spite of that upgrade, the configuration of the spectrometer and the hardware that was available, were not sufficient for the experimental implementation of VOISINER.

The first point of concern was the linear magnetic field gradient coils and their drivers. Although the magnet already had built-in gradient coils, their performance, in the author's opinion, was rather poor; they could produce field gradients of maximum strengths of approximately 1 Gauss/cm with rise times of 5 to 10 ms (see Figures A.1-A.3 in Appendix A) (including pre-emphasis stage to improve rise and fall time performance). Furthermore, a long standing "tail", probably caused by eddy currents induced by gradient coils in the copper cylinder shield covering the bore of the magnet and in the cryostat, would persist at a deteriorating level for as long as 100 ms. It was thus feared at that time that this performance would be insufficient for clean slice-selective irradiation and for data acquisition, shortly following gradient pulses. Hence, a new set of gradient coils was constructed to provide higher gradient magnitudes with shorter rise and fall times. Several configurations have been described in the literature (103-110), but for a superconducting magnet, coils which can be wound cylindrically to conform with the shape of the bore and which simplifies the insertion of the RF probe were preferred. The combination of Golay coils for the x and y field gradients and Maxwell coils for the z field gradient were constructed and since these coil designs have been well-documented in the literature (111-112), no details concerning their magnetic field distribution is given here; only the resulting geometry of the windings is illustrated in Figure 4.5.
Fig. 4.5. Geometry of the windings for: (A) z-field gradient coil (Maxwell coils); (B) y field gradient coil (Golay coils); (C) x field gradient coil, same as in (B) but rotated by 90°.
Numerical evaluation of the field gradients produced by the Golay coils (111-112) show that they are linear to within $-5\%$ over a region $r \leq 0.5a$, deteriorating to $-10\%$ over $r \leq 0.6a$, where $a$ is the coil radius and $r$ is the radius of a spherical region centered at the geometrical centre of the coils. For Maxwell coils, the linearity is within $5\%$ over $z \leq 0.63a$, where $z$ is the axial distance from the geometrical centre of the coils.

Two sets of gradient coils were constructed, based on a previous construction made in our laboratory (113). The gradient coils of the first set were wound in grooves which were machined into the outer surface of a PVC former, 16.5 cm in outer diameter with 0.65 cm wall thickness. The grooves were 5 mm wide and had depth of respectively 3 mm, 2 mm and 1mm for the x, y and z gradient coils. An effective radius of 8 cm for the coils was used for determining the locations of the grooves, according to the configuration of Figure 4.5. The x and y gradient coils of the second set were wound around pegs on a PVC former, identical to the one used for the first set. The z coil was wound in grooves, 2.5 mm deep and 9 mm wide. The location of the grooves and the pegs were determined using an effective radius of 8.2 cm. The major difference between the two sets of coils was the gauge of the wire used for the winding. The specifications of the two sets of gradient coils and the magnitudes of the field gradients they can produce is given in Table 4.1.

The reason which motivated us to use a smaller wire in the first set, was to minimize the linearity distortions created by the finite size of the wire. However, this was at the expense of a decrease in the field gradients obtainable for maximum power outputs from the amplifier. This can be easily explained by the increase of the resistive impedance of the coils that were wound with a smaller copper wire and thus, for a given maximum power output from the amplifier, the maximum current available is consequently reduced.
<table>
<thead>
<tr>
<th>Coil</th>
<th>Wire Gauge</th>
<th># turns</th>
<th>Gradient Magnitude (G cm⁻¹A⁻¹)</th>
<th>Resistance (Ω)</th>
<th>Inductance (μH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>28</td>
<td>20</td>
<td>0.290</td>
<td>11.4</td>
<td>1.00</td>
</tr>
<tr>
<td>Y</td>
<td>28</td>
<td>20</td>
<td>0.287</td>
<td>11.4</td>
<td>1.00</td>
</tr>
<tr>
<td>Z</td>
<td>24</td>
<td>20</td>
<td>0.212</td>
<td>1.6</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Set 1** (radius of coils = 8.0 cm; clear bore = 15.2 cm)

| X    | 20        | 20      | 0.260                            | 1.8            | 1.00           |
| Y    | 20        | 20      | 0.281                            | 1.8            | 0.99           |
| Z    | 20        | 30      | 0.334                            | 1.0            | 0.63           |

**Set 2** (radius of coils = 8.2 cm; clear bore = 15.2 cm)
Essentially, the power audio-amplifier was capable of producing a maximum current of approximately 10 A for the x and y gradient coils of the first set before it started to saturate (see Figure A.8 in Appendix A). For the z gradient coil of the first set and the gradient coils of the second set, currents of up to 20 A were tested and no saturation from the amplifier was observed (see Figures A.9-A.11 in Appendix A). The rise and fall times of the gradient coils of the first set (see Figures A.12-A.13) were less than 100 $\mu$s. However, a rather long tail of 4 to 5 ms could be observed for the final 20% of the rise and fall of the x and y gradient coils, when longer field gradient pulse widths were used (see Figure A.4 in Appendix A); this appeared to be caused by the relatively high resistance of the gradient coils since it was not observed for the x and y gradient coils of the second set (see Figure A.6 in Appendix A) which have identical configurations. For the second set, the rise and fall times were evaluated to be less than 200 $\mu$s for the x and y gradient coils and less than 100 $\mu$s for the z gradient coil. Some ringing was observed for the z gradient coils of both sets (see Figures A.5-A.7); this was probably caused by their very low impedance. Some evaluations with regard to the induced eddy currents was also made and essentially, a magnetic field stabilization delay of at most 10 ms prior to data acquisition was sufficient to considerably reduce their deleterious effects; since the gradient coils that we built have an effective diameter only half that of the bore diameter of the magnet, eddy current contributions from inside the wall of the magnet, such as the cryogenic shim coils were greatly reduced as compared to the in-built Oxford gradient coils. The copper cylinder covering the external wall of the magnet bore was another source of eddy currents and degraded the performance of the our gradient coils (see Figures A.12-A.13 in Appendix A); consequently, it was removed whenever an experiment was performed. An upgrade and some modifications of the field gradient control unit, which is schematically illustrated in Figure 4.6, was also necessary.
FIG. 4.6. Schematic circuit diagram of the audiofrequency apparatus used for driving the field gradient coils.
Before discussing these modifications, it may be appropriate to describe how the unit works. Six DAC (digital to analog converter) outputs which are programmed by the computer, are fed into six electronic gates each of which can be turned on/off at appropriate times during the pulse sequence, by control lines from the Nicolet 293C pulse programmer. The generation of six different pulsed voltage outputs can thus be created. These six outputs can consequently be user-configured to serve as voltage inputs to the field gradient power audio-amplifiers. However, prior to this work, only three outputs were functional and in order to get more flexibility, three more DACs were added and appropriate software was developed to operate all six. To drive those field gradient coils, three TECRON Model 7560 power audio-amplifiers were acquired. They were operated in a so-called "constant current" mode which, briefly, consists of keeping the current output as closely as possible to the voltage input, irrespective of the load impedance. For an inductive load, such as a field gradient coil, this has for consequence of significantly improving the rise and fall time of the latter. No pre-emphasis stage was built to improve the performance of the gradient coils; instead, an analog multiplier which can modulate the amplitude of the voltage output was built. This analog multiplier, which is shown in Figure 4.6 as an optional module, multiplies the voltage from a DAC output with that of a waveform generated by a Wavetek Model 75 Arbitrary Waveform Generator. This feature enables the field gradient to be tailored for various purposes. Finally, to minimize the inductive coupling with the RF probe, high frequency filters on both leads of each gradient coil were installed.

Concerning the radiofrequency aspect of the VOISINER sequence, few additional devices had to be incorporated to the original configuration of the spectrometer in order to enable the carrier frequency to be varied within the pulse sequence and to shift the phase of the latter, anywhere, from 0° to 360°. The first of these features is essential for varying the location of the volume of interest whereas the other one can correct for
potential phase jumps that may occur when switching between different carrier frequencies, as will be discussed in Chapter 5. A frequency selector and an analog phase shifter with an appropriate phase selector were thus built to meet these requirements. The frequency selector enables the selection of four different frequencies which are manually programmable by external switches and computer-selected by two control lines from the pulse programmer. The analog phase shifter complements the built-in digital phase shifter which can shift the phase by only 0°, 90°, 180°, or 270°. It is based upon the use of an Olektron Complex Phase Modulator whose two analog inputs are fed by a RF phase shift selector which enables the selection of eight manually programmable phase shifts, computer-selected from three control lines from the pulse programmer.

The schematic circuit diagram of the radiofrequency section of the spectrometer which is relevant to this work is illustrated in Figure 4.7. It may be instructive at this point to describe the flowpath of the RF transmitter signal through the circuit diagram. A reference Intermediate Frequency (IF) of 11.25 MHz is first fed into the built-in digital phase shifter. It then goes through the analog phase shifter whose arbitrary phase shift is determined by the user. It is then mixed with the frequency of a PTS synthesizer whose frequency is selected by the frequency selector. That double balanced mixer is configured in such a way, that only the component whose frequency corresponds to the frequency difference of the two input signals appears at its output. The frequency of that RF signal corresponds to 80.3 MHz + Δf where Δf is an offset frequency typically in the audio-frequency range. The transmitter signal is then fed into another double balanced mixer which is used in this case as an attenuator in order to perform a continuous amplitude audio-modulation of the RF transmitter signal. A Linear RF power amplifier then drives the NMR probe.
Fig. 4.7. Schematic circuit diagram of the radiofrequency apparatus used for the VOISINER sequence.
In addition to these modifications, new RF probes which serve as transmitters and receivers were also built to fit our set of gradient coils. Their construction is based on previous probe constructions done in our laboratory and has been treated in detail in Lalith Talagala’s Ph.D. thesis (102). Two different designs were used: the first which is illustrated in Figure 4.8A is a conventional saddle shaped coil (114-115) whose length is twice its diameter. A better field homogeneity can be obtained (114) although the most common configuration is when the coil diameter is equal to its length (to reduce inductance of the coil); the second design is illustrated in Figure 4.8B and is based on the design of the "H" resonator (116), which is the most widely used for high-frequency NMR imaging. The success of the H resonator is attributed partly to its flexibility in dimensions which can be varied to suit space available in the magnet, and to its ability to minimize the electric fields inside the probe. However, that design was slightly modified by the author in order to yield the same field distribution as the saddle coil. The reason which motivated us to build that modified H resonator was the rather poor performance of the saddle coil. Three probes were built and some of their specifications are listed as follows; 1. saddle coil: diameter = 8.9 cm, Q factor = 190, 90° pulse = 67 μs; 2. first modified H resonator: diameter = 8.9 cm, Q factor = 320, 90° pulse = 34 μs; 3. second modified H resonator: diameter = 10.7 cm, Q factor = 320, 90° pulse = 65 μs. The second modified H resonator was built for performing some experiments on a human forearm. The saddle coil and the first modified H resonator were capacitively coupled (114) whereas the second modified H resonator was inductively coupled (117-121).

Finally, as part of the author’s contribution in converting the spectrometer into an imaging spectrometer, an image processing unit based on an IBM AT computer using the PC Semper Image Processing Operating Environment (Data Translation, Inc.) was interfaced to our Nicolet 1280 computer with a IEEE-488 interface bus.
Fig. 4.8 RF transmitter coils; (A) Saddle coil; (B) Modified H resonator.
All the images presented in this thesis were downloaded to that image processing unit upon data acquisition and Fourier Transformation on the 1280 computer.

4.2.2 Experimental Parameters

There are several experimental parameters in the VOISINER sequence which must be adjusted to focus on the volume of interest and optimize its performance. A convenient way to describe those parameters is to divide them into two general categories: those which are concerned with the position, size and shape of the volume of interest; and those which are involved with the optimization of the assigned task that each module must accomplish.

The first group includes the pulse length and carrier frequency of the slice-selective pulses, and the field gradient strengths employed during the slice-selective pulses. They are illustrated in Figure 4.9A and are listed as follows:

- $P_1$ Pulse length of the $90^\circ$ slice-selective pulse used in the first module of VOISINER.
- $P_2$ Pulse length of the $90^\circ$ slice-selective pulse used in the second module of VOISINER.
- $P_3$ Pulse length of the $180^\circ$ slice-selective pulse used in the third module of VOISINER.
- $f_x$ RF frequency of the slice-selective pulse which is applied in the presence of the $x$ field gradient.
- $f_y$ RF frequency of the slice-selective pulse which is applied in the presence of the $y$ field gradient.
- $f_z$ RF frequency of the slice-selective pulse which is applied in the presence of the $z$ field gradient.
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![Diagram of the VOISINER sequence and its various user-controllable parameters.]

**Fig. 4.9** The VOISINER sequence and its various user-controllable parameters.
- $G_{sx}$  X field gradient strength employed during the slice-selective pulse of the first module.
- $G_{sy}$  Y field gradient strength employed during the slice-selective pulse of the second module.
- $G_{sz}$  Z field gradient strength employed during the slice-selective pulse of the third module.

The location of the VOI, with coordinates $(x, y, z)$, can be focused on by determining the carrier frequencies $(f_x, f_y, f_z)$ of the slice-selective pulses with the following equations:

\[
\begin{align*}
    f_x &= (\omega_0 + \gamma G_{sx} x)/2\pi \quad [4-1a] \\
    f_y &= (\omega_0 + \gamma G_{sy} y)/2\pi \quad [4-1b] \\
    f_z &= (\omega_0 + \gamma G_{sz} z)/2\pi \quad [4-1c]
\end{align*}
\]

The volume of interest whose dimensions $(\Delta x, \Delta y, \Delta z)$ corresponds to the slice thickness of the three orthogonal slice-selective pulses can be adjusted to the desired size by varying the pulse length of the slice-selective pulse and the field gradient strength applied during slice-selection according to the following relations:

\[
\Delta x \propto 1 / P_1 G_{sx}, \quad \Delta y \propto 1 / P_2 G_{sy}, \quad \Delta z \propto 1 / P_3 G_{sz}
\]

These relations indicate only the dependence of the slice thickness with respect to the pulse length and the field gradient strength. However, a precise determination of the thickness requires a careful analysis of the waveform employed to modulate the amplitude of the slice-selective pulse. An interesting point to mention here is that the sensitive volume is in most cases, cubic in shape. However, the most general shape of the sensitive volume is a parallelepiped; this follows from the fact that the three slices
defined by the slice-selective pulses do not need to be perpendicular to form a basis in the cartesian space.

The second group includes the various time intervals and time delays employed for refocusing and dephasing purposes at different stages of the VOISINER sequence. They also include field gradient rise and fall time delays, introduced to avoid orthogonal field gradient overlap during slice-selective irradiation, and for magnetic field stabilization before data acquisition. They are illustrated in Figures 4.9A-B and are listed as follows:

- **TE¹** Time interval corresponding to the time that has elapsed from the middle of the slice-selective pulse of the first module to the top of the echo that occurs just before the application of the non-selective 90° pulse.

- **TE²** Time interval corresponding to the time that has elapsed from the middle of the slice-selective pulse of the second module to the top of the echo formed upon application of the slice-selective refocusing module.

- **Tr** Time interval following the application of the non-selective 90° pulse of the first module but prior to the application of the slice-selective pulse of the second module. During that time interval, a strong field gradient pulse may be applied to dephase incoherently the transverse magnetization and furthermore, the magnetization may partially recover to thermal equilibrium through T₁ relaxation.

- **D¹** Time interval corresponding to the time duration of the field gradient pulse necessary to refocus the transverse magnetization components that were dephased by the slice-selective pulse of the first module.

- **D²** Time interval corresponding to the time duration of the field gradient pulse necessary to refocus the transverse magnetization components that were dephased by the slice-selective pulse of the second module.
$-D_3$ Time interval preceding the selective refocusing pulse of the third module and
during which the spins will dephase with respect to the field gradient applied
during the slice-selective refocusing pulse. This dephasing destroys transverse 
magnetization that may or may not be refocused by the slice-selective refocusing 
pulse. It ensures that transverse magnetization that is not affected by the refocusing pulse will not persist through the selective pulse and produce an undesirable signal during data acquisition.

$-D_4$ Time interval following the slice-selective refocusing pulse which corresponds to 
the time duration of the field gradient pulse necessary to refocus the transverse magnetization that was dephased during the time interval $D_3$.

$-D_r$ Time delay that allows the field gradient to rise and stabilize to a certain value.

$-D_f$ Time delay that allows the field gradient to fall and stabilize to a null value.

$-D_s$ Time delay between the VOISINER sequence and data acquisition. This delay can reduce signal distortions caused by eddy currents in the cryostat which are induced by the pulsed field gradients.

4.3 Protocol

The task of adjusting the parameters described in the preceding section requires careful attention for optimizing the performance of VOISINER. In practice, complete adjustment is time consuming because of the number of variables. Thus if we wish to adjust simultaneously all the parameters of VOISINER, an efficient and systematic approach is desirable.

One approach that is likely to be effective is to start with just few parameters and gradually incorporate others until we get to the full implementation of the VOISINER sequence. Therefore, before using the complete sequence, it is desirable to implement intermediate stages in which each module is adjusted independently from the other
modules. The experimental protocol that we suggest is illustrated in Figure 4.10. The pulse sequence of Figure 4.10A incorporates the refocusing module of VOISINER. This sequence can be seen as a two-dimensional slice-imaging technique, where the slice is selected by the refocusing pulse. The parameters that can be adjusted are $P_3$, $TE_2$, $D_3$, $D_4$, $f_z$ and $G_{sz}$. Once these parameters are adjusted, the second stage is to incorporate the second module of VOISINER into the sequence of Figure 4.10A, replacing the initial non-selective 90° pulse with the slice-selective 90° pulse of the second module; this gives rise to the pulse sequence illustrated in Figure 4.10B; now the following parameters can be adjusted: $P_2$, $D_2$, $f_y$ and $G_{sy}$. Finally, the third stage consists of incorporating the first module of VOISINER into the sequence of Figure 4.10B; this results in Figure 4.10C which is the complete VOISINER sequence; the following set of parameters can now be adjusted: $P_1$, $TE_1$, $D_1$, $f_x$, $T_r$ and $G_{sx}$.

The reason which motivated us to include some phase-encoding and frequency-encoding field gradients within the pulse sequences of the protocol is that the spatial localization process at intermediate stages can be directly imaged. It is thus easier to control the efficiency of the localization process and, in practice, we have found it more convenient for optimizing the signal intensity of the echo during the final adjustments of the $D_4$, $D_2$ and $D_1$ refocusing time delays.

Before visualizing those intermediate stages, a very important set of parameters that are sometimes neglected but which must be carefully considered, are the ones which ensure that the various flip angles achieved by the RF pulses are properly set. For the non-selective RF pulses, the pulse length must be determined accurately. In practice, we have found that the method of determining the 180° pulse length by obtaining the best null signal from the whole sample was the most effective. For the selective pulses, one may either vary the pulse length, or change the amplitude of the modulation waveform.
Fig. 4.10 The intermediate stages involved in the experimental implementation of VOISINER for adjusting the various user-controllable parameters; (A) sequence used for adjusting the parameters of the third module of VOISINER; (B) sequence used for adjusting the parameters of the second module of VOISINER, including the D2 time delay; (C) sequence used for adjusting the first module of VOISINER. It does actually corresponds to the full imaging version of the VOISINER sequence.
However, when a particular slice thickness is desired, the pulse length is kept constant and the amplitude is varied. To accurately set the flip angle of a selective pulse, we have found that the method which consists of determining the amplitude for a 180° pulse by obtaining the best null signal for spins at resonance (Fig. 3.9F) when using the sequence of Figure 3.8A worked very well.

To visualize that protocol, it is instructive to consider a typical experiment in which we spatially localize a region within a larger sample; we use the model system illustrated in Figure 4.11A which consists of a cylindrical bath (internal diameter, 4 cm; length, 4 cm) filled with water. A two-dimensional image of that system is illustrated in Figure 4.11B.

The action of the slice-selective refocusing pulse of Figure 4.10A is illustrated in Figure 4.11C; this image was obtained by using the z field gradient as the phase encoding gradient and serves to illustrate the efficiency of the slice-selection obtained with a selective refocusing pulse, the slice thickness, and its location along the z axis that was adjusted by the $f_z$ carrier frequency. The same slice is shown in Figure 4.11D but this time, the phase encoding gradient is the y field gradient, as prescribed by the pulse sequence of Figure 4.10A. In practice, we have found that the $D_3$ and $D_4$ time delays, as prescribed in Figure 4.9A, are not equal and that discrepancy increases with longer rise and fall times of the field gradient. This is easily explained by considering that the dephasing angle is proportional to the "area under the curve" and thus, the area under the rise and fall time portions of those delays must be taken into account. The second intermediate stage is illustrated in Figure 4.11E and was obtained by the pulse sequence of Figure 4.10B; the image obtained now illustrates the efficiency of the slice selection, the slice thickness and its location along the y axis. Finally, in the third stage, the first module is adjusted and Figure 4.11F illustrates its action along the x axis; this image was obtained by using the imaging version of the VOISINER sequence (Fig. 4.10C).
Fig. 4.11 Images showing the intermediate stages of the experimental protocol used for implementing VOISINER; (A) experimental model system; (B) two-dimensional image of the model system; (C) image obtained with the pulse sequence of Figure 4.10A with the z field gradient as the phase encoding gradient; (D) image obtained with the pulse sequence of Figure 4.10A with the y field gradient as the phase encoding gradient; (E) image obtained with the pulse sequence of Figure 4.10B; (F) image obtained with the full VOISINER method. The following parameters were used for obtaining the images of (C)-(F): TR=1 s, TE$_1$ = 10 ms, TE$_2$ = 18 ms, 128 phase-encoding steps, data block size = 128, P$_1$ = P$_2$ = 1.5 ms, P$_3$ = 1 ms, non-selective $90^\circ$ pulse = 39 $\mu$s, NA = 8, D$_1$ = D$_2$ = 1.15 ms, D$_3$ = 4 ms, D$_4$ = 3.7 ms, G$_{sz}$ = 1.4 G/cm, G$_{sy}$ = 1 G/cm, G$_{sx}$ = 1 G/cm.
FIG. 4.11 continued...
When all the parameters are adjusted, the next step, if high-resolution NMR measurements are needed, is to remove the phase- and frequency-encoding gradients and use the high-resolution version of VOISINER that is illustrated in Figures 4.9A-B. So far we have not mentioned anything about the $D_r$, $D_f$ and $D_s$ time delays. Their use is prescribed in Figure 4.9B; they should be assigned conservative values in a first instance to ensure that they will not cause any slice-selection and field homogeneity distortions. For the first set of field gradient coils, we have used $D_r$, $D_f$ and $D_s$ of, respectively, 4 ms, 4 ms and 10 ms.
5. OPTIMIZATION OF VOISINER

In this Chapter, several aspects of the VOISINER technique are examined more closely in order to evaluate the experimental factors that can degrade or improve the efficiency of the spatial selectivity of VOISINER and its detection sensitivity. These studies should provide us useful insight concerning the applicability and experimental robustness of the technique.

5.1 Volume Selectivity

The signal suppression process involved in VOISINER is critical for obtaining a spatially localized NMR signal that is free from any signal contamination arising from the periphery of the volume of interest. However, under particular experimental conditions, that process partially fails and suffers from a loss of spatial discrimination. During the development of VOISINER, important sources of signal contamination have been identified; in what follows, we examine them and also suggest some solutions to considerably reduce their deleterious effects.

5.1.1 Experimental

The experiments that are described in sections 5.1.2 through 5.1.4 were performed on a "phantom" (model system) which was made of a bulb (volume, 1.1 ml; internal diameter, 1.3 cm) immersed in a cylindrical bath (length, 7 cm; internal diameter, 5.8 cm) of water. The water was slightly doped with manganese chloride to yield T₂ and T₁ relaxation times of 75 ms and 680 ms. The bulb contained a 1:1 mixture of cyclohexane and benzene and was doped with a 15 mM concentration of chromium acetoacetonate. The T₂ and T₁ relaxation times of cyclohexane and benzene were measured to be, respectively, 100 ms and 150 ms, 160 ms and 290 ms.
To help visualize that phantom, two orthogonal slice images were obtained, as shown in Figure 5.1. The image of Figure 5.1A was obtained by conventional spin echo imaging (Fig. 3.3) but with a slice-selective 180° refocusing pulse (P3 pulse of VOISINER) applied in the presence of a z field gradient. The image of Figure 5.1B was also obtained by conventional spin echo imaging but with an initial slice-selective 90° excitation pulse (P2 pulse of VOISINER) applied in the presence of a y field gradient.

To evaluate the losses of spatial discrimination, two sets of experiments were performed: the first set consisted of imaging the localized volume by using the imaging version of VOISINER, and the second set consisted of acquiring a high-resolution spectrum from the localized volume with the high-resolution version of VOISINER. These two sets of experiments were complementary; the high-resolution spectrum constituted the ultimate test but did not give any indication concerning the locations of those possible contaminations; the imaging experiment was thus necessary in order to identify those possible locations. In these experiments, the localized volume was centered inside the bulb and its dimensions were: 10 mm x 10 mm x 7 mm. The reason for filling the bulb with chemical species different from that of the bath was to be able to efficiently evaluate, from the high-resolution spectrum of the VOI, the possible signal contamination from the surroundings.

All the images presented in this section using the imaging version of VOISINER were obtained with the following set of parameters: $P1 = P2 = 1.5 \text{ ms}, P3 = 1 \text{ ms}, TR = 1 \text{ s}, TE_2 = 24 \text{ ms}, 128$ phase-encoding steps, image size = $128 \times 128$, non-selective 180° refocusing pulse = $70 \mu \text{s}$, $x$ slice thickness = $10 \text{ mm}$, $y$ slice thickness = $10 \text{ mm}$, $z$ slice thickness = $7 \text{ mm}$, $D_r = D_f = 4 \text{ ms}, D_1 = D_2 = 1.15 \text{ ms}, D_3 = 4 \text{ ms}, D_4 = 3.65 \text{ ms}$. All the spectra presented in this section using the high-resolution version of VOISINER were obtained with a similar set of parameters except for the following: $TE_2 = 9 \text{ ms}, D_s = 10 \text{ ms}$. 
FIG. 5.1 Two orthogonal slice images visualizing the model system employed during the experiments described in sections 5.1.2 - 5.1.4. (A) Slice image of the xy plane in the laboratory frame. (B) Slice image of the xz plane. The cavity that appears in both images is the immersed bulb filled with a 1:1 mixture of cyclohexane and benzene. The non-uniformity of the slices is caused by the $B_1$ field inhomogeneity which becomes more apparent at the edges.
5.1.2 Effects of Flip Angle Inaccuracies

Two sources are responsible for flip angle inaccuracies; the first one is a missetting of the pulse lengths or amplitudes of the various RF pulses (with our apparatus, only the selective pulses can have their amplitude varied); the second source arises from $B_1$ field inhomogeneities produced by the RF transmitter coil. To evaluate the deleterious effects that these two sources may produce, we have deliberately subjected VOISINER to those flip angle inaccuracies.

To start with, Figure 5.2 illustrates the selected volume obtained in a single scan under "normal" operating conditions ("normal": flip angles are properly set). The effects of $B_1$ inhomogeneities appears in Figure 5.2A and 5.2B along the x direction and are clearly visible at both ends where the RF field becomes less uniform. The high-resolution spectrum of Figure 5.2C confirms the signal contamination from those artifacts along the x direction. Fortunately, the efficiency of the spatial discrimination of the second (y slice) and the third module (z slice) are such that only the signal contamination which is at the intersection of the y and the z slice remains, as shown by Figures 5.2A-B. The pulses which are responsible for these artifacts are the non-selective pulses used in the first module; the non-selective 90° pulse which flips into the transverse plane the magnetization outside the x slice is particularly important, because for an efficient suppression of the signal arising from those portions of the sample, it is essential that no longitudinal magnetization persists upon application of that 90° pulse. Otherwise, it would directly compete with the magnetization from the selected slice that was kept along the longitudinal axis (z axis) by the first module. To further investigate the effects caused by the non-selective 90° pulse, the latter was misadjusted by −20% from its nominal value and in this particular case, it was set to 28 μs instead of 35 μs; figure 5.3 illustrates the artifacts created by this pulse misadjustment.
FIG. 5.2 Images and high-resolution spectrum of the volume of interest obtained under "normal" operating conditions. (A) Slice image of the xy plane. (B) Slice image of the xz plane. (C) High-resolution spectrum from the volume of interest.
Fig. 5.3 Images and high-resolution spectrum of the volume of interest obtained with an arbitrary missetting of the non-selective $90^\circ$ pulse contained in the first module of VOISINER. (A) Single scan slice image of the xy plane. (B) Single scan image of the xz plane. (C) High-resolution spectrum from the volume of interest obtained in a single scan.
As previously, the effects are aligned with the x direction but only from that portion of the sample which is at the intersection of the y slice (discriminated by the second module) and the z slice (discriminated by the third module). Since the nature of this study was mainly to identify and qualitatively analyze the potential problems, other missetting values of the non-selective 90° pulse were not imaged. Nevertheless, Figure 5.4 illustrates a set of spectra obtained for three different flip angle misadjustments. An interesting thing to note which further confirms that the signal contamination originates from the remaining longitudinal magnetization upon application of the first module, is that the phase of the spurious response from the surroundings has changed by 180° (Fig. 5.4A and 5.4C) from a 90° misadjustment of −20% to +20%. This phenomenon can be easily explained by considering that, for a misadjustment of −20% (flip angle < 90°), the remaining longitudinal magnetization is along the positive z direction, whereas the remaining magnetization for a misadjustment of +20% (flip angle > 90°), is along the negative z direction.

Flip angle inaccuracies of the slice-selective pulses were also tested. However, it was found that the spatial selectivity of VOISINER is practically insensitive to those flip angle missettings; only a decrease in the signal intensity from the volume of interest was observed. To demonstrate that, the amplitude of the slice-selective pulses was varied (the reason for not varying their pulse length is to keep the slice thickness constant). Furthermore, since it was expected that the potential problems would only affect the spatial discrimination along the direction perpendicular to the slice they irradiate, only projections along those directions were obtained. The first slice-selective pulse that was tested is the selective refocusing pulse of the third module. Three different amplitudes were tested to produce flip angle misadjustments of, respectively, −50%, 0%, +50%. Figure 5.5 shows a set of excitation profiles that was obtained for those various flip angle misadjustments.
Fig. 5.4 Series of high-resolution spectra arising from the volume of interest for different flip angle misadjustments of the non-selective 90° pulse of the first module; (A) misadjustment = −20%; (B) misadjustment = 0%; (C) misadjustment = +20%.
Fig. 5.5 Series of excitation profiles obtained for various flip angle misadjustments of the slice-selective 180° refocusing pulse. The projection direction is along the z axis in the laboratory frame. (A) Intersection of the x and the y slice defined by the first and the second module of VOISINER before it is spatially discriminated along the z direction. (B) Misadjustment = -50%; (C) Misadjustment = 0%; (D) Misadjustment = 50%.
Fig. 5.6 Series of high-resolution spectra arising from the volume of interest for various flip angles of the refocusing pulse of the third module. (A)-(C) Spectra corresponding to the profiles obtained in Figures 5.5B-D.
Fig. 5.7 Series of excitation profiles obtained for various flip angle misadjustments of the slice-selective 90° excitation pulse of the first module. The projection direction is along the x axis in the laboratory frame. (A) Intersection of the y and the z slice defined by the second and the third module of VOISINER before it is spatially discriminated along the x direction. (B) Misadjustment = -67%; (C) Misadjustment = 0%; (D) Misadjustment = 67%.
Fig. 5.8 Series of high-resolution spectra arising from the volume of interest for various flip angles of the selective 90° pulse of the first module. (A)-(C) Spectra corresponding to the profiles obtained in Figures 5.7B-D.
Figure 5.5A serves to illustrate the projection of that portion of the sample which corresponds to the intersection of the x and the y slice before it is spatially discriminated by the refocusing pulse. Another interesting thing to note is that the shape of the excitation profile of the 180° refocusing pulse is fairly insensitive to the flip angle. Figure 5.6 shows the high-resolution spectra obtained for the various flip angle misadjustments of the 180° refocusing pulse. It confirms that no spurious response from the surroundings is observed and that it is accompanied by a loss in the detection sensitivity. The slice-selective 90° excitation pulses of the first and the second module were also tested with flip angle misadjustments of, respectively, -67%, 0%, and 67%. Since the effects for both pulses were found to be very similar, only the slice-selective 90° excitation of the first module is discussed. The results obtained for the three flip angles are illustrated in Figure 5.7. The projection axis is now the x axis and Figure 5.7A shows the projected portion of the sample which corresponds to the intersection of the y and the z slice defined by the second and the third module of VOISINER. Unlike the results obtained for the 180° refocusing pulse, the excitation profile for the slice-selective excitation pulse is dependent upon the flip angle and the non-linear behaviour becomes more apparent for a flip angle of 150°, as shown in Figure 5.7D. Figure 5.8 shows the corresponding high-resolution spectra obtained for the three flip angles. A loss in detection sensitivity is also apparent and furthermore, the non-uniform excitation profile created by the non-linear behaviour of a flip angle of 150° (Fig. 5.7D) produces an amplitude distortion of the peaks present in the spectrum (Fig. 5.8C).

5.1.3 Relaxation Effects from the Surroundings

The major source of potential loss of spatial discrimination arises from $T_1$ relaxation of the magnetization outside the slice discriminated by the first module. More specifically, this effect manifests itself between the first and the second module of
VOISINER, also identified in Chapter 4 as the $T_r$ time interval. The explanation is similar to the case of the non-selective $90^\circ$ pulse discussed in section 5.1.2.; the appearance of a longitudinal magnetization from outside the $x$ slice defined in the first module. Even if an ideal non-selective $90^\circ$ pulse is applied and then followed by an ideal incoherent dephasing of the unwanted transverse magnetization, during the time interval $T_r$, that transverse magnetization will nevertheless partially recover to equilibrium along the longitudinal axis to an extent that depends on its $T_1$ relaxation time. Thus, just prior to the application of the second module, that partially recovered longitudinal magnetization, irrespective of the magnetization from the desired slice which was arbitrarily kept along the longitudinal axis by the first module, will generate a detectable signal upon application of VOISINER. To illustrate this effect, an arbitrarily long $T_r$ time interval of 100 ms (instead of 5 ms, as normally used) was used to spatially localize the volume of interest. Figure 5.9 shows the effects produced by the $T_1$ relaxation of the surroundings.

The effects of $T_2$ relaxation of the spins from the surroundings emanates directly from the residual longitudinal magnetization that was produced, either by improper non-selective pulses or by $T_1$ relaxation; the coherent signal that is subsequently created from that residual longitudinal magnetization will decay exponentially with a $T_2$ time constant, and thus if data acquisition occurs before that signal has totally decayed, the contamination will appear in the NMR spectrum. However, if the $T_2$ relaxation of spins from the surroundings is much shorter than $T_2$ relaxation of the spins from the volume of interest, one can considerably reduce the effects of the surroundings by increasing the $TE_2$ period or delaying the data acquisition in order to provide a very strong $T_2$ weighting for the signal contamination.
Fig. 5.9 Images and high-resolution spectrum of the volume of interest when subjected to $T_1$ relaxation effects originating from the surroundings. The $T_r$ time interval was set to 100 ms.
In the preliminary results presented in Chapter 4, a strong $T_2$ weighting of the surrounding water ($T_2 = 30$ ms) contributed largely to the reduction of signal contamination even with a $TE_2$ period of approximately 4 ms and a field stabilization delay of 10 ms.

5.1.4 Phase Cycling Scheme

We saw in sections 5.1.2 and 5.1.3 that the flip angle inaccuracies of the non-selective 90° pulse and the $T_1$ relaxation of the spins from the surroundings could considerably affect the efficiency of the spatial selectivity of VOISINER. It was also demonstrated that those contaminations resulted from a residual longitudinal magnetization of the spins outside the slice discriminated by the first module, upon application of the latter. Fortunately, there is a method to eliminate that residual magnetization, but at the expense of signal suppression in a single scan. The method relies upon a phase cycling routine of the first module and requires the acquisition of two transients prepared in a prescribed manner. More specifically, it consists of shifting by 180° the phase of the slice-selective 90° excitation pulse of the first module and that of the receiver on alternate scans. Thus in the first experiment, upon application of the first module, the magnetization from the selected slice is along the $-z$ direction whereas the residual longitudinal magnetization from the surroundings is along, say the $+z$ direction. The FID that is subsequently acquired is thus the combination of two signals which are out of phase by 180°. In the second experiment, the phase of the slice-selective pulse of the first module is shifted by 180°. Upon application of the first module, the magnetization of the selected slice is now along the $+z$ direction whereas the residual longitudinal magnetization from the surroundings is still along the $+z$ direction, if the conditions are similar to the first experiment. The FID that is subsequently acquired is now the combination of two signals which are in phase. Thus if we subtract the two FIDs,
the signal arising from the residual longitudinal magnetization will cancel and the magnetization from the slice will add.

To test that procedure, the non-selective 90° pulse was misset by −20% and the $T_1$ time interval was set to an arbitrarily long value of 100 ms. The VOISINER sequence was then subjected to the phase cycling routine and the results are shown in Figures 5.10A-C. Figures 5.10D-E illustrates the use of that phase cycling routine for removing artifacts from $B_1$ inhomogeneities when VOISINER is operating under "normal" conditions. The phase cycling routine is thus a very efficient procedure to largely reduce the effects of $T_1$ relaxation and flip angle inaccuracy of the non-selective pulses. The negative point is that it requires the averaging of two transients, and a long enough time delay between two consecutive scans to allow the magnetization from the surroundings to properly recover to equilibrium. However, in a context where it is anyway necessary to perform signal averaging to improve the signal-to-noise (S/N) ratio, this procedure is therefore not too inconvenient.

5.1.5 Alternative Schemes for Inversion Module

The practical difficulties (stringent demands on field gradient rise time) of implementing the original version of the first module (see preliminary results in Chapter 4) prompted the investigation of alternative schemes. Several variants of the first module which is conceptually similar to that of the VSE method have been proposed in the literature. The necessary background to the methodology that can be employed is thus available and four different schemes were tested: these include the original first module of VOISINER (Fig. 5.11A); the module that is now in use in the current version of VOISINER (Fig. 5.11B), and which is based on the SPACE module; the module of the SPARS method (Fig. 5.11C); and finally, the VSE module (Fig. 5.11D). The latter was tested for pedagogical reasons only.
Fig. 5.10 Images and high-resolution spectrum of the volume of interest obtained with the phase cycling routine. (A)-(C) The non-selective 90° pulse of the first module was misadjusted by -20% and the $T_r$ time interval was set to 100 ms. (D-E) Under "normal" conditions.
FIG. 5.10 Continued...
The experimental setup used for testing those modules was identical to the one described in section 5.1.1, with the only difference that the bath was filled with pure water ($T_1 = T_2 = 2.3$ s) and that the bulb was positioned at coordinates (1,1,0) instead of (-1,1,-1). To visualize that phantom, two orthogonal slice images were obtained and are shown in Figure 5.12. The image of Figure 5.12A was obtained by conventional spin echo imaging (Fig. 3.3) but with a slice-selective 180° refocusing pulse (P3 pulse of VOISINER) applied in the presence of a z field gradient. The image of Figure 5.12B was also obtained by conventional spin echo imaging but with a slice-selective 180° refocusing pulse (P3 pulse of VOISINER) applied in the presence of a y field gradient.

The first module that was tested consists of an initial non-selective 90° pulse that flips the magnetization of the whole sample into the transverse plane. This non-selective pulse is then followed by a slice-selective 90° pulse that flips back along the longitudinal axis (direction of $B_0$) the magnetization of the selected slice. The transverse magnetization outside that slice is incoherently dephased by the field gradient that was employed during slice-selection. The major problem associated with this module is that in order to minimize the chemical shift dispersion, the time between the non-selective and selective pulses must be kept as short as possible. On the other hand, to perform a clean slice-selection, the amplitude of the field gradient during slice-selection must be very uniform, and thus, to meet these two requirements the field gradient must have a very short rise time. Figure 5.13 illustrates the spatial selectivity of that module and it is clear that the performance is rather poor. The z field gradient was used in the first module instead of the usual x field gradient. The reason is that the rise time of the z field gradient is shorter than that of the x field gradient. The square shape function employed for the slice-selective pulse is the source of the sidebands which are visible in the image of the xz plane (Fig. 5.13A). To reduce these artifacts the phase cycling routine described in section 5.1.4 was used and the results obtained are illustrated in Figure 5.14.
Fig. 5.11 Four tested schemes of the first module of VOISINER. (A) Original module of VOISINER. (B) Module currently used in VOISINER (based on the SPACE module). (C) SPARS module. (D) VSE module.
Fig. 5.12 Two orthogonal slice images visualizing the model system employed during the experiments described in section 5.1.5. (A) Slice image of the xy plane in the laboratory frame. (B) Slice image of the xz plane. The cavity that appears in both images is the immersed bulb filled with a 1:1 mixture of cyclohexane and benzene. The non-uniformity of the slices is caused by the $B_1$ field inhomogeneity which becomes more apparent at the edges.
Fig. 5.13 Image of the xz plane and high-resolution spectrum of the volume of interest obtained by using the original version of the first module of VOISINER. The results were obtained in a single scan.
Fig. 5.14 Image of the xz plane and high-resolution spectrum of the volume of interest obtained by using the original version of the first module of VOISINER, but subjected to the phase cycling routine. These results were obtained in two scans.
From Figure 5.14, it is clear that although the effects of flip angle inaccuracies of the non-selective pulses have been removed, the sidebands produced by the slice-selective pulse remains and thus, a water signal contamination persists.

The second module that was tested is the module of the current version of VOISINER and since it was described in detail in Chapter 4, for purpose of comparison, only the results are illustrated in Figures 5.15-5.16.

The third module that was tested is the SPARS module which comprises three RF pulses. The first pulse is a non-selective pulse which flips into the transverse plane the magnetization from the whole sample. This non-selective pulse is then followed by a pulsed field gradient which dephases the transverse magnetization. After the gradient has been turned off, a non-selective 180° refocusing pulse is applied to correct for chemical shift dispersion and magnetic field inhomogeneities. A second pulsed field gradient in the same direction rephases the transverse magnetization. Then a non-selective 90° pulse is applied which coincide with the spin echo. The results obtained with this module are illustrated in Figures 5.17-5.18.

Finally, the last module that was tested is the VSE module and the results are shown in Figures 5.19-5.20. The major problem with this module is the very high radiofrequency power requirement needed by the non-selective 90° pulse which has to flip into the transverse plane, all the spins of the sample in the presence of large resonance offsets artificially created by the field gradient. In Figure 5.19, the effects caused by an improper 90° flip angle is clearly visible at both ends along the x direction, where the resonance offset created by the field gradient is very large. The phase cycling routine could only partially remove those artifacts, as shown in Figure 5.20.
Fig. 5.15 Image of the xy plane and high-resolution spectrum of the volume of interest obtained by using the current version of the first module of VOISINER which is based on the SPACE module. These results were obtained in a single scan.
FIG. 5.16 Image of the xy plane and high-resolution spectrum of the volume of interest obtained by using the current version of the first module of VOISINER, but subjected to the phase cycling routine. These results were obtained in two scans.
FIG. 5.17 Image of the xy plane and high-resolution spectrum of the volume of interest obtained by using the SPARS module. These results were obtained in a single scan.
FIG. 5.18 Image of the xy plane and high-resolution spectrum of the volume of interest obtained by using the SPARS module, but subjected to the phase cycling routine. These results were obtained in two scans.
Fig. 5.19 Image of the xy plane and high-resolution spectrum of the volume of interest obtained by using the VSE module. These results were obtained in a single scan.
FIG. 5.20 Image of the xz plane and high-resolution spectrum of the volume of interest obtained by using the VSE module, but subjected to the phase cycling routine. These results were obtained in two scans.
In summary, of the four tested modules, the module from the current version of VOISINER and that of the SPARS technique have demonstrated the best performance while the module from the original version of VOISINER and that of the VSE technique have demonstrated a rather poor performance.

## 5.2 Detection Sensitivity

As we saw in Chapter 4, the full transverse magnetization from the volume of interest can, under ideal conditions, be totally restored. However, in practice, it is subjected to various experimental imperfections that can affect the efficiency with which the magnetization is recovered from the volume of interest. Thus, to obtain the best possible signal intensity, it is important to optimize each module and identify the factors that can deteriorate their performance. Equally important are the effects of $T_1$ and $T_2$ relaxation of the spins in the volume of interest which can also erode that magnetization through the intermediate stages of the sequence.

The first imperfection that can be considered is the excitation profile of the slice-selective pulses. In the present implementation of VOISINER, the slice-selective refocusing pulse which produces an approximate $\sin^2$ shape frequency response is the major source of signal losses that can be attributed to a non-uniform excitation profile; a loss of approximately 50% in signal intensity has been observed. The slice-selective pulses of the first and the second module, on the other hand, have a fairly uniform excitation profile. However, as was briefly discussed in Chapter 3, their use is accompanied with an off-resonance phase shift of the transverse magnetization components within the slice. That phase change with resonance offset creates a dephasing of the magnetization which results in a loss of signal intensity. In Figure 5.21, the amplitude uniformity and phase change with resonance offset was theoretically calculated and experimentally evaluated for the case of a $\sin(x)/(x)$ pulse shape.
Fig. 5.21 Calculated (solid line) and experimentally measured (+) variation of the magnitude and the phase of the transverse magnetization versus resonance offset, generated by a $\sin(x)/x$ shape selective 90° excitation pulse. (A) Magnitude. (B) Phase. The theoretical predictions were calculated by numerical analysis of the Bloch equation with no relaxation term. A fifth-order Runge-Kutta with adaptative stepsize (123) was used (see Appendix C). The experimental results were performed on a 1.3 cm bulb filled with water. The magnitude and the phase of the water peak were extracted from the NMR spectrum. The resonance offset was varied by changing the carrier frequency of the selective pulse. A pulse length of 1 ms was used for the selective pulse.
The pulse shape was time-windowed to include only the main lobe with two side lobes on either side. We note from Figure 5.21B that within the bandwidth of the pulse, the phase change with resonance offset is linear with a slope that corresponds to a time $\tau$ equal to 53% that of the RF pulse length. Consequently, the application of a 180° refocusing pulse immediately following the slice-selective pulse will cause a refocusing within the bandwidth of the pulse at a time $\tau$. To obtain maximum refocusing of the magnetization following the application of the slice-selective excitation pulse of the first and the second module, the field gradient delays $D_1$ and $D_2$ must then be adjusted according to the manner that was just described.

Another source of signal losses and which can be attributed to the first module has been observed, and, in the author's knowledge, has not been reported elsewhere. This loss in signal intensity is caused by the excitation profile of the first module which loses its uniformity in a cyclic fashion, as the carrier frequency $f_x$ of the slice-selective pulse of the first module is varied (Fig. 5.22). This intriguing phenomenon was found to be simply caused by the emergence of a phase difference (other than 0° or 180°) between the initial slice-selective pulse and the non-selective 90° pulse when the carrier frequency $f_x$ differed from $f_0$. A phase difference of 0° or 180° between those two pulses is essential for a proper flipping of the magnetization from the transverse plane to the longitudinal axis. However, that phase difference could be compensated by simply phase shifting the non-selective 90° by an appropriate phase angle. It was also found that the period of that cycle was inversely proportional to the pulse length of the slice-selective pulse. This can be explained by the following; during slice-selection, seen from the rotating frame ($f_0$), the RF field precesses at a frequency which corresponds to the frequency difference ($f_x - f_0$). Upon application of the RF pulse, the phase of the RF field is not equal to its initial phase unless it made an integer number of revolutions during slice-selection.
Fig. 5.22 Excitation profile of the first module for various carrier frequencies of the slice-selective pulse. The slice-selective pulse used in this experiment had a pulse width of 1.5 ms and the carrier frequency was incremented by step of 200 Hz.
Concerning the effects of relaxation on the intensity of the NMR signal, $T_2$ relaxation can produce a strong $T_2$ weighting of the transverse magnetization during the $TE_2$ period, the $TE_1$ period and the magnetic field stabilization delay prior to data acquisition. Consequently, it is advisable to keep these time intervals as short as possible.

Concerning the effects of $T_1$ relaxation, one potential loss of signal intensity may arise if the time interval $T_r$ is such that it corresponds to half-recovery of the inverted magnetization, i.e. to a null longitudinal magnetization. However, this is unlikely to happen unless $T_1$ is very short, or $T_r$ is set to a rather long value, which is not advisable for reasons mentioned in section 5.1.3.
6. VOISINER APPLICATIONS

There is a wide variety of information that can be extracted from the sensitive volume by combining VOISINER with other conventional NMR methodology. Those combinations can take different forms, depending on the complexity of the spin physics involved in a particular experiment. VOISINER can be regarded as a "localization module" that can be inserted at an appropriate stage in the NMR experiment. To test the applicability of VOISINER, we have tested two extensions: high spatial resolution imaging and spatially localized T1 measurements. Since the major application area of the method will most likely be in the biomedical field, the method was also tested in a clinical environment by extracting spatially localized spectra from a human forearm.

6.1 High Spatial Resolution Imaging of Small Regions within Large Objects

Although much of the impetus to develop very high spatial resolution imaging has been directed to studies of very small objects (124-126), there are many circumstances where it is desirable to have equivalently high resolution for smaller portions of a larger object. In what follows, we briefly exercise the options available to achieve that end, and then illustrate a procedure which involves the VOISINER sequence for spatially localized NMR.

The simplest means of obtaining a higher spatial resolution display of a region of an image is by zoom-expansion of that region; obviously this necessitates that the digital resolution of the complete image be sufficient to support that expansion. In turn, that requires a longer data acquisition time and a substantial increase in the size of the data file; for instance, in conventional spin-echo imaging, an n-fold increase in pixel resolution (decrease in pixel size) involves an n-fold increase of the acquisition time (65); this also increases the size of the data set by a factor n^2 and this leads, therefore, to a
significant increase in imaging computation time. On the other hand, if the field of view is reduced down to the region of interest, either by increasing the imaging field gradient strengths or by reducing the frequency bandwidths of each dimension, signals from the periphery of the region of interest will be folded back into the image.

From this it follows that the most convenient approach likely to be effective is one that involves excitation of NMR responses solely from the region of interest by the use of a suitable means of volume selective excitation. Although a similar approach using the stimulated echo method (127-129) has already been demonstrated (130), we have chosen to combine the VOISINER sequence with phase- and frequency-encoding gradients.

6.1.1 Method

Briefly, as was seen in Chapter 4, the present implementation of the VOISINER sequence involves three distinct modules, each of which contains a slice-selective pulse applied along one of three orthogonal directions (Fig. 6.1C). The first module preserves the longitudinal magnetization of the selected slice and saturates the magnetization elsewhere. The second module flips into the transverse plane, the longitudinal magnetization which is at the intersection of the two orthogonal planes defined at that stage. Then, the third module selects a plane orthogonal to the two previously defined planes and refocuses the magnetization which is at the intersection of the three orthogonal planes. To obtain a slice image of the region of interest, a phase-encoding gradient is applied between the second and the third modules and a frequency-encoding gradient is applied during data acquisition. The frequency-encoding gradient is also applied between the second and the third modules, enabling the signal to be observed as an echo, following the application of the selective refocusing pulse (third module) which also selects the slice.
Fig. 6.1 Schematic illustration of the three pulse sequences used for obtaining the images shown in Figure 6.2. (A) Modified spin-warp imaging pulse sequence using a slice-selective 180 pulse (see Fig. 6.2A). (B) This sequence is obtained by replacing the hard 90 pulse of sequence A by a slice-selective 90 pulse (see Fig. 6.2B). (C) The VOISINER sequence with phase- and frequency-encoding gradients (see Fig. 6.2C and Fig. 6.2E).
6.1.2 Experimental

This sequence was tested on a phantom comprising a Perspex cylinder of water (length, 7 cm; internal diameter, 5.8 cm) filled with an array of glass tubes (length, 6 cm; internal diameter, 7 mm; wall thickness, 1 mm). This was mounted horizontally in the homebuilt 8.9 cm elongated H-resonator which was modified to yield the same $B_1$ field distribution as a saddle coil (Chapter 4). The probe was then placed inside our first set of field gradient coils with a clear bore of 15 cm, each driven by a Tecron power audio-amplifier Model 7560. Following data acquisition and FT processing, the image files were downloaded via a IEEE-488 interface from the 1280 computer to the image processing unit based on an IBM-AT computer using the PC Semper Image Processing Operating Environment (Data Translation, Inc.).

6.1.3 Results

The set of images shown in Figure 6.2 serves to compare the relative efficiencies of zoom-expansion of a normal image (Fig. 6.2D) with those of the VOISINER method (Fig. 6.2E), together with the intervening stages of the latter. Initially, a slice-image of the object (Fig. 6.2A) was obtained in a usual fashion using a modified 2-D spin-warp imaging method (77) as illustrated in Figure 6.1A (the experimental details are given in the figure caption): that image provided the reference frequencies $(f_x, f_y)$ subsequently used to define the two remaining intercepting slices, and also constituted the slice defined by the third module of VOISINER. Figure 6.2B shows the location of the slice (slice thickness = 1.2 cm) along the x-axis obtained using sequence B (Fig. 6.1B); that image constitutes the interception of the two orthogonal slices defined by the second and third modules of VOISINER. The region of interest is finally defined by adding the first module of VOISINER which slice-selects (slice thickness = 1.3 cm) along the remaining orthogonal direction.
Fig. 6.2 Set of images showing the intermediate stages involved in producing a zoomed image by the VOISINER sequence. The following parameters were used to obtain these images: slice thickness = 3 mm, TR = 1 s, TE2 = 24 ms, 128 phase-encoding steps, block size = 256, selective 180 pulse width = 667 μs, selective 90 pulse width = 1 ms, hard 90 pulse width = 37 μs, water doped with manganese chloride (T₁ = 680 ms, T₂ = 75 ms). (A) Image obtained with sequence A (Fig. 6.1A), NA = 4. (B) Image obtained with sequence B (Fig. 6.1B), NA = 4. (C) Image of the region of interest obtained with sequence C (Fig. 6.1C), NA = 4. (D) Image obtained by software zoom-expansion of image C. A magnification factor of 4 and bilinear interpolation were used to produce this image. (E) Zoomed image of the region of interest obtained with sequence C (Fig. 6.1C) using imaging gradients four times stronger than those used for obtaining (A)-(C), NA = 64.
FIG. 6.2 Continued...
This is illustrated in Figure 6.2C, which was obtained using sequence C (Fig. 6.1C); it also clearly indicates the selectivity with which each dimension can be defined. The region of interest was deliberately chosen to include a glass tube that contained 10 capillary tubes (length, 6 cm; internal diameter, 1.3 mm; wall thickness, 190 μm). The same region was then magnified using the sequence in Figure 6.2C, but with imaging gradients four times stronger than those used for obtaining Figures 6.2A-C; this reduced the pixel size by a factor 16, as shown in Figure 6.2E. Comparison with the magnified image (Fig. 6.2D) obtained by a simple software zoom-expansion of Figure 6.2C clearly shows the enhancement of spatial resolution.

6.1.4 Discussion

Notwithstanding the overall advantages of selective excitation zoom imaging, it is necessary to examine critically what is involved. The first point concerns the signal-to-noise (S/N) ratio of the images. If it is desired to improve the resolution by a factor $n^{1/2}$ in each dimension, then the pixel size will be reduced by a factor $n$ and the S/N will be reduced by the same factor. Thus the time required to obtain the high resolution image with the same S/N ratio as that in the low resolution image must be increased by a factor $n^2$. Another point of concern is the position of the region of interest relative to the center of the image. After zoom-expansion, achieved by increasing the imaging gradient strengths, the field of view will have decreased and, if the region of interest is off-center by $(f_x, f_y)$, then portions of it might be outside the new field of view. If the image is only off-center by $(0, f_y)$ along the frequency-encoding direction, this can be easily corrected by shifting the frequency of the receiver by $f_y$. However, if the image is also off-center along the phase-encoding direction, a correction is again possible but is somewhat more subtle. Although we have not yet fully evaluated them, two solutions are possible. The first is simply to change the orientation of the phase- and frequency-encoding directions
by appropriate combination of the $G_x$ and $G_y$ gradients so that the new frequency-encoding axis intercepts the center of the zoomed region of interest; the second is to increment the phase of the receiver at each phase-encoding step by an angle $\phi$, expressed as

$$\phi = -\gamma x_0 G_{xi} \tau$$  \hspace{1cm} [6.1]$$

where $x_0$, $G_{xi}$, $\tau$, are, respectively, the $x$ coordinate of the center of the region of interest, the $G_x$ gradient phase-encoding increment and the phase-encoding time.

In summary then, the present study clearly demonstrates that high resolution images of restricted regions within a larger object can be obtained with considerable ease, but not without cost. The basic compromises between resolution and time, between signal-to-noise per voxel and filling factor for the probe, between efficiency of the spin physics involved and the combined influence of the inhomogeneities of the $B_0$ and $B_1$ fields, all require careful attention. Given the plethora of compromises which must be optimized, only one thing is clear, namely that there is unlikely to be any single global solution or approach which is uniquely suited to all the many possible applications which can benefit from this area. On the other hand, the present study suggests that solutions optimized to specific problems can be achieved.

### 6.2 Volume-Selective Measurements of Spin-Lattice Relaxation Times

Thus far, studies of spectra (51-54, 127-129, 131-134) from well-defined volumes within large objects have tended to concentrate on measurement of the relative concentration of the chemical species involved. In a welcome departure, the work of Luyten and colleagues (135) and another group (129) has drawn attention to the additional opportunities for measuring spin-lattice relaxation times. This topic has also been of concern to us in the development of the VOISINER sequence, since it was
important to know the overall range of $T_1$ relaxation times accessible experimentally by this procedure. We now present data which demonstrate that volume selective $T_1$ values in the range of 38 ms to 1.4 s can be measured.

6.2.1 Method

The method is based on the inversion-recovery (136) sequence and consists of the following: a hard 180° pulse inverts the spin populations of the whole sample and, after a recovery time $T$, the conventional 90° read-pulse is replaced by the VOISINER sequence which induces a coherent free induction signal exclusively from the region of interest within the sample. The recovery to thermal equilibrium of the entire spectrum from the volume of interest (VOI) is monitored by repeating the experiment for different values of $T$. The recovery to thermal equilibrium of the entire spectrum from the volume of interest (VOI) is monitored by repeating the experiment for different values of $T$. The radiofrequency (RF) and gradient time-sequence combination of the inversion-recovery (IR) and the original VOISINER methods which we have named IR-VOISINER is illustrated in Figure 6.3.

To partially compensate for inversion-pulse imperfections, such as $B_1$ inhomogeneities, resonance offsets and flip angle missettings, the conventional 180° inversion pulse was replaced by a $90°_x$-$180°_y$-$90°_x$ composite pulse (99,100). The residual transverse magnetization following the inversion pulse that might otherwise have persisted through the recovery time was eliminated by the use of a phase cycling procedure (137,138) originally described for the conventional inversion-recovery experiments. This procedure was adapted to IR-VOISINER by phase shifting by 180° relative to the inversion pulse, the RF pulses of VOISINER, as well as the phase of the receiver on alternate scans.
Fig. 6.3 IR-VOISINER pulse sequence. A composite $180^\circ$ inversion pulse inverts the z magnetization of the whole sample under study. After an inversion delay time $T$, the VOISINER sequence produces by means of a combination of slice-selective pulses a coherent transverse magnetization from the region of interest within the sample.

Fig. 6.4 Illustration of the phantom used for the experimental demonstration of volume-selective $T_1$ measurements with IR-VOISINER. Five bulbs (internal diameter, 1.3 cm) are immersed in a cylindrical water bath (length, 7 cm; internal diameter, 5.8 cm) and are configured as in a $AX_4$ tetrahedral conformation. The water bath was doped with manganese chloride and has a $T_1$ of approximately 180 ms. Each bulb is filled with a 1:1 mixture of cyclohexane and benzene and doped with a specific concentration of chromium acetoacetate.
6.2.2 Experimental and Results

The performance of IR-VOISINER was tested on a phantom made of a set of five bulbs (volume, 1.1 ml; internal diameter, 1.3 cm) immersed in a doped water bath and configured as in Figure 6.4. Each bulb contained a 1:1 mixture of cyclohexane and benzene and was doped with a specific concentration of chromium acetoacetonate (CrAcAc). The magnetization recovery to thermal equilibrium of cyclohexane and benzene from each individual bulb inside the bath was followed (Fig.6.5) by using thirty inversion delay times in the range $0 < T < 2T_1$, with a delay between successive scans of at least $5T_1$, with $T_1$ the longest relaxation time anticipated from the VOI. No attempts were made to measure the equilibrium magnetization corresponding to $T > 5T_1$, since a three-parameter exponential fitting (139,140) provided by the NMR Nicolet software was used to calculate $T_1$. Figure 6.5 shows the efficiency of the spatial localization achieved with VOISINER. Each partially relaxed spectrum resulted from the signal averaging of only two transients following the phase cycling procedure previously described; no phase alternation routine (141) was employed to equalize the two channels of the quadrature detector. The region of interest was specified from the intersection of three orthogonal slice-images, thus defining the transmitter frequencies ($f_x$, $f_y$, $f_z$) for the three orthogonal slice-selective pulses used in VOISINER. The size of the VOI was adjusted by applying those slice-selective pulses in the presence of appropriate field gradient strengths; for the experiments described here volumes of approximately $8 \times 8 \times 4$ mm$^3$ were spatially resolved. Once the VOI was centered on a bulb, the signal from it was shimmed and final adjustments of the location were made by minimizing the water peak. One of the reasons for choosing cyclohexane and benzene as chemical species is that their respective chemical shift do not overlap with the water peak. Another reason was to verify that the technique works for the overall width of a multi-line spectrum, and to evaluate any phase
and amplitude anomalies across the spectrum that could be attributed to VOISINER. In figure 6.5, all the spectra are plotted in the absorption mode, and no significant distortions are apparent; nevertheless, both the phase and the amplitude have been found to be sensitive to the frequency bandwidth of the slice-selective pulses used in VOISINER.

To evaluate the accuracy of the spin-lattice relaxation times obtained with IR-VOISINER, careful independent measurements were made by the conventional inversion-recovery experiment on each individual bulb placed alone in the centre of the magnet. The results obtained by the two methods are shown in Table 6.1 and it is encouraging to see that there is no apparent systematic errors from the IR-VOISINER sequence. Despite careful control of the room temperature, a variation of up to 2 K was observed for readings taken inside the magnet and, since the probe used was not thermostatted, those temperature variations certainly contributed to the observed $T_1$ variations.

Our second set of field gradient coils with a clear bore of 15 centimeters were used. The slice-selective pulses had pulse widths of respectively 500 $\mu$s and 1 ms for the $90^\circ$ and $180^\circ$ pulses, in the presence of field gradients of approximately 1.0 to 1.2 G/cm in strength. Our home-built saddle coil of 8.9 cm in diameter was used as the RF transmitter and receiver. The hard $180^\circ$ inversion pulse was adjusted to obtain the best null from the whole bath and was found to be 130 $\mu$s. A delay for magnetic field stabilization of 10 ms just before the acquisition and gradient fall delays of 1 ms were used. The dephasing gradient in the first module of VOISINER had a pulse width of 3 ms and an amplitude of approximately 2 G/cm.
FIG. 6.5 Five sets of spectra showing the recovery to equilibrium of cyclohexane and benzene from the five different bulb locations. Thirty inversion delay times (T) were used for these experiments. The resonance frequency of water was chosen as the central frequency.
Comparison of Spin-Lattice Relaxation Times Determined by Conventional Inversion-Recovery (IR) and by IR-VOISINER.

<table>
<thead>
<tr>
<th>Bulb [CrACAC] no. (mM)</th>
<th>T1 (s) cyclohexane</th>
<th>T1 (s) benzene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IR</td>
<td>IR-VOISINER</td>
</tr>
<tr>
<td>1 50</td>
<td>0.077</td>
<td>0.073 (-5.2%)</td>
</tr>
<tr>
<td>2 20</td>
<td>0.19</td>
<td>0.16 (-15.8%)</td>
</tr>
<tr>
<td>3 8</td>
<td>0.43</td>
<td>0.43 (0.0%)</td>
</tr>
<tr>
<td>4 3</td>
<td>0.92</td>
<td>0.94 (+2.2%)</td>
</tr>
<tr>
<td>5 1</td>
<td>1.5</td>
<td>1.4 (-6.7%)</td>
</tr>
</tbody>
</table>

Table 6.1

*Percentage difference.*

6.2.3 Discussion

In summary, we have developed a volume selective method for measuring $^1$H spin-lattice relaxation times, by combining the inversion-recovery and the VOISINER sequences. The choice of the inversion-recovery method over some other options such as progressive saturation (PSFT) (142) or saturation recovery (SRFT) (143,144) was guided by its relative ease of implementation with VOISINER, and by its relative insensitivity to flip angle inaccuracies (145). It is comforting to find that the IR-VOISINER method can cope with the range of T1 values likely to be encountered in mammalian tissues and, although we have not presented any data here, no major difficulty should prevent the
technique coping with relaxation times outside that range; the lower limit depends on the
time-duration of the VOISINER sequence. In retrospect, we have found that the
excellent signal suppression of the surroundings benefitted from the short $T_2$ relaxation
time of water which was approximately 30 ms.

6.3 Spatially Localized Spectroscopy on a Human Forearm

To test the applicability of VOISINER in a clinical environment, high-resolution
spectra were obtained from different portions of a human forearm. The same protocol as
described in Chapter 4 was used to focus on the desired volume of interest although no
imaging experiment was performed to visualize the sensitive volume; only a slice image
(using a slice-selective refocusing pulse) was obtained to help determine the location of
the volume of interest. That slice image is illustrated in Figure 6.6A.

Two regions were subsequently interrogated by VOISINER and their location is
indicated by boxes superimposed on the image (Fig. 6.6A). The size of these boxes are
actually the real size of the regions that were spatially selected and the dimensions are:
10 mm x 10 mm x 3 mm. The two selected regions originate from muscle tissue (location
B in Fig. 6.6A) and from bone marrow in the cubicus (location C in Fig. 6.6A). Their
respective proton spectra are illustrated in Figures 6.6B-C. In the spectrum of the muscle
tissue in Fig. 6.6B, the main peak corresponds to the water signal. In the spectrum of the
bone marrow, the water signal is greatly reduced and few signals are visible from fatty
acid chains.

These experiments were performed with our first set of field gradient coils and
our modified RF H-resonator coil of 10.7 cm in diameter. The slice-selective pulses had
pulse widths of, respectively, 1.5 ms and 1 ms for the $90^\circ$ and $180^\circ$ pulses. A non-
selective $90^\circ$ pulse of 65 μs was used.
FIG. 6.6 (A) Slice image of a human forearm showing the two locations where high-resolution NMR measurements were extracted. Image parameters: slice thickness = 3 mm, TR = 1 s, TE = 20 ms, 128 phase-encoding steps, image size = 256 x 256, slice-selective 180° = 1 ms, non-selective 90° = 65 μs, NA = 8. (B) High-resolution spectrum from muscle tissue, NA = 32. (C) High-resolution spectrum from bone marrow, NA = 32.
7. CONCLUSION

7.1 Summary

The central theme of the work presented in this thesis has involved the development and experimental implementation of a new method incorporating NMR methodology, and which enables a volume to be accurately defined and interrogated within a larger object, by a sequence of radiofrequency and linear magnetic field gradient pulses.

The most important feature of the VOISINER method is its flexibility with respect to the location and size of the region of interest. The essential ingredient that makes this flexibility possible is the use of frequency-selective RF pulses in the presence of field gradients of the static field. Furthermore, because both conventional NMR imaging and VOISINER rely on the same field gradients, the spatial coordinates and the size of the VOI can be directly selected from conventional NMR images, and then converted into VOISINER by an appropriate setting of the carrier frequencies of the slice-selective pulses and an appropriate scaling of the field gradient strengths applied during slice-selection. Both methods can actually be combined in order to facilitate the selection of the VOI, and examine and optimize the spatial sensitivity profile of the localization process of each module. This procedure was demonstrated in Chapter 4 as part of our experimental protocol for adjusting the various parameters of VOISINER.

Another important feature of VOISINER is its ability to acquire NMR information from the VOI in a single scan. This is made possible by the spatial discrimination of three orthogonal slices within the same sequence. Since the observable localized signal represents an integrated response from the whole sample, any observable signal from the periphery of the volume of interest is thus destroyed; the suppression
process of VOISINER on the periphery of the VOI is such that, either the magnetization is kept along the longitudinal axis, or any transverse component is incoherently dephased.

To evaluate the robustness and applicability of VOISINER under various experimental conditions and imperfections, it was necessary to examine more closely what was involved in the localization process. Essentially, two aspects were studied; these include its volume selectivity and its detection sensitivity.

Concerning the first aspect, the spatial selectivity of the excitation profile of each module was evaluated under "normal" operating conditions and under some constraints, such as flip angle missettings and relaxation effects. The first module (inversion module) has revealed to be the most delicate module to implement and for that reason, four different schemes were experimentally tested. The schemes with the best spatial selectivity were found to be the ones which are conceptually similar to the SPACE and SPARS techniques, whereas the performance of the schemes suggested in the original version of VOISINER and in the VSE method were found to be rather poor. The first module was also the most susceptible to flip angle inaccuracies caused by $B_1$ inhomogeneities or flip angle missettings, and spin-lattice relaxation. The second (excitation module) and third (refocusing module) modules appeared to be very robust to flip angle inaccuracies, although each was accompanied with some loss of signal intensity from the sensitive volume. Spin-lattice ($T_1$) relaxation from the surroundings was found to be a source of loss in the spatial discrimination during the time interval between the two first modules ($T_r$). Fortunately, the deleterious effects caused by both, $T_1$ relaxation and flip angle inaccuracies could be cancelled by a two phase cycling scheme of the slice-selective pulse of the first module.

With regard to the detection sensitivity of the signal arising from the selected volume, the VOISINER method can in principle recover the full transverse magnetization. However, in practice, it is subjected to losses arising from imperfect flip
angles in the second and third modules, nonuniform excitation profiles of the slice-selective pulses, spin-spin relaxation decay during TE₁ and TE₂ periods, and incomplete refocusing conditions for echo formation during TE₁ and TE₂.

To explore potential extensions and offer new opportunities for extracting more information from the sensitive volume, the VOISINER sequence was combined with some standard pulse sequences; in particular, it was combined with the inversion recovery method in order to measure spatially localized spin-lattice relaxation times. The range of ¹H relaxation times that were measured demonstrates that the method can cope with nuclei likely to be encountered in mammalian tissues. With regard to imaging, a new method for achieving high-spatial resolution imaging of restricted regions within a larger sample was proposed. This was achieved by inserting some phase- and frequency-encoding gradients, as prescribed in Chapter 4, and by driving them at four to five times the amplitude normally used for conventional imaging. Finally, to demonstrate that the technique is applicable for studies of living systems, it was tested on a human forearm and spatially localized high-resolution spectra were successfully obtained from muscle tissue and bone marrow.

7.2 Comparative Study

The field of Spatially Localized NMR continues to attract considerable interest and since this work was initiated, several other three-dimensional localization techniques that employ frequency-selective irradiation in the presence of pulsed field gradients of B₀ have been proposed in the literature. Thus, to put VOISINER into perspective and highlight its distinctive features we now focus our discussion on reviewing and comparing the essential features and development trends of the methods that are now in use.

These are categorized according to some general points of comparison:
Elimination of the unwanted signal

There are basically two ways of eliminating the signal from the periphery of the volume of interest: elimination by suppression which enables volume-selection in a single scan; or elimination by a subtraction procedure which requires several scans. The single scan approach has the advantage of minimizing potential dynamic range problems associated with the subtraction of signal contributions that may be orders of magnitude larger than the signal originating from the selected volume. This problem usually results in a loss of detection sensitivity. It also makes the technique less susceptible to artifacts produced by irregular motions of the sample that may occur during the experiment. It also enables a rapid optimization of the homogeneity of $B_0$ from the localized volume. The available single scan methods are listed in Table 7.1 where they are further categorized according to their excitation scheme: the first one includes all the techniques which are conceptually similar to the VSE (51) technique (SPARS (53), SPACE (54), DIGGER (147), SPALL (150)); the second group includes the techniques which are based upon the stimulated echo concept (VEST (127), VOSY (128), STEAM (129)); the third group includes the VOISINER technique. No detailed description of these techniques is given here and the reader is referred to the references cited herein. The multiple scan methods are listed in Table 7.2, and are also categorized according to their excitation scheme. The ISIS (52) and OSIRIS (149) methods are similar to each other, but differs in so far that OSIRIS partially saturates the signal that is subsequently to be subtracted; this alleviates the dynamic range problem. The SPIRE (148) method can be considered as being a two scan version of VOISINER.
**Table 7.1**  
Single-Scan Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>X-slice</th>
<th>Y-slice</th>
<th>Z-slice</th>
<th>Read pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IN</td>
<td>OUT</td>
<td>IN</td>
<td>OUT</td>
</tr>
<tr>
<td>VSE</td>
<td>180°</td>
<td>sat</td>
<td>180°</td>
<td>sat</td>
</tr>
<tr>
<td>SPARS</td>
<td>180°</td>
<td>sat</td>
<td>180°</td>
<td>sat</td>
</tr>
<tr>
<td>SPACE</td>
<td>180°</td>
<td>sat</td>
<td>180°</td>
<td>sat</td>
</tr>
<tr>
<td>DIGGER</td>
<td>180°</td>
<td>sat</td>
<td>180°</td>
<td>sat</td>
</tr>
<tr>
<td>SPALL</td>
<td>180°</td>
<td>sat</td>
<td>180°</td>
<td>sat</td>
</tr>
<tr>
<td>VEST</td>
<td>90°</td>
<td></td>
<td>90°</td>
<td></td>
</tr>
<tr>
<td>VOSY</td>
<td>90°</td>
<td></td>
<td>90°</td>
<td></td>
</tr>
<tr>
<td>STEAM</td>
<td>90°</td>
<td></td>
<td>90°</td>
<td></td>
</tr>
<tr>
<td>VOISINER</td>
<td>180°</td>
<td>sat</td>
<td>90°</td>
<td></td>
</tr>
</tbody>
</table>

*a saturation*
<table>
<thead>
<tr>
<th>Method</th>
<th>X-slice</th>
<th>Y-slice</th>
<th>Z-slice</th>
<th>Read acq. pulse</th>
<th>exp no.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IN</td>
<td>OUT</td>
<td>IN</td>
<td>OUT</td>
<td>IN</td>
</tr>
<tr>
<td>180°</td>
<td>90°</td>
<td>+</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sat*</td>
<td>90°</td>
<td>−</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180°</td>
<td>90°</td>
<td>−</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sat*</td>
<td>90°</td>
<td>−</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180° sat*</td>
<td>180° sat*</td>
<td>90°</td>
<td>+</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>ISIS</td>
<td>180°</td>
<td>sat*</td>
<td>90°</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>OSIRIS</td>
<td>180° sat*</td>
<td>180° sat*</td>
<td>90°</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>180° sat*</td>
<td>180° sat*</td>
<td>90°</td>
<td>−</td>
<td>8</td>
</tr>
<tr>
<td>SPIRE</td>
<td>90°</td>
<td>180°</td>
<td>+</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>180°</td>
<td>90°</td>
<td>180°</td>
<td>−</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*a OSIRIS only.
-Signal from the volume of interest

Among the single scan methods, there are basically two ways for obtaining the final read out of the NMR signal from the volume of interest: the methods that necessitate the formation of an echo signal (VEST, VOSY, STEAM, VOISINER) and the methods that necessitate the application of a non-selective 90° read pulse to generate transverse magnetization from the volume of interest whose magnetization was kept along the z-axis (VSE, SPARS, SPACE, DIGGER, SPALL).

All the methods mentioned herein can in principle recover the full signal from the localized volume, with the important exception of those which are based on the stimulated echo technique (VEST, VOSY, STEAM); for them, only 50% of the full signal can be recovered (this is an intrinsic limitation imposed by the stimulated echo concept).

-Effects of $T_1$ and $T_2$ relaxation processes

The relaxation processes can affect the efficiency of the spatial localization and the detection sensitivity of the spatially localized NMR signal. These effects can appear at different stages; during the slice-selective pulses; during the time intervals between successive slice-selective modules; and during the field stabilization delay that usually precedes data acquisition to allow any time-dependent field fluctuations to decay.

The methods which necessitate spin echo formation within their pulse sequence will be affected by $T_2$, and which leads to a decrease of the detection sensitivity. The methods which recover the signal from the localized volume as a spin echo may be particularly affected during the field stabilization delay (VEST, VOSY, STEAM, VOISINER) because the signal from the VOI will be decaying.
On the other hand, the methods which use a non-selective 90° read pulse are very susceptible to signal contamination from outside the volume of interest because during the localization process and the field stabilization delay, the magnetization from the periphery of the VOI partially recovers to equilibrium by T1 relaxation. Consequently, its non-null longitudinal magnetization component will be rotated into the transverse plane by the non-selective 90°. Such methods include all the VSE-like methods (VSE, SPARS, SPACE, DIGGER, SPALL). The VOISINER method can also be affected by T1 relaxation between the first and the second module. However, since this applies to one slice, rather than the whole sample, the relaxation artifact is considerably reduced. At this point, it is interesting to note that Bottomley et al. (151) have suggested on similar grounds that a "straightforward improvement to the VSE, SPARS, and ISIS sequences", should be by use of a pulse sequence which is identical to that of VOISINER. However, they did not provide any experimental verification to confirm their suggestion.

In this brief comparative study, the flexibility of the various methods for combining other pulse sequences in order to extract a variety of NMR information has not been addressed, even though this is in practice an important consideration when implementing such a method. However, it is clear that the VOISINER method has a distinctive excitation scheme which shares some advantages and disadvantages with its competitors. In the author’s opinion, there is unlikely to be any single approach which is uniquely suited to all of the many possible applications. However, the work presented in this thesis clearly demonstrates that the VOISINER sequence works very well and can efficiently be optimized for certain applications.

7.3 Suggestions for Future Work

All the experiments that were performed in this thesis were limited to one specific nucleus: 1H. However, VOISINER is by no means restricted to 1H spectroscopy. For
instance, $^{31}$P would certainly be a candidate because of its importance in studies of metabolic processes of living systems. However, with the present field gradient technology, the applicability of VOISINER for $^{31}$P spectroscopy may be precluded by the very short $T_2$ relaxation times of many phosphorus containing biochemical species.

Concerning the use of $^1$H spectroscopy for studying biological systems, the studies which have showed great potential focus upon small metabolites which may be orders of magnitude smaller than the intense water and lipid peaks usually present in $^1$H NMR of living systems. To extend the range of applications of VOISINER, it would thus be important to combine it with some solvent-suppression techniques. One possible way of implementing such an experiment would be to apply a strong presaturation pulse centered on the intense peak to be suppressed, prior to VOISINER.

Finally, the VOISINER method was not tested in a clinical environment with a larger scale system. This would certainly be the next major step in its development because the most important application area will most likely be in the biomedical field. Moreover, based on the work presented in this thesis, the author believes that VOISINER has reached the maturity to be promoted to that environment.
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APPENDIX A : FIELD GRADIENT PULSE SHAPE

In this appendix, a pulse shape evaluation of the field gradients used in this thesis is presented. The method relied upon the use of a flat "pick up" coil which was properly positioned inside the gradient coils. The signal that was induced by a time variation of the magnetic flux during rise and fall time of the gradients was then integrated (see circuit diagram Appendix B) to yield the shape of the pulse.
**X Field-Gradient Oxford**

![Graph of X Field-Gradient Oxford with various pulse lengths: 16 ms, 8 ms, 4 ms, 2 ms, and 1 ms.](image)

**Fig. A.1** Pulse shape of the Oxford x field gradient when subjected to various pulse lengths.
Y Field-Gradient Oxford

FIG. A.2 Pulse shape of the Oxford y field gradient when subjected to various pulse lengths.
Fig. A.3 Pulse shape of the Oxford z field gradient when subjected to various pulse lengths.
FIG. A.4 Pulse shape of the x field gradient of the first set of gradient coils when subjected to various pulse lengths.
FIG. A.5 Pulse shape of the $z$ field gradient of the first set of gradient coils when subjected to various pulse lengths.
Fig. A.6 Pulse shape of the x field gradient of the second set of gradient coils when subjected to various pulse lengths.
FIG. A.7 Pulse shape of the z field gradient of the second set of gradient coils when subjected to various pulse lengths.
FIG. A.8 Pulse shape of the x field gradient of the first set of gradient coils when subjected to various input amplitudes. (0.79 Gauss/cm) / 300 units.
FIG. A.9 Pulse shape of the z field gradient of the first set of gradient coils when subjected to various input amplitudes. (0.69 Gauss/cm) / 300 units.
FIG. A.10 Pulse shape of the x field gradient of the second set of gradient coils when subjected to various input amplitudes. (0.83 Gauss/cm) / 300 units.
Fig. A.11 Pulse shape of the z field gradient of the second set of gradient coils when subjected to various input amplitudes. (1.08 Gauss/cm) / 300 units.
X Field-Gradient Set 1

A - no Cu cylinder
   - no Cu mesh

B - no Cu cylinder

C

FIG. A.12 Pulse shape of the x field gradient of the first set of gradient coils when subjected to different surrounding couplings. The copper cylinder recovers the surface of the magnet bore whereas the copper mesh recovers the surface of the gradient coil bore.
Z Field-Gradient Set 1

A
- no Cu cylinder
- no Cu mesh

B
- no Cu cylinder

C

Fig. A.13 Pulse shape of the z field gradient of the first set of gradient coils when subjected to different surrounding couplings.
FIG. B.1 Circuit diagram of the integrator that was used in the experiments of Appendix A.
Fifth-order Runge-Kutta driver with adaptable stepsize

This routine calculates the solution of a set of N coupled first-order ordinary differential equations by using the fifth-order Runge-Kutta method with monitoring of local truncation error to ensure accuracy and adjust stepsize.

The set of differential equations is expressed as:

\[
dy/dx = f(y,x)
\]

where y and f are vectors of dimension N. The solution y is calculated from an initial x (XI) to a final x (XF).

Subroutine Arguments

YIN -------- Vector which contains the initial values of the variable y of dimension N at XI. The final solution of y at XF is returned to YIN.

N -------- Dimension of the variable YIN.

XI -------- Initial x.

XF -------- Final x.

FCN ------- User supplied subroutine which returns the value of f at X. FCN must be listed in an EXTERNAL statement.

Important variables used in RK5ASC

HI -------- Initial stepsize.

HMIN ------ Minimum allowed stepsize.

EPS ------ Fractional error per step.

DXSAV ---- Required stepsize for intermediate storage.

NYSCAL --- Accuracy criterion

= 1 constant absolute error

= 2 constant fractional error

NOK ------ Number of good steps taken.

NBAD ------ Number of bad steps taken (but retried and fixed).

KMAX ------ Maximum number of intermediate steps that can be temporarily stored.

KOUNT ---- Counter which keeps track of the number of stored temporary steps.
SUBROUTINE RK5ASC(YIN,N,XI,XF,FCN)
EXTERNAL FCN
REAL YIN(N),YSCAL(3),Y(3),DYDX(3)

COMMON /RK5/ HI,HMIN,EPS,DXSAV,NYSCAL,NOK,NBAD,
* KMAX,KOUNT,XP(201),YP(3,201)

c Variable initialization.

EPSS=EPS
MXSTEP=1000
X=XI
H=SIGN(HI,XF-XI)
NOK=0
NBAD=0
KOUNT=0
DO 10 I=1,N
   Y(I)=YIN(I)
   YSCAL(I)=1.
10 CONTINUE

Assures storage of first step.
IF (KMAX.GT.0) XSAV=X-DXSAV*2.

Begin Runge-Kutta calculation with at most MXSTEP steps.
DO 60 NSTP=1,MXSTEP
   CALL FCN(X,Y,DYDX)

Scaling used to monitor accuracy. Constant fractional error mode.
IF (NYSCAL.EQ.2) THEN
   DO 20 I=1,N
      YSCAL(I)=ABS(Y(I))+ABS(H*DYDX(I))+1.E-30
20 CONTINUE
CONTINUE
END IF

Store intermediate y and x in YP and XP.

IF (KMAX.GT.0) THEN
  IF (ABS(X-XSAV).GE.ABS(DXSAV)) THEN
    IF (KOUNT.LT.KMAX-1) THEN
      KOUNT=KOUNT+1
      XP(KOUNT)=X
      DO 30 I=1,N
        YP(I,KOUNT)=Y(I)
      30 CONTINUE
      XSAV=X
    END IF
  END IF
END IF

If step can overshoot end, cut down stepsize.

IF ((X+H-XF)*(X+H-XI).GT.0.) H=HF-X

Take one fifth-order Runge-Kutta step with adaptative stepsize control.

CALL RKQC(Y,DYDX,N,X,H,HDID,HNEXT,EPSS,YSCAL,FCN)

Monitor the number and good and bad (but retried and fixed) steps taken.

IF (HDID.EQ.H) THEN
  NOK=NOK+1
ELSE
  NBAD=NBAD+1
END IF

Are we done?

IF ((X-XF)*(XF-XI).GE.0.) THEN

The final solution y is returned to YIN.

DO 40 I=1,N
  YIN(I)=Y(I)
40 CONTINUE
Appendix C Program Listing of RK5ASC / 189

```c
  c Store final step.
  c
    IF (KMAX.GT.0) THEN
      KOUNT=KOUNT+1
      XP(KOUNT)=X
      DO 50 I=1,N
          YP(I,KOUNT)=Y(I)
    50      CONTINUE
      END IF

  c Return to main program
  c
      RETURN
      END IF

  c If we are not done, check if stepsize is not smaller
  c than the allowed minimum value.
  c
      IF (ABS(HNEXT).LT.ABS(HMIN)) PAUSE
        * 'Stepsize smaller than minimum !'
        H=HNEXT
    60    CONTINUE

  c The maximum number of steps has been exceeded.
  c
      PAUSE 'Too many steps'
      RETURN
      END
```

```
cccc c c
  c Fifth-order Runge-Kutta with adaptable stepsize control c
  c ----------------------------------------------- c
  c This routine advances the solution y one "quality- c
  c controlled" fifth-order Runge-Kutta step in which the c
  c local truncation error is carefully monitored to ensure c
  c accuracy and adjust stepsize.
  c
  c Subroutine Arguments
  c ---------------------- c
  c Y ------- Vector of dimension N which contains the c
```
Appendix C  Program Listing of RK5ASC  / 190

Solution y at X.

DYDX ----- Vector which contains the evaluation of f at X.

N --------- Dimension of the variables YIN, YOUT and DYDX.

X -------- x which should be between XI and XF.

HTRY ------ Stepsize to be attempted.

HDID ------ Stepsize which was actually accomplished.

HNEXT ------ Estimated next stepsize.

EPS ------ Fractional error per step.

YSCAL ------ Vector against which the error is scaled.

FCN ------ User supplied subroutine which returns the value of f at X. FCN must be listed in an EXTERNAL statement.

SUBROUTINE
*RKQC(Y,DYDX,N,X,HTRY,HDID,HNEXT,EPS,YSCAL,FCN)
EXTERNAL FCN
REAL Y(N), DYDX(N), YSCAL(N)
REAL YTEMP(3), YSAV(3), DYSAV(3)

Variable initialization at compile time.
ERRCON is equal to (4/SAFETY)**(1/GROW).

DATA GROW/-0.20/, SHRINK/-0.25/, SAFETY/0.9/,
* ERRCON/6.E-4/

Save initial values.

XSAV=X
DO 10 I=1,N
  YSAV(I)=Y(I)
  DYSAV(I)=DYDX(I)
10 CONTINUE

Set stepsize to the initial trial value.

H=HTRY

Take two half steps.

H2=0.5*H
CALL RK4(YSAV,YTEMP,DYSAV,N,XSAV,H2,FCN)
X=XSAV+H2
CALL FCN(X,YTEMP,DYDX)
CALL RK4(YTEMP, Y, DYDX, N, X, H2, FCN)
X=XSAV+H
IF (X.EQ.XSAV) PAUSE
* 'Stepsize not significant in RKQC'
CALL RK4(YSAV, YTEMP, DYSAV, N, XSAV, H, FCN)

c
Evaluate accuracy. YTEMP contains the error estimate.
c
ERRMAX=0.
DO 30 I=1,N
   YTEMP(I)=Y(I)-YTEMP(I)
   ERRMAX=AMAX1(ERRMAX, ABS(YTEMP(I)/YSCAL(I)))
30 CONTINUE

c
Scale relative to required tolerance.
c
ERRMAX=ERRMAX/EPS

c
Truncation error too large, reduce stepsize and try again.
c
IF (ERRMAX.GT.1.) THEN
   H=SAFETY*H*(ERRMAX**SHRINK)
   GO TO 20

c
Step succeeded. Compute size of next step.
c
ELSE
   HDID=H
   IF (ERRMAX.GT.ERRCON) THEN
      HNEXT=SAFETY*H*(ERRMAX**GROW)
   ELSE
      HNEXT=4.*H
   END IF
END IF

c
Improve estimate to fifth order accuracy.
c
DO 40 I=1,N
   Y(I)=Y(I)+YTEMP(I)/15.
40 CONTINUE

RETURN
END
Fourth-order Runge-Kutta with Constant Stepsize

This routine uses the fourth-order Runge-Kutta method to advance the solution $y$ over an interval $x \rightarrow x+h$ with a constant stepsize $h$.

Subroutine Arguments

- **YIN**: Vector which contains the initial values of the variable $y$ of dimension $N$ at $X$.
- **YOUT**: Vector which contains the solution $y$ at $X+H$.
- **DYDX**: Vector which contains the evaluation of $f$ at $X$.
- **N**: Dimension of the variables YIN, YOUT and DYDX.
- **X**: $x$ which should be between $XI$ and $XF$.
- **H**: Stepsize.
- **FCN**: User supplied subroutine which returns the value of $f$ at $X$.

This routine carries out the Runge-Kutta step. It advances the solution over an interval $H$ from YIN to YOUT.

$$y_{out} = y_{in} + \frac{k1}{6} + \frac{k2}{3} + \frac{k3}{3} + \frac{k4}{6}$$

where

- $k1 = H \times FCN(Yin,X)$
- $k2 = H \times FCN(Yin+k1/2,X+H/2)$
- $k3 = H \times FCN(Yin+k2/2,X+H/2)$
- $k4 = H \times FCN(Yin+k3,X+H)$

```fortran
SUBROUTINE RK4(YIN,YOUT,DYDX,N,X,H,FCN)
  REAL YIN(N),YOUT(N),DYDX(N)
  REAL Kl (3) ,K2 (3) ,K3 (3) ,K4 (3) , YT (3) ,DYX(3)
  XH2=X+H/2.
  DO 10 I=1,N
    K1(I)=H*DYDX(I)
    YT(I)=YIN(I)+K1(I)/2.
  10 CONTINUE
  CALL FCN(XH2,YT,DYX)
  DO 20 I=1,N
```
K2(I) = H * DYX(I)
YT(I) = YIN(I) + K2(I) / 2.

20 CONTINUE
CALL FCN(XH2, YT, DYX)
DO 30 I = 1, N
   K3(I) = H * DYX(I)
   YT(I) = YIN(I) + K3(I)
30 CONTINUE
CALL FCN(X + H, YT, DYX)
DO 40 I = 1, N
   K4(I) = H * DYX(I)
   YOUT(I) = YIN(I) + (K1(I) + 2. * (K2(I) + K3(I)) + K4(I)) / 6.
40 CONTINUE
RETURN
END
REAL*8 PHI,PHIF,PHIINC,THEI,THEF,THEINC,ARG,ANGRAD,ANGDEG,
* WZOFMN,WZOFMX,WZOFIC,WZOFF,WZROT,WZ(20),PI,VFS(3),
* W1OFMN,W1OFMX,W1OFIC,W1OFF,W1ROT,W1(20),PHASE(20),
* ROT(4,20),RESROT(4),RMTX(3,3),VI(3),VIS(3),VF(3),
* PHI,SINPH,COSPH,THETA,SINTH,COSTH,PSI,SINPS,COSPS,
* W1OFMN
CHARACTER*1 IOUT,ISTA,IFORM
CHARACTER*12 NFILE

PI=3.141592653589793

C output to data file ? y : to DOS file
 n : to display monitor
 anything else : exit

10 WRITE(0,800)
800 FORMAT(' output to data file ? : '
)
READ(0,810) IOUT
810 FORMAT(A1)

IF (IOUT.EQ.'Y'.OR.IOUT.EQ.'y') THEN
WRITE(0,820)
820 FORMAT(' enter filename : '
)
READ(0,830) NFILE
830 FORMAT(A12)
WRITE(0,840)
840 FORMAT(' is it a NEW or an OLD file ? (n or o) :'
)
READ(0,810) ISTA
IF (ISTA.EQ.'N'.OR.ISTA.EQ.'n') THEN
OPEN(8,FILE=NFILE,ACCESS='SEQUENTIAL',STATUS='NEW')
ELSE
OPEN(8,FILE=NFILE,ACCESS='SEQUENTIAL',STATUS='OLD')
END IF
IO=8
ELSE IF (IOUT.EQ.'N'.OR.IOUT.EQ.'n') THEN
IO=0
ELSE
STOP
END IF

C initial vector settings

20 WRITE(0,850)
850 FORMAT('/ initial vector')
WRITE(0,860)
860 FORMAT(' (initial phi, final phi, number of steps) :'
)
READ(0,*) PHI,PHIF,NPHI
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WRITE(0,870)
870 FORMAT(’ (initial theta, final theta, number of steps) :’)
READ(*,*) THEI, THEF, NTHE
IF (NPHI.LT.1.0 OR NPHI.GT.101) GO TO 20
IF (NTHE.LT.1.0 OR NTHE.GT.101) GO TO 20

C C
C rotation settings
C C

30 WRITE(0,880)
880 FORMAT(’ number of rotations :’)
READ(0,*) NUMROT
IF (NUMROT.LE.0.0 OR NUMROT.GT.20) GO TO 30

DO 40 I=1,NUMROT
   WRITE(0,890) I
40 CONTINUE

C C
C wl and wz offset settings
C C

50 WRITE(0,900)
900 FORMAT(’ wz offset range (min,max,number of steps) :’)
READ(0,*) WZOFMN, WZOFMX, NWZOF
IF (NWZOF.LT.1.0 OR NWZOF.GT.101) GO TO 50

60 WRITE(0,910)
910 FORMAT(’ wl offset range (min,max,number of steps) :’)
READ(0,*) W1OFMN, W1OFMX, NW1OF
IF (NW1OF.LT.1.0 OR NW1OF.GT.101) GO TO 60

C C
C output to data file : -nominal rotations
C -wl and wz offset ranges
C C

IF (IO.EQ.8) THEN
   WRITE(IO,920)
920 FORMAT(’rotation’,6X,’wl(deg)’,3X,’phase(deg)’,6X,’wz(deg)’/)
   DO 70 I=1,NUMROT
      WRITE(IO,930) I, W1(I), PHASE(I), WZ(I)
70 CONTINUE
WRITE(IO,900)
WRITE(IO,940) WZOFMN,WZOFMX,NWZOF
WRITE(IO,910)
WRITE(IO,940) WIOFMN,W10FMX,NW10F
940 FORMAT(2(F10.5,2X),I3)

END IF

C
C selection of the data output format and print out of an
C appropriate title
C
WRITE(0,950)
950 FORMAT(/' Cartesian or Spherical outputs (c or s) :
READ(0,810) IFORM

IF (IFORM.EQ.'C'.OR.IFORM.EQ.'c') THEN
960 FORMAT(/7X,'wl',8X,'wz',8X,'xi',8X,'yi',8X,'zi', 
* 8X,'xf',8X,'yf',8X,'zf' /1X,8(8(' -' ),2X))
ELSE
WRITE(IO,970)
970 FORMAT(/9X,'wl',11X,'wz',8X,'Phi I',6X,'Theta I',8X, 
* 'Phi F',6X,'Theta F' /1X,6(10(' -' ),3X))
END IF

C
C calculation of the phi of initial vector
C increment for theta of initial vector
C w1 offset
C wz offset
C
C phi increment of initial vector
C
IF (NPHI.EQ.1) THEN
PHIINC=0.
ELSE
PHIINC=(PHIF-PHII)/(NPHI-1)
END IF

C
C theta increment of initial vector
C
IF (NTHE.EQ.1) THEN
THEINC=0.
ELSE
THEINC=(THEF-THEI)/(NTHE-1)
END IF

C wz offset increment

IF (NWZOF.EQ.1) THEN
   WZOFIC=0.
ELSE
   WZOFIC=(WZOFMX-WZOFMN)/(NWZOF-1)
END IF

C w1 offset increment

IF (NW10F.EQ.1) THEN
   W10FIC=0.
ELSE
   W10FIC=(W10FMX-W10FMN)/(NW10F-1)
END IF

C conversion of w1 phase(deg) to w1 phase(rad)

DO 80 I=1,NUMROT
   PHASE(I)=ANGRAD(PHASE(I))
80 CONTINUE

C first loop increments phi of initial vector

DO 130 I1=0,NPHI-1
   PHII=ANGRAD(PHI+PHIINC*I1)
   SINPH=DSIN(PHI)
   COSPH=DCOS(PHI)
130 CONTINUE

C second loop increments theta of initial vector

DO 120 I2=0,NTHE-1
   THEI=ANGRAD(THEI+THEINC*I2)
   SINTH=DSIN(THETA)
   COSTH=DCOS(THETA)
120 CONTINUE

C calculation of VI() in cartesian from spherical

VI(1)=SINTH*COSPH
VI(2)=SINTH*SINPH
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VI(3)=COSTH

third loop increments wz offset

DO 110 I3=0,NWZOF-1
  WZOFF=WZOFMN+WZOFC*I3

fourth loop increments wl offset and calculates the overall rotation vector. It then transforms it to a 3*3 rotation matrix and then performs the rotation of VI (initial vector) to give VF (final vector).

DO 100 I4=0,NW1OF-1
  W1OFF=W1OFMN+W1OFIC*I4

fifth loop calculates the effective rotation vector of each nominal rotation vector by taking into account the wl and wz offsets. It then transforms in cartesian coordinates each rotation vector initially expressed in spherical coordinates.

DO 90 I=1,NUMROT
  W1ROT=W1(I)*(1+W1OFF)
  WZROT=W1(I)*WZOFF+WZ(I)
  WMROT=DSQRT(W1ROT*W1ROT+WZROT*WZROT)

  PSI=ANGRAD(WMROT)
  THETA=DACOS(WZROT/WMROT)
  PHI=PHASE(I)
  IF (W1ROT.LT.0.) PHI=PHI-PI

  SINTH=DSIN(THETA)
  ROT(1,I)=SINTH*DCOS(PHI)
  ROT(2,I)=SINTH*DSIN(PHI)
  ROT(3,I)=DCOS(THETA)
  ROT(4,I)=PSI

90 CONTINUE

ROTPRD: calculates the overall rotation vector
ROTMTX: calculates the 3*3 rotation matrix of RESROT
VECROT: performs the rotation VF=[3*3] * VI
CARSPH: cartesian <------> spherical
CALL ROTPRD(NUMROT, ROT, RESROT)
CALL ROTMTX(RESROT, RMTX)
CALL VECROT(VI, VF, RMTX)

C writes to display or data file in the chosen format: cartesian or spherical.

C cartesian

IF (IFORM.EQ. 'C' .OR. IFORM.EQ. 'c') THEN
WRITE(IO, 980) WIOFF, WZOFF, VI, VF
980 FORMAT (1X, 7(F8.4, 2X), F8.4)

C spherical

ELSE
CALL CARSPH(VI, VIS, 'S')
CALL CARSPH(VF, VFS, 'S')

C ANGDEG: angle(rad) ------> angle(deg)

VIS(2) = ANGDEG(VIS(2))
VIS(3) = ANGDEG(VIS(3))
VFS(2) = ANGDEG(VFS(2))
VFS(3) = ANGDEG(VFS(3))

C writes to display or data file w1, wz offsets and VI, VF

WRITE(IO, 960) WIOFF, WZOFF, VIS(3), VIS(2),
     * VFS(3), VFS(2)
960 FORMAT (1X, 6(F10.5, 3X))

100 CONTINUE
110 CONTINUE
120 CONTINUE
130 CONTINUE
GO TO 10
END

C

SUBROUTINE ROTPRD(NUMROT, ROT, RESROT)
REAL*8 VECT(4, 3), A(3), B(3), C(3), D(3), SINN(2),
     * VMAG, PI, RESROT(4), ROT(4, NUMROT)
PI=3.141592653589793
DO 10 I=1,4
    VECT(I,3)=ROT(I,1)
10 CONTINUE
DO 40 I1=2,NUMROT
    DO 20 I=1,4
        VECT(I,1)=VECT(1,3)
        VECT(I,2)=ROT(I,I1)
    20 CONTINUE
    DO 30 I=1,2
        SINN(I)=DSIN(VECT(4,I)/2)
        A(I)=VECT(1,I)*SINN(I)
        B(I)=VECT(2,I)*SINN(I)
        C(I)=VECT(3,I)*SINN(I)
        D(I)=DCOS(VECT(4,I)/2)
    30 CONTINUE
    IF (SINN(1).EQ.0.) GO TO 40
    A(3)= D(2)*A(1)-C(2)*B(1)+B(2)*C(1)+A(2)*D(1)
    B(3)= C(2)*A(1)+D(2)*B(1)-A(2)*C(1)+B(2)*D(1)
    C(3)=-B(2)*A(1)+A(2)*B(1)+D(2)*C(1)+C(2)*D(1)
    D(3)=-A(2)*A(1)-B(2)*B(1)-C(2)*C(1)+D(2)*D(1)
    VMAG=DSQRT(A(3)*A(3)+B(3)*B(3)+C(3)*C(3))
    VECT(1,3)=A(3)/VMAG
    VECT(2,3)=B(3)/VMAG
    VECT(3,3)=C(3)/VMAG
    VECT(4,3)=2*DACOS(D(3))
    IF (VECT(4,3).GT.PI) THEN
        VECT(4,3)=VECT(4,3)-2*PI
    END IF
40 CONTINUE
DO 60 I=1,4
    RESROT(I)=VECT(I,3)
60 CONTINUE
RETURN
END

FUNCTION ANGDEG(ANGLER)
REAL*8 ANGDEG
ANGDEG=ANGLER*57.29577951308232
RETURN
END

FUNCTION ANGRAD(ANGLED)
REAL*8 ANGRAD
ANGRAD=ANGLED*0.017453292519943
SUBROUTINE ROTMTX(AXIS, RMTX)
REAL*8 RMTX(3,3), AXIS(4), VC(3), VS(3)

VC(1) = AXIS(1)
VC(2) = AXIS(2)
VC(3) = AXIS(3)
CALL CARSPH(VC, VS, 'S')
SINTH = DSIN(VS(2))
COSTH = DCOS(VS(2))
SINPH = DSIN(VS(3))
COSPH = DCOS(VS(3))
SINPS = DSIN(AXIS(4))
COSPS = DCOS(AXIS(4))

RMTX(1,1) = SINTH*SINTH*COSPH*COSPH*(1-COSPS) + COSPS
RMTX(2,1) = SINTH*SINTH*SINPH*COSPH*(1-COSPS) + COSTH*SINPS
RMTX(3,1) = SINTH*COSTH*COSPH*(1-COSPS) - SINTH*SINPH*SINPS
RMTX(1,2) = SINTH*SINTH*SINPH*COSPH*(1-COSPS) - COSTH*SINPS
RMTX(2,2) = SINTH*SINTH*SINPH*SINPH*(1-COSPS) + COSPS
RMTX(3,2) = SINTH*COSTH*SINPH*(1-COSPS) + SINTH*COSPH*SINPS
RMTX(1,3) = SINTH*COSTH*COSPH*(1-COSPS) + SINTH*SINPH*SINPS
RMTX(2,3) = SINTH*COSTH*SINPH*(1-COSPS) - SINTH*COSPH*SINPS
RMTX(3,3) = COSTH*COSTH*(1-COSPS) + COSPS
RETURN
END

SUBROUTINE VECROT(VI, VF, RMTX)
REAL*8 VI(3), VF(3), RMTX(3,3)
DO 10 I = 1, 3
VF(I) = RMTX(I,1) * VI(1) + RMTX(I,2) * VI(2) + RMTX(I,3) * VI(3)
10 CONTINUE
RETURN
END

SUBROUTINE CARSPH(VC, VS, SELECT)
REAL*8 VC(3), VS(3), PI, ANGRAD
CHARACTER*1 SELECT

PI = 3.141592653589793
IF (SELECT.EQ.'C') THEN
  VC(1) = VS(1) * DSIN(VS(2)) * DCOS(VS(3))
  VC(2) = VS(1) * DSIN(VS(2)) * DSIN(VS(3))
VC(3) = VS(1) * DCOS(VS(2))
ELSE IF (SELECT.EQ.'S') THEN
  VS(1) = DSQRT(VC(1) * VC(1) + VC(2) * VC(2) + VC(3) * VC(3))
  VS(2) = DACOS(VC(3) / VS(1))
  IF (VC(1).EQ.0.) THEN
    VS(3) = ANGRAD(90.D0)
    IF (VC(2).LT.0.) VS(3) = ANGRAD(-90.D0)
  ELSE IF (VC(1).GT.0.) THEN
    VS(3) = DATAN(VC(2) / VC(1))
  ELSE IF (VC(1).LT.0.) THEN
    VS(3) = PI + DATAN(VC(2) / VC(1))
    IF (VC(2).LT.0.) VS(3) = VS(3) - 2*PI
  END IF
END IF
END IF
RETURN
END