EXPERIMENTAL AND THEORETICAL ANALYSIS OF PERFUSION
AND DIFFUSION IN MRI

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ABSTRACT

The work in this thesis falls into three sections:

(i). the development and application of a computer simulation of the MRI experiment based on the Bloch Equations incorporating all flow and motion effects that would be expected in the body,

(ii). a theoretical analysis of factors affecting the efficacy of perfusion and diffusion imaging techniques and

(iii). the proposal and evaluation of a new technique for the MRI measurement of perfusion.

The simulation provided a powerful analytical tool used in the theoretical work of this thesis. The modularity of the design will enable simple development for future applications.

The purpose of the theoretical analysis was to resolve many of the controversial issues arising from the various diffusion and perfusion imaging techniques including: the applicability of the various techniques in different in-vivo systems, the effects of motion artifacts, noise and eddy currents. Some conclusions of great significance were arrived at specifically the importance choosing a flow measurement technique appropriate to the tissue and flow type and the severe effects of motion artifacts in IVIM and phase display imaging.

From this analysis a new perfusion imaging technique was derived which was implemented and evaluated in a perfusion phantom and in the calf muscle. Very good results were achieved in the phantom studies, and the results from the calf muscle were promising. On a clinical MRI system the technique could prove very useful.
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NMR AND MRI THEORY
1.1 NMR/MRI THEORY

The phenomena of nuclear magnetic resonance (NMR) arises due to two properties of nuclei - specifically angular momentum and magnetic moment resulting from the nuclear spin angular momentum (spin).

The relationship between angular momentum (p) and nuclear spin (I) is given by

\[ \hat{p} = \hat{I} \hbar \]  

(1.1)

where \( \hbar \) is Planck's constant.

Nuclei have a variety of different values of spin and all nuclei which possess angular momentum have an associated magnetic dipole moment \( \mu \). In simplistic terms it could be said that because the nucleus is spinning (i.e. it has spin) it has a resulting moment caused by the motion of a charged particle. The magnetic dipole moment is related to angular momentum by

\[ \mu = \gamma p \]  

(1.2)

1.2 NMR THEORY

It is possible to understand NMR using either the quantum mechanical or classical description. Each is suited to explaining different aspects of the phenomena. Consider first the quantum mechanical treatment.
1.2.1 Quantum Mechanical Description

The angular momentum $p$ of atomic nuclei can only have discrete values governed by the spin quantum number $I$ i.e.,

$$p = \sqrt{I(I+1)}$$

(1.3)

The spin $I$ can be zero for nuclei with even number of both neutrons and protons e.g., $^{12}\text{C}$ and $^{16}\text{O}$, integral for nuclei with an even mass number, and half integral for nuclei with an odd mass number e.g., $^{1}\text{H}$, $^{13}\text{C}$ and $^{31}\text{P}$. When $I = 0$ there is no resulting angular momentum and there is no resonance. Those nuclei with $I \geq 1$ have a non-spherical nuclear charge distribution and have an electric quadrupole moment. If an electric field is applied across these nuclei then there is splitting of the atomic energy levels, and nuclear quadrupole resonance (NQR) is possible. The effect is biggest in solids - in liquids the effects of a non-spherical charge distribution is averaged out by motion.

A second quantum number $m_j$ is introduced in order to specify the direction of the angular momentum. $m_j$ describes discrete values of the angular momentum of the system. In a given direction, say $z$, the component of angular momentum is given by

$$p_z = m_j \hbar$$

(1.4)

$m_j$ is allowed any of the values $I, I - 1, ..., - I$. As an example, $^{1}\text{H}$ which has a spin of a 1/2 will have two discrete values of angular momentum : $-1/2\hbar$ and $+1/2\hbar$. This can be visualized as in Figure
The same quantization is applied to the magnetic dipole moment i.e.,

$$\mu_z = \gamma \hbar m_1$$  \hspace{1cm} (1.5)

If the nuclei are placed into a magnetic field $B_o$, the system acquires energy shifts given by

$$E = -\mu_z B_o$$  \hspace{1cm} (1.6)

or from equation (1.5)

$$E = -\gamma \hbar m_1 B_o$$  \hspace{1cm} (1.7)
For nuclei with spin 1/2 this means that there will be two distinct energy levels, the difference between these two being given by

$$\Delta E = \gamma h B_0$$  \hspace{1cm} (1.8)

If electromagnetic radiation is applied whose quantum of energy, $h\nu_0$, exactly matches this energy difference then transitions may be induced and resonance occurs i.e.,

$$h\nu_0 = \gamma h B_0$$  \hspace{1cm} (1.9)

Since $\nu = h/2\pi$ and $\nu_0 = \omega_0/2\pi$

$$\omega_0 = \gamma B_0$$ \hspace{1cm} (1.10)

This relationship is called the Larmor equation and can be visualized in an energy level diagram as in Figure 1.2 below.

![Figure 1.2 Simple energy level diagram.](image)

The relative number of spins in the two energy levels are governed by the Boltzmann distribution i.e.,
\[ n^-/n^+ = \exp(-\Delta E/kT) \]  
\[ = \exp(-\gamma h B_0/kT) \]

where \( n^- \) and \( n^+ \) are the population of nuclei in the states \( m = -1/2 \) and \( +1/2 \) respectively, \( k \) is the Boltzmann constant and \( T \) is the temperature. At absolute zero all the spins are in the energy level that corresponds to the least energy, but as the temperature increases the thermal energy causes changes in the relative populations. Typical values for protons at 20°C are, \( \Delta E \approx 10^{-6} \text{eV} \) and \( kT \approx 2.5 \times 10^{-3} \text{eV} \). This makes \( n^-/n^+ \) very nearly equal to one and explains the inherent insensitivity of NMR. The sensitivity can be increased by increasing the field \( B_0 \) or decreasing the temperature of the nuclei.

1.2.1.1 Effect of R.F. Radiation

The frequency range required to induce transitions between the energy levels is in the radio frequency (r.f.) region of the electromagnetic spectrum. Upon application of r.f. radiation, energy will be absorbed by the system causing transition of spins between the energy levels, but with an overall movement from the lower to the higher energy levels. The number of spins moving to the higher levels will depend on the power and duration of the radiation. It is possible to apply a pulse of r.f. such that the number of spins in the lower and upper energy levels become equal. This is called a 90° pulse. An inversion of the population difference is achieved with a 180° pulse.
1.2.2 Classical Description

Consider a bar magnet placed in a magnetic field. It will align itself parallel to the field direction since this is the direction of least energy. If however, the magnet is tilted it will actually precess about the field direction. The nucleus with its angular momentum can also be regarded as precessing around the direction of the field i.e., an individual nuclei with a magnetic moment would lie at an angle $\theta$ to the direction of the applied field $B_0$. See Figure 1.3.

Figure 1.3 Illustration of precession of angular momentum.
A typical sample will contain many thousands of nuclei and their combined effect will be a net magnetization \( M \) in the applied field direction with no resultant in the x-y plane.

1.2.2.1 Rotating Frame of Reference

In order to understand from a classical point of view, how macroscopic changes in the system can be induced it is necessary to change the frame of reference from the laboratory frame \((x,y,z)\) to the rotating frame \((x',y',z')\). If an observer is placed in a frame rotating at frequency \( \omega_0 \), the observer will not see a precessing magnetic moment - it will appear to be stationary. They will therefore deduce that there is no applied magnetic field because they cannot see any effect of one. If a field \( B_1 \) is applied along the \( x' \) axis the magnetization vector will rotate about this axis in a manner analogous to the precession about \( B_0 \). The angle through which it rotates is given by \( \gamma B_1 t_p \) where \( t_p \) is the time for which the pulse is applied.

In the laboratory frame \( B_1 \) corresponds to a field rotating about the \( z \) axis at the precession frequency \( \omega_0 \). This field is generated in practice by applying an oscillating field in the x-y plane i.e., along the \( x \) axis. It can be resolved into two counter-rotating components as in Figure 1.4 overleaf.
(This is equivalent to the separation of polarized light into right and left handed circularly polarized light).

The two components are given by

\[ B_r = B_x \cos \omega t + B_y \sin \omega t \]  \hspace{1cm} (1.13)

\[ B_l = B_x \cos \omega t - B_y \sin \omega t \]  \hspace{1cm} (1.14)

The effective frequency difference of the component rotating in the opposite direction to the precession is considerable and so this component has negligible effect.

90° and 180° r.f. pulses are a more appropriate concept in the classical description of NMR because they refer to the angle through which the net magnetization is tipped. See Figure 1.5 overleaf.
1.2.3 Observation of Relaxation

The process of relaxation can be viewed using either the quantum mechanical or classical model. From the quantum mechanical description, as soon as the nuclei enter a magnetic field the energy levels become separated as mentioned in 1.2.1, but the number of spins in each level is identical at first. However, as it was noted, the equilibrium state does not have an equal number of spins in each level, instead it is governed by the Boltzmann Distribution. The term describing the transition of spins to an equilibrium state is called relaxation. Relaxation also causes a system which has absorbed r.f. radiation (and may now have identical numbers in the energy levels) to lose energy and move back to the equilibrium state. Relaxation effects are also responsible for broadening of the energy levels.
Following the tipping of the magnetization into the x-y plane (as described by the Classical model), the magnetization returns gradually back to alignment along the z axis.

Another form of relaxation is seen in the x-y plane. Following a 90° pulse the net magnetization lies in the plane. However, due to relaxation (and field inhomogeneities) the components of the magnetization begin to fan out. See Figure 1.6 below.

![Figure 1.6 Fanning out of components of magnetization in x-y plane.](image)

1.2.3.1 Mechanisms of Relaxation

Relaxation occurs through exchange of energy - either between nuclei and the molecular lattice, or between similar nuclei. The processes are known as spin-lattice ($T_1$) and spin-spin ($T_2$) relaxation respectively, and they occur because of the interactions of molecules. $T_1$ relaxation is responsible for transitions between the energy levels or, from the classical model, the growth or decay of $M$ along the z axis. It is essentially a change in the total energy of the system.

The probability of spins moving from the lower to higher ($W_+$) is related to the probability of movement from higher to lower ($W^\circ$) by the Boltzmann distribution
\[ W_{\downarrow}/W_{\uparrow} = \exp(-\Delta E/kt) \]  

(1.15)

where the terms are as the same as those in equation (1.11).

For nuclei with spin 1/2 the rate of change of population between the upper \((N_+\rangle\) and lower \((N_\downarrow)\) is given by

\[ \frac{dN_+}{dt} = -\frac{dN}{dt} = N_+W_{\uparrow} + N_+W_{\downarrow} \]  

(1.16)

Or letting \(n = N_+ - N_\downarrow\) and \(N = N_+ + N_\downarrow\)

\[ \frac{dn}{dt} = N(W_{\uparrow} - W_{\downarrow}) - n(W_{\uparrow} + W_{\downarrow}) \]  

(1.17)

which describes the approach to spin equilibrium.

Equation (1.17) can be rewritten as

\[ \frac{dn}{dt} = (n_0 - n)/T_1 \]  

(1.18)

with the substitution \(n_0 = N(W_{\uparrow} - W_{\downarrow})/(W_{\uparrow} + W_{\downarrow})\) and \(1/T_1 = W_{\uparrow} + W_{\downarrow}\).

The solution to (1.18) is

\[ n = n_0A\exp(-t/T_1) \]  

(1.19)

\(T_1\) is therefore a measure of the rate in which the spin system comes into equilibrium with its environment.

\(T_2\) relaxation is responsible for line broadening or dephasing of \(M\) in the \(x-y\) plane and is essentially a phase effect. Broadening occurs due to dipole-dipole interactions (see following paragraph).
causing a spread in the local field and hence a spread in the resultant energies. Also there is a finite lifetime of a spin being in a certain level due to $T_1$ relaxation, and there will therefore be an uncertainty in the energy $\Delta E$ from the Uncertainty Principle i.e., $\Delta E \sim \hbar/T_1$.

1.2.3.2 Dipolar Interactions

In a liquid the molecules will be undergoing motion described by Brownian Motion. It can be either rotational or translational motion. If these molecules have individual magnetic moments then they will cause time varying perturbations of magnetic field in their locality. If the frequency of these perturbations matches the Larmor frequency of the nuclei then transitions will occur. These dipole-dipole interactions depend upon the size of the magnetic moment, the proximity of the nuclei and the frequency distribution of the molecular motion.

Direct dipolar interactions between the nuclear magnetic moments make contributions to the Hamiltonian of the form\(^1\):

$$\mathcal{H}_D = \sum_{k < l} b_{ki} \left[ I_k I_l - 3.1/r^2_k \left( I_k r_{kl} \right) \left( I_l r_{kl} \right) \right]$$

(1.20)

where $k$ and $l$ describe the two nuclei, $r$ is the radius vector between the two moments and $b_{ki}$ is given by $\mu_0 \gamma_k \gamma_l (4\pi r_{kl}^3)$.

Converting to polar coordinates, the Hamiltonian can now be given by

13
\[ 3t_D = \sum_{k < 1q = -2}^{2} F^{(q)}_{kl} A^{(q)}_{kl} \]

where

\[ A^{(0)}_{kl} = \beta_{kl} (l_{-8}^z l_{-8}^z - 1/4 (l_{-8}^+ l_{-8}^- + l_{-8}^- l_{-8}^+)) \]  

(1.22)

\[ A^{(1)}_{kl} = -3/2 \beta_{kl} (l_{-8}^z l_{-8}^z + l_{-8}^z l_{-8}^z) \]  

(1.23)

\[ A^{(-1)}_{kl} = -3/2 \beta_{kl} (l_{-8}^z l_{-8}^z + l_{-8}^z l_{-8}^z) \]  

(1.24)

\[ A^{(2)}_{kl} = 3/4 \beta_{kl} l_{-8}^z l_{-8}^z \]  

(1.25)

\[ A^{(-2)}_{kl} = 3/4 \beta_{kl} l_{-8}^z l_{-8}^z \]  

(1.26)

and

\[ F^{(0)}_{kl} = 1 - 3\cos^2\theta_{kl} \]  

(1.27)

\[ F^{(1)}_{kl} = \sin\theta_{kl} \cos\theta_{kl} \exp(-i\phi_{kl}) \]  

(1.28)

\[ F^{(-1)}_{kl} = \sin\theta_{kl} \cos\theta_{kl} \exp(+i\phi_{kl}) \]  

(1.29)

\[ F^{(2)}_{kl} = \sin^2\theta_{kl} \exp(-2i\phi_{kl}) \]  

(1.30)

\[ F^{(-2)}_{kl} = \sin^2\theta_{kl} \exp(+2i\phi_{kl}) \]  

(1.31)
where $\theta_{kl}$ is the angle between the magnetic field $B_0$ and the internuclear vector $r_{kl}$, and $\phi_{kl}$ is the azimuthal angle with respect to the x-axis. This can be broken into six terms known as the ‘dipolar alphabet’.

$$H_D = b_{kl} [A + B + C + D + E + F] \quad (1.32)$$

where

$$A = (1 - \cos^2\theta_{kl}) I_{kz} I_{lz} \quad (1.33)$$

$$B = -1/4 \ (1 - \cos^2\theta_{kl})(I^{+}_{k} I^{-}_{l} + I^{-}_{k} I^{+}_{l}) \quad (1.34)$$

$$C = \sin\theta_{kl} \cos\theta_{kl} \exp(-i\phi_{kl})(I^{-}_{k} I^{+}_{l} + I^{+}_{k} I^{-}_{l}) \quad (1.35)$$

$$D = \sin\theta_{kl} \cos\theta_{kl} \exp(+i\phi_{kl})(I^{-}_{k} I^{+}_{l} + I^{+}_{k} I^{-}_{l}) \quad (1.36)$$

$$E = -3/4 \sin^2\theta_{kl} \exp(-2i\phi_{kl}) I^{+}_{k} I^{+}_{l} \quad (1.37)$$

$$F = -3/4 \sin^2\theta_{kl} \exp(+2i\phi_{kl}) I^{-}_{k} I^{-}_{l} \quad (1.38)$$

and where $I^{+} = I_{x} + iI_{y}$ and $I^{-} = I_{x} - iI_{y}$.

These terms contain information about the allowed transitions and the likelihood of a transition at a particular frequency. The energy level diagram of Figure 1.2 can be expanded to show a fuller picture for the case of a two spin system in a magnetic field as illustrated in Figure 1.7 overleaf.
A is effectively a static field which changes all the energy levels simultaneously such that the energy of the system remains the same. B is a ‘flip-flop’ interaction - one spin flips up as the other one simultaneously flips down. A and B do not change the energy of the system, so do not contribute to $T_1$, but they do change the phase and so contribute to $T_2$.

C and D both flip one spin only and induce transitions across the energy gap of $\hbar\omega_0$.

E and F flip two spins either up or down and so correspond to transitions of the order of $2\hbar\omega_0$.

Out of the six terms there are only four that contribute to $T_1$, whereas all six contribute to $T_2$. $T_2$ is therefore always equal to or shorter than $T_1$, i.e., $T_2$ is a more effective process since there are more contributing terms.
1.2.3.3 Factors Influencing Relaxation

A useful concept is the correlation time, $\tau_c$, which was proposed by Bloembergen Purcell and Pound as a measure of the time that two nuclei remain in a given orientation (so influencing relaxation). They showed that

$$\frac{1}{T_1} = \frac{k \cdot \tau_c}{(1 + 4\pi^2\nu_0^2\tau_c^2)} \tag{1.39}$$

where $k$ is a constant. For rapid molecular motions $1/\tau_c \gg \omega_0$ so that equation (1.39) reduces to

$$\frac{1}{T_1} \propto \tau_c \tag{1.40}$$

and for very slow motion $1/\tau_c \ll \omega_0$, so that

$$\frac{1}{T_1} \propto \frac{1}{\tau_c} \tag{1.41}$$

This variation is shown in Figure 1.8 below.

![Figure 1.8 Correlation time versus $T_1$ relaxation time.](image)
The most effective $T_1$ relaxation therefore occurs when $\tau_c = 1/\omega_0$. $T_2$ is also plotted and differs greatly from $T_1$ at higher correlation times since for slow molecular motions the dipole-dipole interactions become very effective at line-broadening i.e., short $T_2$s.

The temperature of the system also affects the efficiency of relaxation. Figure 1.9 below illustrates the amplitude of the motions at the resonance frequency.

![Amplitude of motion diagram](image)

*Figure 1.9 Amplitudes of motions varying with frequency.*

At low temperatures the motions of the molecules are relatively slow so there are likely to be little or no motions corresponding to the Larmor frequency. At higher temperatures there are many more motions at the Larmor frequency.
1.2.4 Motion of Macroscopic Magnetization - the Bloch Equations

The Bloch equations \(^2\) were derived some 40 years or more ago to describe the motion of the macroscopic magnetization in the presence of an applied magnetic field.

The classical equation of motion of a magnetic moment in a magnetic field is given by

\[
\frac{dp}{dt} = \mu \times \mathbf{B} \quad (1.42)
\]

where \(p\) is the angular momentum of a spinning nucleus and \(\mu \times \mathbf{B}\) is the torque exerted on a magnetic moment by the applied field and \(\mathbf{B} = \mathbf{B}_0 + \mathbf{B}_1\) where \(\mathbf{B}_0\) is in the \(z\) direction and \(\mathbf{B}_1\) is in the \(xy\)-plane.

Multiplying (1.42) by \(\gamma\) we obtain

\[
\gamma \frac{dp}{dt} = \frac{d\mu}{dt} = \gamma \mu \times \mathbf{B} \quad (1.43)
\]

since \(\mu = \gamma p\).

To find the relationship for the bulk magnetization allow \(M = \sum \mu\)

\[
\frac{dM}{dt} = \gamma M \times \mathbf{B} \quad (1.44)
\]

However this is over simplified with relaxation effects neglected.

It is reasonable for \(M_z\) to be established according to the equation

\[
\frac{dM_z}{dt} = \left( M_0 - M_z \right) / T_1 + \gamma (M \times \mathbf{B})_z \quad (1.45)
\]
where $M_0$ is the equilibrium value i.e., $M_z$ returns exponentially to the equilibrium value of $M_0$. (See equation (1.19))

And

$$\frac{dM_x}{dt} = - \frac{M_x}{T_2} + \gamma(M \times B)_x \tag{1.46}$$

$$\frac{dM_y}{dt} = - \frac{M_y}{T_2} + \gamma(M \times B)_y \tag{1.47}$$

i.e., $M_x$ and $M_y$ both decay exponentially to zero with $T_2$.

Combining these equations gives

$$\frac{dM}{dt} = \gamma M \times B - \frac{(M_x i + M_y j)}{T_2} - \frac{(M_z - M_0) k}{T_1} \tag{1.48}$$

This equation is valid in the laboratory frame, the rotating frame is a little more complicated. The time derivative of $M$ is

$$\frac{\partial M}{\partial t} i + M_x \frac{\partial i}{\partial t} + \frac{\partial M_j}{\partial t} j + M_y \frac{\partial j}{\partial t} + \frac{\partial M_k}{\partial t} k + M \frac{\partial k}{\partial t}$$

$$= (\frac{\partial M_x}{\partial t} i + \frac{\partial M_y}{\partial t} j + \frac{\partial M_z}{\partial t} k)$$

$$+ (M_x \frac{\partial i}{\partial t} + M_y \frac{\partial j}{\partial t} + M_z \frac{\partial k}{\partial t}) \tag{1.49}$$

and $\frac{\partial i}{\partial t} = \omega x i \quad \frac{\partial j}{\partial t} = \omega x j \quad \frac{\partial k}{\partial t} = \omega x k$

$$\therefore \frac{dM}{dt} = \partial M/\partial t + \omega \times (M_x i + M_y j + M_z k) \tag{1.50}$$

or
\[
\frac{dM}{dt}_{\text{fixed}} = \left(\frac{dM}{dt}\right)_{\text{rotation}} + \omega \times \left(M_x i + M_y j + M_z k\right)
\]

(1.51)

if \( \left(\frac{dM}{dt}\right)_{\text{fixed}} = \gamma M \times B \)

then

\[
\left(\frac{dM}{dt}\right)_{\text{rotation}} = \gamma M \times B - \omega \times M
\]

\[
= \gamma M \times (B + \omega/\gamma)
\]

\[
= \gamma M \times B_{\text{eff}}
\]

(1.52)

where

\[
B_{\text{eff}} = B_0 + B_1 + \omega/\gamma
\]

\[
= (B_0 + \omega/\gamma) k + B_1 i
\]

(1.53)

If \( \omega = \gamma B_0 \) (in the absence of \( B_1 \)) then \( B_{\text{eff}} = 0 \).

With all the relaxation terms added

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

(1.54)

This equation is fundamental in describing the motion of the net magnetization and forms the basis of the simulation described in Chapter Four.
1.2.5 Detection of R.F. Signal

Figure 1.10 illustrates the basic components of signal detection.

![Diagram of R.F. detection](image)

*Figure 1.10 Schematic diagram of R.F. detection.*

The axis of the solenoid (r.f. coil) is placed perpendicular to the magnetic field. If an r.f. pulse is applied, the magnetization is tipped into the x-y plane (or at least it will have a *component* in the plane for a non-90° pulse) and will then rotate about the z-axis. The effect of this precession is to generate a rotating magnetic field which cuts the solenoid. An oscillating field within a solenoid will produce an EMF, and it is this which is detected.
1.2.6 NMR Pulse Sequences

Relaxation times can provide important physiological information about structure and function and as such are of great interest to the clinician. However, in order to measure $T_1$ and $T_2$ it is necessary to apply a sequence of r.f. pulses.

1.2.6.1 Measurement of $T_1$ Relaxation

In order to measure $T_1$ it is necessary to monitor the rate at which the equilibrium state is restored. In the classical treatment this is equivalent to monitoring the growth of the net magnetization $M$ along the z-axis. The phase of the detector is referenced to the transmitted r.f. so that it essentially detects along a fixed axis in the rotating frame in the x-y plane. In order to measure $T_1$ it is therefore necessary to 'tip' $M$ into the x-y plane, monitoring the size of the received signal as a function of the inter-pulse time.

The Inversion Recovery sequence is a standard technique for the measurement of $T_1$, and is illustrated in Figure 1.11 overleaf.
The first r.f. pulse of the pair disturbs the thermal equilibrium whilst the second acts as a detection pulse. A suitable time needs to be left between pairs of pulses in order for $M$ to have recovered fully. The time between successive pairs of pulses is called the repetition time, $TR$, and is usually of the order of $5T_1$.

The equation describing the dotted line of Figure 1.11 is found by assuming that equilibrium is established exponentially (from equation (1.19)) i.e.,

$$
dM_z/dt = -(M_z - M_o)/T_1
$$

(1.55)

This is then solved for $M_z(0)=M_o$. The solution is

$$
M_z(t) = M_o(1 - 2\exp(-t/T_1))
$$

(1.56)
1.2.6.2 Measurement of $T_2$ Relaxation

If $T_2$ relaxation was the only mechanism by which dephasing of the signal in the x-y plane occurred, then $T_2$ could be measured as the exponential decay of the FID. Unfortunately this is not the case. It is not practically possible to achieve a perfectly homogeneous $B_0$ magnetic field and as a result, different spins 'see' slightly different fields and so their precession frequencies are slightly different. This leads to dephasing of the signal in addition to that caused by $T_2$ relaxation.

Hahn devised a way of overcoming this effect in what is called a spin-echo sequence\(^3\). It consists of a $90^\circ$ and $180^\circ$ pulse illustrated in Figure 1.12 below.

![Spin Echo Pulse Sequence](image)

**Figure 1.12 Spin Echo pulse sequence.**

Following the $90^\circ$ pulse M is tipped into the x-y plane and then begins to decay via $T_2$ relaxation and inhomogeneity effects. S and F refer respectively to slower and faster precession with respect to $\omega_0$. Following a $180^\circ$ pulse the spins are 'reflected' and come back into phase - reversing the effect of the inhomogeneity of the field. The signal reforms at $2\tau$ (or the echo time, TE) with a
decrease in magnitude from the beginning of the sequence governed only be $T_2$. The equation describing the decay of the magnetization in the x-y plane is found by assuming that

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

(1.57)

i.e., $M_{xy}$ decays exponentially away to zero. Therefore

$$M_y(t) = M_0 \exp(-t/T_2)$$

(1.58)

$T_2$ can be determined by repeating the pulse sequence several times with a variety of values of $\tau$.

Alternatively the Carr-Purcell sequence$^4$ applies a $90^\circ$ pulse then a train of $180^\circ$ pulses each separated by $2\tau$. $T_2$ can then simply be measured by tracing the decay of the echo sizes. This reduces the time of the experiment because it is not necessary to wait $5T_1$ between each detected signal.

It should be noted that if the $90^\circ$ and $180^\circ$ pulses are applied along the same axis in the rotating frame then the detected ‘echo’ will occur alternately along the $y'$ and $-y'$ (or $x$ and $-x'$) axes. Unfortunately if there is inaccurate setting up of the $180^\circ$ pulse the error will be compounded on successive applications.

A simple but important variation of this sequence is to apply the $180^\circ$ pulses with a phase shift of $90^\circ$ to the original $90^\circ$ pulse. This has a two-fold effect : all the echoes will now occur along the same axis i.e., will all be of the same phase and, more importantly, any inaccuracy of the $180^\circ$ pulses will be canceled out by successive $180^\circ$ pulses. This is known as the
1.2.6.3 Effect of Diffusion

The 180° pulse of the spin-echo sequence is able to rephase spins assuming that after inversion the spins would ‘see’ the same magnetic field and so would continue precessing at the same frequency. However if diffusion of molecules is occurring then the spins will be moving and experiencing different fields and thus precessing at different frequencies. There can be no perfect rephasing of these spins leading to additional attenuation. The equation describing diffusion attenuation in a spin echo sequence is given by:

\[
\frac{S(2\tau)}{S(0)} = \exp(-2\gamma^2DG^2\tau^3/3)
\]

where \(S(2\tau)\) is the echo amplitude, \(S(0)\) is the amplitude at the beginning of the FID, \(\tau\) is the delay between the two r.f. pulses, \(D\) is the diffusion coefficient and \(G\) is the strength of a steady linear magnetic field gradient. The attenuation can be minimized by keeping \(\tau\) very short, however diffusion coefficients are very useful and are often measured from the attenuation of the echo signal.
In order to produce an image of an object it is necessary to obtain spatial information from the detected r.f signals. In conventional MRI it is normal to select a slice through an object and display its 2D cross-section, so there must be information from three orthogonal axes.

1.3.1 Standard 2DFT Imaging Technique

The following is a brief description of the most common form of image generation - two-dimensional Fourier Transform (2DFT) imaging. Throughout this thesis the cartesian coordinates $x$, $y$, and $z$ will represent frequency encoding, phase encoding and slice selection respectively.

1.3.1.1 Slice Selection

If a square shaped r.f pulse is applied to a sample then this will excite all of the spins within the probe. In order to select a well-defined slice within the sample recall that the Larmor equation states that the frequency of precession is proportional to the applied magnetic field.

$$\omega_0 = \gamma B_0 \quad (1.60)$$

If a magnetic field gradient is applied then the frequency becomes
proportional to position \((r)\) within the gradient

\[
\omega_o = \gamma B_o + \gamma G r
\]

(1.61)

So in order to select a slice a bandwidth of frequencies is required which corresponds to the desired slice thickness.

The Fourier Transform of frequency is time. The two are related by

\[
f(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} F(\omega) \exp(i\omega t) d\omega
\]

(1.62)

For a rectangular bandwidth in frequency space the corresponding shape in time is a sinc, illustrated in Figure 1.13 below.

An r.f. pulse modulated by a sinc shaped envelope is therefore transmitted during application of a gradient which selects the required slice as in Figure 1.14 overleaf.
An appropriate slice is then selected according to

\[ z = \frac{n}{\gamma G_z t_p} \]  

(1.63)

Where \( z \) is the slice thickness, \( G_z \) is the applied gradient, \( t_p \) is the duration of the r.f. pulse and \( n \) is the number of nodes of the r.f. pulse.

The position of the slice can be changed by varying the frequency of the transmitted pulse because from (1.62) \( \omega \propto r \).

The second 'lobe' of the slice selection gradient (Fig.1.16) is required to refocus the spins that acquired phase due to the presence of the initial gradient.
1.3.1.2 Frequency Encoding

As just mentioned, in the presence of a magnetic field gradient the frequency of the spins is proportional to position in the gradient direction. If, whilst the signal is being received, a gradient is applied as in Figure 1.15 then this will \textit{spatially encode} the information.

![RF signal and gradient](image)

\textit{Figure 1.15 Frequency encoding by application of gradient.}

The signal from these sampling points is given by

\[ S_m = D(x) \exp(i \gamma G_x x) \]  

(1.64)

where $D(x)$ is the density of protons as a function of $x$. If this signal is Fourier Transformed it is equivalent to changing domains between time $t_m$ and $\gamma G_x x$ (where in fact $x$ is the only variable). Therefore, the Fourier Transform of the time data gives spatial information.

Figure 1.16 overleaf shows a typical object and the Fourier Transform of the signal acquired from it whilst applying a gradient. The shape of the graph is called the \textit{projection} of the
object - the vertical axis which shows the absorption is proportional to the density of protons and the horizontal or frequency axis is proportional to distance.

![Spin density vs Frequency diagram]

*Figure 1.16 Projection of an object from frequency encoding.*

Since the gradient is applied during the period when data is acquired it is often called the *read gradient*. The time between sample points determines the total bandwidth, and the size of the gradient determines the spread of frequencies of the object within the field of view (FOV). Once the bandwidth is defined by the sampling time it is possible to choose the FOV \(x_{\text{TOT}}\) or the read gradient strength. Frequency is related to gradient strength by

\[
\omega = \gamma G x_{\text{TOT}} \tag{1.65}
\]

or since \(\omega = 2\pi f\)

\[
2\pi f = \gamma G x_{\text{TOT}} \tag{1.66}
\]
rearranging this gives

\[ G_x = \frac{2\pi f}{\gamma x_{\text{TOT}}} \]  

(1.67)

1.3.1.3 Phase Encoding

It was seen in 1.2.2 that the Fourier Transform of the signal sampled in real-time gives rise to a profile of the object along one direction. It is in fact possible to acquire information for the perpendicular direction by sampling in another ‘dimension’.

Figure 1.20 shows the timing of the phase encoding gradient.

\[ \frac{dG_y}{\text{scan}} \]

*Figure 1.20 Phase encoding gradient.*

The size of the gradient is incremented from ‘scan’ to ‘scan’. The effect of the gradient pulse is an additional phase shift to the spins which varies linearly with \( y \). The incremental increase in gradient amplitude causes a whole range of phase shifts variations as shown in Figure 1.17 overleaf.
If the signal is detected with a phase sensitive detector (see 3.1.2.3) then it will detect the signal varying sinusoidally with distance $y$, implying a range of spatial frequencies. This is illustrated in Figure 1.18.

**Figure 1.17** Phase shifts resulting from incremental gradient increases.

**Figure 1.18** Spatial frequencies detected by PPD.
The signals from each of the gradient increments \( n \) is given by

\[
S_n = D(y)\exp((iy^T G_y).y)
\]  

(1.68)

where \( D(y) \) is the density of protons as a function of \( y \) and \( T \) is the duration of the phase encoding gradient. Equation (1.69) can be rewritten as

\[
S_n = D(y)\exp(i\Phi_y.y)
\]  

(1.69)

Equation (1.69) is one half of a Fourier Transform pair which transforms to give spatial information from spatial frequencies. The equation governing the gradient strength, time and FOV \( (y_{TOT}) \) is given by

\[
dG_y = \frac{2\pi}{(y_{TOT} T)}
\]  

(1.70)
1.3.2 Imaging Sequences

A huge variety of imaging sequences exist to date, this section will be limited to three key sequences used in flow imaging. These are spin echo, gradient echo and echo planar imaging.

1.3.2.1 Spin Echo Imaging

This imaging sequence is based upon the spin echo sequence described in 1.1.4.2. The timing diagram below in Figure 1.19 illustrates the main components of the sequence.

![Timing diagram of spin echo imaging sequence.](image)

It is shown with selective 90° and 180° pulses but it should be noted that it is not necessary for both pulses to be selective. If the 90° is selective (or soft) and the 180° is non-selective (or hard), then there will still only be signal from the slice selected by the 90° because all those spins excited by the 180°
(i.e., all the sample) will not have seen the original pulse and so will not have been tipped into the x-y plane. The same is true of a hard 90° and a soft 180°. Only spins which see both the 90° and 180° will contribute to the echo.

1.3.2.2 Gradient Echo Imaging

An alternative to rephasing spins with a 180° pulse is to apply a gradient. An echo will be formed at a time 2τ where τ is the time from the beginning of the sequence to the centre of the rephasing gradient. This sequence is illustrated below in Figure 1.20.

![Diagram of Gradient Echo Imaging Sequence](image)

*Figure 1.20 Timing diagram of gradient echo imaging sequence.*

1.3.2.3 Echo Planar Imaging

Echo planar imaging (EPI) was the forerunner of the rapid imaging
techniques and was proposed in 1978. Unlike conventional imaging techniques which require the whole sequence to be repeated a number of times to spatially encode in the second direction, all of the spatial information can be obtained in one scan. The group of rapid imaging sequences which EPI initiated are therefore known as *single-shot* imaging techniques.

In order to understand how EPI works it is necessary to consider the experiment in the spatial frequency or *k*-space domain. The concept is well-defined in optics where it represents frequency space. In NMR the spatial frequency information is related to the application of the gradients. The relationship is given by

\[
k_n(t) = \gamma \int_0^t G_n(s) \, ds
\]  

(1.71)

where \( k_n \) is the \( k \)-space displacement along the \( G_n \) axis.

The \( k \)-space representation is shown in Figure 1.21 below.

![Figure 1.21 k-space.](image)

In the conventional imaging experiment, data is obtained during application of a frequency encoding gradient (equivalent to
tracking along the \( k_{\text{frequency}} \) axis) and the phase encoding gradient is increased linearly for each scan (equivalent to tracking along the \( k_{\text{phase}} \) axis). This can be visualised in the following \( k \)-space diagram in Figure 1.22.

![Figure 1.22 k-space representation of conventional imaging experiment.](image)

The EPI technique obtains all of the required \( k \)-space data in just one scan. Figure 1.23 below shows the timing diagram.

![Figure 1.23 Timing diagram of the EPI sequence.](image)
After an r.f. pulse the phase and frequency encoding gradients are simultaneously applied. The frequency encoding is rapidly switched for an appropriate number of times (usually 64) until a data set is obtained. The k-space diagram below in Figure 1.24 illustrates what happens.

![k-space diagram](image)

*Figure 1.24 k-space representation of EPI experiment.*

The technique is problematic due to the k-space not being sampled uniformly so leading to difficulties in carrying out the Fourier transforms. Many different techniques have been proposed to overcome these difficulties with good results\textsuperscript{9,10}.
CHAPTER TWO

FLOW AND MOTION IN THE HUMAN BODY
2.1 INTRODUCTION

The human body is made up of many complex interdependent flow systems, their basic purposes being to either deliver or remove substances e.g., oxygen, nutrients, blood, waste products. Depending upon the task, these flow systems are structured in different ways, delivering different amounts of fluid to and from their destination. Figure 2.1 below illustrates the four basic flow systems.

![Diagram of flow systems in the human body]

*Figure 2.1 Flow Systems in the human body.*
2.2 MAJOR BLOOD VESSELS

These vessels run between the heart and the rest of the body and are estimated to carry of the order of 8400 litres per day\textsuperscript{11}. They have thick impermeable walls - transport occurring only along the direction of the vessel.

The arteries which remove blood from the heart have walls which are built up of several different layers of tissue and muscle. The closer the artery is to the heart the greater the amount of elastic tissue in the vessel wall there is in order to smooth out the stroke of the heart. The further the artery is from the heart, the greater the proportion of smooth muscle. In many places there exist \textit{anastomoses} which are alternative routes along which the blood can flow. These are important should there be a blockage along one of the other paths.

The arteries branch down into smaller vessels called arterioles whose walls are composed almost entirely of smooth muscle. These deliver blood to the organs and tissue.

The veins are the vessels which form the return circuit back from the arteries (through the capillaries - see section 2.3) to the heart. They start off as venules (the equivalent of arterioles) and branch back to larger and larger vessels finally re-entering the heart through the two venae cavae. They are of similar composition to arteries except that the vessel walls are thinner and the overall diameter larger.

In strategic places there are \textit{arteriovenous anastomoses} which bypass the capillaries forming direct connections between arterioles and venules. These are important in enabling a faster
flow of blood such as in rapid regulation of temperature in the skin.

2.3 MICROCIRCULATION

The microcirculation forms the junction between the arterious and venous sides of the circulation and it is here that transfer of substances occur.

The capillary volume does not fill the whole space. In fact it is typically only of the order of 2-3% of the volume of tissue.

The vessels making up the microcirculation are called capillaries and are the smallest in the body with an average diameter of around 5μm. Since the purpose of capillaries is delivery and uptake of molecules their walls have to be permeable. The exact construction of the vessel walls depend on the location of the capillaries, but there are three different types:

(i). non-fenestrated i.e., continuous sheaths of endothelial cells with 10nm gaps between cells. This distance is suitable for diffusion of water-soluble substances,

(ii). fenestrated capillaries which are endothelial intracellular openings permitting large and rapid transfer of fluid and

(iii). discontinuous capillaries which possess a thin layer of endothelial cells interspersed with large gaps between the cells. These are suitable for exchange of large protein molecules.

These are illustrated in Figure 2.2 overleaf.
The arrangement of the capillaries varies for different parts of the body. In most organs there is random branching of the capillary network and hence an essentially isotropic pattern of flow. This is illustrated simply in Figure 2.3 below.

![Figure 2.2 Different types of capillaries](image)

The speed of the flow within these capillaries determines the 'regime' of the flow i.e., whether the flow changes direction during measurement time or not. The terms given to these two regimes are incoherent and coherent respectively.

In some parts of the body e.g., the muscles of the limbs, the
capillaries are arranged essentially *anisotropically*.

The orientation of the capillaries and the regime of the flow affect how the flow can be detected as can be seen later in 2.6.3.

There are three mechanisms for transport *across* the capillary walls - filtration-absorption, diffusion and micropinocytosis\(^\text{12}\).

*Filtration-absorption* is governed by hydrostatic pressure on the vessel wall. The rate of filtration-absorption is very slow - only 0.3% of the rate of blood flow. The process regulates the blood volume of the capillaries.

*Diffusion* on the other hand is the process whereby nutrients and waste products are transferred to and from the tissue cells. Molecules which are lipid-soluble (oxygen, carbon dioxide etc.) can diffuse across any part of the capillary wall through the plasma wall of the endothelial cells. Lipid-insoluble molecules (glucose, NaCl, serum etc.) are limited to diffusing through intracellular pores. Calculations of diffusion rates are complex but, for example, the rate of diffusion of water across the capillary wall is forty times the rate of blood flow. (This figure varies for different size and types of molecule.)

The third transport phenomena is *micropinocytosis* which is very slow and contributes insignificantly to the total capillary exchange. It involves the transport of macromolecules which cannot undergo diffusion. Details of this process are sketchy, but electron microscope studies have revealed 'vacules' (fluid filled space in cell) which seem to have been in the process of traversing the endothelial cells of the capillary wall.
2.4 LYMPHATIC SYSTEM

The body’s tissues are bathed in a fluid which constantly traverses the capillary walls. Most of it is taken up by the capillaries and travels back through the venous system. The remainder flows through the lymphatic system which is the network through which lymph flows. Lymph is the substance which carries away infecting organisms such as viruses and bacteria. The network begins as blind capillaries in the tissue and goes on to form vessels which pass through lymph nodes and finally empty into veins at the root of the neck. Lymphatic capillaries are of a similar construction to blood capillaries and are found in the same location. It is thought that proteins pass through to the lymph system by diffusion through the capillary walls.

2.5 MOTION OF THE BODY

In addition to flow in the body there are various types of motion which accompany normal bodily function. The force behind the blood flow is the beating heart - this motion affects the whole chest area. Another obvious motion accompanies the inhalation of oxygen into the lungs. This respiratory motion affects the chest and abdomen. Other motion effects are due to the eyes and movements in the gut.
2.6 PATHOLOGIC FLOW

Normal patterns of flow in the body are obviously highly complex but when disease or injury occurs this very often disrupts or destroys the pattern - the new one that is established can be indicative of the original event and subsequent effects.

For example, narrowing of the major coronary vessels causes angina. This would readily be detected on an ECG (recording of currents in the heart) or the restricted vessel could be pictured on an angiogram (a ‘map’ of blood vessels). Tumours, whether benign or malignant, can also alter the normal flow pattern. Increased flow may result due to vascularization of the tissue, or there could be a complete flow void (necrosis). A map of the microcirculatory flow would enable this to be seen. Another example would be in the rupture of the blood brain barrier where fluids would cross over a previously restraining barrier.

It is therefore of great importance to be able to monitor or measure flow patterns in the body.
2.7. NMR DETECTION OF FLOW AND MOTION

As just described in 2.1 there are many different types of flow systems. Each of these will have a different effect on the NMR signal and there will consequently be different detection methods depending upon the type of flow being investigated.

Some of the motions in the body will be indicators of physiological states and so are actively measured whilst others will simply be a nuisance and techniques exist which seek to minimize their effects.

There are currently three different distinct types of flow that can be detected. These are macroscopic flow, diffusion and capillary flow.
2.7.1 Macroscopic Flow

This term describes the flow that occurs in the major blood vessels of the body. The dimensions of the vessel are such that they occupy several pixels on an image. Depending upon the sequence being executed, macroscopic flow may appear on an image as a decreased or increased intensity, or as a blur or as an artifact. It can also be detected in the phase of an image.

There are several different methods of detecting macroscopic flow with the following forming the main categories.

2.7.1.1 Time of Flight Effects

In a spin echo sequence with selective 90° and 180° pulses, if nuclei flow at such a rate that they 'see' the 90° pulse but not the 180°, as they move out of the image plane, they will not be rephased and therefore will not contribute to the spin-echo. This is known as spin washout. The absence of signal in part of an image may therefore be a pointer to the presence of flow perpendicular to the image plane.

For nuclei flowing at relatively slow speeds, an enhancement of the signal can be observed. Stationary nuclei within the defined slice, are partially demagnetized due to the r.f. pulses - fresh nuclei flowing into the slice will be fully magnetized and so will provide a greater signal intensity. The resultant effect is a signal greater than that for stationary nuclei alone and is called slow flow enhancement\textsuperscript{15}.

Experiments exist which use time of flight phenomena to 'track'
flow and give quantitative measurements. The advantage of these techniques is that there is no upper limit to the flow rate that can be measured. The most simple experiment is where there are two parallel spatially offset planes for excitation and refocusing\textsuperscript{16}. Velocities can be deduced from velocity=displacement/TE where TE is the echo time. Variations on the theme include standard multiple spin-echo sequences\textsuperscript{17} and excitation planes orthogonal to the rephase slice\textsuperscript{18}.

2.7.1.2 Phase Techniques

Nuclei will experience phase changes due to the different gradients and r.f pulses within the sequence. For stationary nuclei in a spin echo sequence all the phase changes cancel each other out - the 180° pulse rephases the fanning out of the spins in the rotating frame, and the gradients are balanced which negates their effect. However for moving nuclei the phase changes will not be cancelled out as is illustrated in Figure 2.3 below.

![Figure 2.3. Timing diagram for a standard spin echo sequence.](image)

For the sequence illustrated in Figure 2.3 the phase $\phi$ at the
centre of the echo is given by

$$\phi(2t_o)/\gamma = \int_0^{t_o} (\Delta B + g z + g v t) \, dt$$

$$+ \int_{2t_o}^{t_o} (\Delta B + g z + g v t) \, dt \quad (2.1)$$

where $\Delta B$ is the change in field due to the gradient, $g$ is the flow encoding gradient strength in the direction of flow, $z$ is the position and $v$ is the velocity. Expanding this

$$\phi(2t_o)/\gamma = \int_0^{t_o} \Delta B \, dt + \int_{t_1}^{t_1+T} (g z + g v t) \, dt$$

$$+ \int_{2t_o}^{t_o} \Delta B \, dt + \int_{t_2}^{t_2+T} (g z + g v t) \, dt \quad (2.2)$$

$$= \Delta B t_o + \left[ g z t + g v t^2/2 \right]_{t_1}^{t_1+T}$$

$$+ \left[ \Delta B t \right]_{t_2+T}^{t_2} + \left[ g z t + g v t^2/2 \right]_{t_2+T}^{t_2+T} \quad (2.3)$$

$$= -g v T(t_2-t_1) \quad (2.4)$$

$$\therefore \phi = -\gamma g v T(t_2-t_1) \quad (2.5)$$

where $T$ is the duration of the gradient and $(t_2-t_1)$ is the difference in time between the beginning of the second gradient and the first.
This phase can be viewed directly by calculating a phase image from the real and imaginary parts of the signal - the intensity of the image being proportional to the velocity of the nuclei. A problem with looking at the phase of the signal is aliasing. The range of velocities needs to provide a phase change in the range of $-\pi$ to $+\pi$ to avoid ambiguity. Axel has suggested a method whereby phase aliasing in an image may be corrected. They looked at the phase variation with position assuming smooth variations. Where a discontinuity was found they deduced that it was due to 'phase wrapping' and therefore the $+/-\pi$ jump could be restored and the correct velocity obtained.

Spins which undergo acceleration will also acquire a phase that will not be cancelled out.

(The gradients shown in Figure 2.3 could be the frequency encoding gradients or an additional pair of flow encoding gradients.)

2.7.1.3 Rephasing Effects

The signal from flowing material can be refocused in several different ways. If the flow consists of constant velocity then one can take advantage of even echo rephasing. This is an enhancement of the NMR signal for even echoes of a multiple spin echo sequence. At the first echo rephasing due to the 180 pulse is incomplete due to flow but following an additional 180° pulse rephasing is complete, producing a more intense second echo. Figure 2.4 overleaf illustrates this phenomenon.
Alternatively, specially designed gradient waveforms can be used to compensate for different orders of flow (i.e., velocity, acceleration, pulsatility etc.) Figure 2.5 below illustrates this.

**Figure 2.4** Phase diagram of an even echo sequence.

**Figure 2.5.** Flow compensating gradient waveforms.
The calculation of these profiles is explained in section 2.8.2.9.

2.7.1.4 Cine Mode MRI

A useful macroscopic flow imaging technique is cine mode MRI. A number of images are displayed throughout the duration of the cardiac cycle using a gradient echo sequence. The images are obtained by exploiting the different effects that flow has on the NMR signal. Nayler et al\textsuperscript{21} devised an experiment which combined a gradient echo sequence with an even echo sequence to overcome the problem of loss of signal due to flow. Included in the sequence were flow encoding pulses. In addition to this there was a second sequence interleaved in time with the first which was identical except that it contained no flow encoding gradients. Subtracting the two resulting sets of images yields images with information on flowing material only, since static tissue would produce the same signal for both sequences. (This technique of subtracting images has been used by a number of different investigators in simpler sequences either using different magnitudes of flow encoding gradients ($g$) or different timings of the gradients ($t_2-t_1$)$^{22}$. Benefits of doing this include being able to cancel phase shifts due to field nonuniformities and chemical shift phenomena). The two sequences are repeated up to 12 times during the cardiac cycle. The (difference) phase images were displayed and used to calculate the flow rate at a number of times during the cardiac cycle knowing the cross-sectional area of the vessel being imaged. Bendel et al\textsuperscript{23} did
a similar experiment for the carotid arteries but without the even-echo rephasing.

Guo et al\textsuperscript{24} used three gradient echo sequences in cine mode with different amounts of flow rephasing. Rephasing of spins that have been dephased by flow can be achieved by the application of specific gradients as mentioned in section 2.7.1.3. If the gradients shapes (profiles) are altered then the amount by which they are rephased changes. They obtained difference images between the three different sequences at the same time in the cardiac cycle and also between the sequences at various points in time. In either case subtraction of the stationary tissue yielded magnitude images of the content of the vessels.

Metcalfe\textsuperscript{25} used field echo cine MRI for cardiac imaging at low fields. The low field reduces errors due to artifacts, chemical shift and noise.

2.7.1.5 Fourier Flow Imaging

A technique which has the ability to separate out flow within different velocity ranges - even within the voxel - is \textit{Fourier flow imaging}\textsuperscript{26,27}. This uses a method analogous to phase encoding of one spatial direction to encode one directional component of velocity. Each increment of velocity encoding gives an image in which the intensity of the signal is proportional to the velocity in a certain range. In the image where the velocity encoding gradient is zero the stationary tissue is seen. This technique is very time consuming however and so is limited in use in a clinical
environment. Feinberg et al\textsuperscript{28} used this technique to image one spatial dimension and one velocity component. A novel approach was suggested by Xiang and Nalcioglu\textsuperscript{29} which they called Projection images of the Position-Velocity Joint Spin Density Distribution. This is basically a projection of an object along an oblique direction somewhere between the direction of spatial phase encoding and the direction of velocity encoding. They obtained magnitude difference images of the object.

2.7.1.6 MR Angiography

One section of macroscopic flow imaging that has been touched upon is MR Angiography (MRA) where magnitude images of flowing material only are displayed. Conventional angiography involves the injection of a suitable contrast agent into the vessel under consideration in order to obtain an image of the vessels. MRA needs no such contrast agent for imaging vessels and a variety of sequences exist to date. Projective angiography involves using a sequence which has no slice select gradient so that all the blood vessels can be imaged. When this is combined with static tissue suppression ie. obtaining a difference image, excellent images of the vessels can be obtained. A variety of different methods of displaying or acquiring the angiograms exist to date\textsuperscript{30}. The technique relies on time of flight effects and can be coupled with fast MRI sequences to provide excellent images of vessels, but at the present time little quantitative information.
2.7.2 Diffusion

From the discussion of section 2.3 it can be seen that diffusion processes play an important role in the body. The concept of diffusion is well defined and so undertaking measurement of diffusion coefficients should provide valuable physiological information.

Diffusion can be pictured as a random walk. The diffusion coefficient being defined as \(^{31}\)

\[
D = \frac{l \cdot v}{6} \tag{2.6}
\]

where \(l\) is the mean free path (m.f.p.) and \(v\) is the average velocity. If the m.f.p. exceeds the space that is available then the diffusion is said to be restricted. Diffusion coefficients are temperature dependent i.e., at higher temperatures the molecules will have greater energy and so \(l\) and \(v\) increase.

For a normal spin echo sequence the signal at the centre of the echo is given by

\[
\frac{S(TE)}{S(0)} = \exp (-\frac{TE}{T_2})(1-\exp(-\frac{T}{T_1})) \tag{2.7}
\]

where \(TE\) is the echo time, \(T_1\) and \(T_2\) are the longitudinal and transverse relaxation times respectively and \(T\) is the repetition rate.

However if diffusion is present, \(T\) is at least \(5T_1\) and a constant linear gradient is applied then equation (2.7.) becomes\(^6\)
S(TE)/S(0) = \exp\left(-\frac{\text{TE}}{T_2}\right) \cdot \exp \left[ -\frac{\gamma^2 G D \text{TE}^3}{12} \right] \tag{2.8}

as mentioned in 1.2.6.3.

The diffusion coefficient $D$ can thus be calculated if the gradient strength $G$ is known.

2.7.2.1 Pulsed Field Gradients

This technique is limited by a number of experimental problems arising from the static gradient. A better idea is to use pulsed gradients shown in Fig. 2.6 below.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{pulsed_gradients.png}
\caption{Pulsed diffusion gradients.}
\end{figure}

The signal thus generated is given by

$$S(\text{TE})/S(0) = \exp(-\frac{\text{TE}}{T_2}) \cdot \exp \left[ -\frac{\gamma^2 G D \delta^2}{6} \cdot \left( \Delta - \frac{\delta}{3} \right) \right] \tag{2.9}$$

Because the gradient is not on during the r.f. pulses and data acquisition, a greater $G$ can be used which means that lower diffusion coefficients can be measured. Also $\Delta$ can easily be
In an imaging experiment the gradients typically applied in *all three* directions could lead to diffusion related attenuation. This observation has been put forward as a possible source of errors in T2 imaging.\(^{33}\)

Taking account of the imaging gradients leads to a signal given by\(^{33}\)

\[
S(n\text{TE})/S(0) = \exp(-n\text{TE}/T_2) \cdot \exp(-b_n \cdot D) \tag{2.10}
\]

where \(n\) is the number of echoes and

\[
b_n = \gamma^2 \sum_{k=1}^{n} \sum_{l=x,y,z} G_{kl}^2 \delta_{kl} (\Delta - \delta_{kl}/3) \tag{2.11}
\]

where \(l\) is the axis of the gradient pulses and \(k\) is the interval between echoes. This is valid for rectangular non-interlaced pulses with a negligible background gradient.

Carefully done the imaging gradients can be exploited to provide a form of diffusion imaging. Wesbey et al\(^{34}\) used variable sizes of the slice select gradient to obtain different images, comparing them to doped water. The phantom was thinner than the thinnest imaging slice, but for clinical work a constant slice is desirable for purposes of comparison.
2.7.2.2 Spin Echo Diffusion Measurements

Le Bihan et al.\textsuperscript{33} apply additional gradients along the readout axis. The first sequence that they run has no additional gradients to minimize any attenuation due to diffusion. Under these circumstances equation (2.9) reverts back to equation (2.7). The second sequence has the same TE and repetition rate as the first so that the effect of T1 and T2 relaxation are the same but additional gradients are used in the readout direction as shown below in Figure 2.7.

![Diagram](https://via.placeholder.com/150)

*Figure 2.7 Spin echo sequences for diffusion measurements.*
The difference between the two is due entirely to the diffusion factor. The diffusion can be calculated from equation (2.10) hence

\[ D = \log \left( \frac{S_o}{S_{i}} \right) \frac{(b_i - b_o)}{S_{i}} \]  

(2.12)

where \( S_o \) is the signal at the echo. They call this intravoxel incoherent motion imaging. However this sequence is sensitive to all so-called intravoxel incoherent motions which includes microcirculation, so the diffusion coefficient \( D \) should be replaced by an apparent diffusion coefficient ADC.

Ahn et al\textsuperscript{35} put forward a technique very similar to that of Le Bihan, but instead of one sequence with gradients and the other without, their two sequences had different timings of the diffusion gradients (which were the readout gradients).

2.7.2.3 STEAM Diffusion Measurements

Another method of diffusion imaging uses stimulated echoes\textsuperscript{36}. The stimulated echo acquisition-mode (STEAM) sequence consists of three 90° pulses where the second and third pulses are delivered at times \( \tau_1 \) and \( \tau_2 \) respectively, and the first stimulated echo appears at \( \tau_1 + \tau_2 \). This sequence is combined with balanced diffusion gradients which are placed in the interval between the first and second pulses and after the third. For this sequence the echo amplitude is
\[ \ln\left(\frac{M}{M_0}\right) = -\frac{\tau_2}{T_1} - 2\frac{\tau_1}{T_2} - \ln 2 - \gamma^2 D g^2 \delta^2 (\Delta - \delta/3) \] (2.13)

where the symbols mean the same as before. This method is particularly useful for \( T_2 < T_1 \) e.g., in vivo conditions.

2.7.2.4 Fast Imaging Diffusion Measurements

Alternatives to the spin echo and stimulated echo diffusion sequences have been proposed to overcome its limitations in a clinical environment. To measure diffusion coefficients within the body gradients of considerable size are required. The alternative solution by standard techniques is to increase the gradient duration which means increasing the sequence length. This has two effects: a movement towards the upper limit of the acceptable imaging time and an increase in the susceptibility of the sequence to motion artifacts since there is a greater opportunity for movement.

Fast imaging techniques have been suggested by Le Bihan\textsuperscript{37} which use a steady state free procession (SSFP) sequence. The SSFP is a string of r.f. pulses with the same flip angle and constant repetition time. There is an FID after each pulse and an echo signal before each pulse. The echo is made up of a spin echo component and a stimulated echo. As in their previous experiments two sequences are run - one with the gradient present, and the other not. From the two images the ADC can be calculated.
Unfortunately, the gradient factor cannot be calculated for the SSFP pulse sequence using the previous relationship (equation (2.11)) and so must be determined experimentally.

Coincidentally a group lead by Merbolt worked on a similar idea, obtaining diffusion weighted images based on SSFP sequences\textsuperscript{38}. They provided a theoretical description of what they call a CE-FAST sequence (which is essentially the same as Le Bihan’s SSFP-IVIM sequence).

Most recently Echo Planar Imaging has increased further the potential of diffusion imaging\textsuperscript{39} enabling all the data to be obtained within a very short space of time and hence minimizing the effects of motion.
2.6.3 Capillary Flow

As was discussed in section 2.2 microcirculation describes the structure of capillaries that connect the arterious and venous sides of the blood circulation and allow transfer of nutrients and waste products. NMR is able to detect this blood flow in the microscopic capillaries.

Before discussing this however, a matter of terminology arises\(^4\). Capillary flow has long been an important quantity to measure and the flow has been called perfusion. This classical term of perfusion describes the pattern of blood delivery. For example, in isotopic deposition techniques radiolabelled microspheres which are too big to flow in capillaries are injected into the arterious side of the circulation. They then become lodged in the capillary bed or the tissue and can be picked up by PET or radionuclide imaging. The units of this classical perfusion are given as ml/min/100g. However, current NMR techniques measure quite different capillary factors which should be borne in mind when reading the following.

2.7.3.1 IVIM Imaging

It was mentioned that standard diffusion imaging techniques actually provide not the diffusion coefficient but the apparent diffusion coefficient (ADC) which includes all microscopic random motion. This motion can include the microcirculation if there is a random orientation of capillaries. Le Bihan et al\(^31\) proposed a technique of separating out microcirculatory flow from diffusion by
extending their original spin echo technique to include a third sequence with an even stronger gradient. They called it the Intravoxel Incoherent Motion (IVIM) technique. The values of the gradients are such that the diffusion coefficient can be determined from sequences 2 and 3 and this can be used to extract the ‘perfusion’ fraction from sequence 1. (See 6.2.1. for detailed maths). This ‘perfusion’ fraction comes from a simple model that they propose, of a small fraction $f$ of perfused capillaries and a remainder $(1-f)$ of tissue in which only diffusion occurs. Therefore, the perfusion fraction that is measured is actually the fraction of tissue which contains perfused capillaries. The IVIM technique is valid only if the capillaries are *isotropically orientated*. However, it does not matter whether the flow is *incoherent* (changes direction during measurement time) or *coherent* (does not change direction). See Figure 2.8 below for illustration of the two regimes.

![Figure 2.8: Incoherent and coherent flow regimes.](image)

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Again it should be mentioned that EPI has enabled the investigator to obtain images much faster so minimizing the effects of motion and has been effectively combined with Le Bihan’s IVIM technique.

2.7.3.2 Rephasing Techniques

The next technique is only valid when the flow in the capillaries is coherent. It was proposed by Ahn et al\textsuperscript{41} who were able to obtain ‘perfusion’ images by virtue of the fact that coherent flow produces no attenuation at even echoes (even echo rephasing). There are two sequences - the first a single spin echo, the second a double spin echo but with the second echo occurring at the same time as the echo in the first sequence. This produces two images with the same effects of $T_1$, $T_2$ and diffusion. The perfusion image is obtained by subtracting the two images. Another method using a refocusing technique was proposed by Maki\textsuperscript{42}. Instead of a double spin echo to refocus coherent flow they used a spin echo sequence with motion compensating gradient waveforms. The subtraction of the two images yields similar information as the above technique i.e., a map of the perfused blood vessels but again can provide no quantitative measurement due to other irrelevant information such as T2 and proton density represented in the image.
A model of microcirculation which assumes anisotropic distribution of capillaries but again coherent flow was explored by Young et al.\textsuperscript{43} It was mentioned in section 2.7.1.2 that the effect of coherent motion is a phase shift for each voxel. However, flow in capillaries forms only a very small fraction of the total volume and this must be taken account of when measuring the phase. Figure 2.9 below illustrates how the measured phase ($\phi_m$) relates to the flow-related phase ($\phi_v$) of the capillaries.

$$\Phi_m = \tan^{-1}(f \cdot \sin \Phi_v / ((1-f)+f \cdot \cos \Phi_v))$$  \hspace{1cm} (2.14)

$\phi_v$ is given in equation (2.6).

They obtained images of 'perfusion' from phase difference images where the flow encoding gradients are sensitized to the order of 1mm/s.

Figure 2.9 Measured phase in terms of flow-related phase.
2.8 MOTION ARTIFACTS

2.8.1 Occurrence of Artifacts

The appearance of artifacts in MR images is an enormous problem especially in the clinical environment where diagnosis is dependent on an accurate representation. The artifacts considered here are those caused by flow and motion.

There are three categories of errors induced by flow and motion. Firstly there are the view-to-view misregistration errors caused by breathing, heart and great vessel motion, peristaltic gut motion, ocular motion and uncooperative patient motion. Secondly there are the time of flight and saturation errors phenomena described earlier in 2.7.1.1. Pulsatile blood flow will cause the signal intensity to be different between successive data acquisitions. Finally there are motion induced phase errors.

An unexpected addition to an image is called a ghost. It will either add to or subtract from underlying tissue intensity, potentially causing mis-diagnosis. The addition of intensity can result in a bright artifact on a T2-weighted image, the subtraction in a loss of contrast in a T1-weighted image both mimicking certain disease forms.

There are distinct artifacts peculiar to the Fourier or 2DFT imaging technique arising from the separation of frequency and phase encoding. Any movement during a scan will often be very slight during the frequency encoding which has a duration of a few msecs but quite substantial between each phase encoding step which may be of the order of a second or so apart. The effect of this is
to introduce a modulation into the phase encoded data. If the motion is periodic e.g., breathing, then a number of ghosts will appear as a periodically displaced image of the original object in the phase encoding direction. It is important to note that the ghosts appear in the phase encoding direction whatever the direction of the displacement. The separation of the ghosts is given by the total imaging time divided by the period of the motion:

$$Y_{TOT} \times n_{av} \times TR / T$$

(2.15)

where $Y_{TOT}$ is the total number of pixels across the field of view, $n_{av}$ is the number of acquisitions averaged before each new phase encoding step, TR is the repetition rate and T is the period of the motion.

The intensity of the ghosts is proportional to the intensity of the structure and the amplitude of the motion.

2.8.2 Removal of Motion Artifacts

The following is an overview of the different methods employed to remove the artifacts due to flow and motion.

2.8.2.1 Gating

The most obvious way to overcome respiratory motion is to use
respiratory gating\textsuperscript{45}. The basis of this technique is to only accept data which is gained when the position of the abdomen falls inside a certain ‘window’. The respiratory motion is monitored using a transducer\textsuperscript{46}. The data is obtained during the end expiration which is the longest part of the cycle. The use of respiratory gating reduces ghosts and also blurring. The disadvantages of this technique are the much increased acquisition times. This can be partially overcome by applying gating to only part of the data. Another possibility is to trigger the acquisition of data from some part of the breathing cycle. However this is experimentally quite difficult to do and causes variable TR which in turn can lead to ghosts.

\textit{Cardiac gating} is an easier technique to put into practice\textsuperscript{44}. The data acquisition is triggered of the R-wave or alternatively by plethysmographic gating (detection the capillary blush in a finger). Both of which are standard practices. The disadvantages of these are that TR is limited by the cardiac rate which can mean an increase in the imaging time. Patients with an arrhythmia would cause variable TR leading to ghosts again. There is also the inability to reduce motion artifacts not in synchrony with the cardiac cycle. In addition the probes recording the ECG may become detached.
2.8.2.2 Reordering of Phase Encoding

There are a variety of methods to eliminate motion induced artifacts by reordering the phase encoding steps. These include ROPE (respiratory ordered phase encoding)\(^7\) COPE (centrally ordered phase encoding) and *exorcist*. The basic idea is to reorder the phase encoding steps such that the acquisition makes the apparent motion much slower\(^45\). The respiratory motion is monitored as in respiratory gating with the signals being acquired at an arbitrary rate applying a suitable phase encoding gradient depending on the phase of the respiratory cycle. It eliminates ghosts but makes the image slightly more blurred. The blurring depends on the rate at which the displacement varies and also on the order in which the acquisitions are placed\(^48\). There are obvious difficulties in the implementation of this technique due to its complexity.

2.8.2.3 Restraining

A couple of crude but sometimes effective methods of motion artifact reduction are *breath holding*\(^49\) and *physical restraining*\(^45\). Breath holding can be used only when the sequence is short so suiting fast MRI techniques. A drawback of breath holding is that pulsatile blood flow ghosts can become more conspicuous.

Physical restraining can be carried out on the abdomen. This can be restrained by the use of an inflexible band. This method has an additional benefit in that it reduces blurring as well as
ghosting. However there are still motion artifacts due to blood flow and peristaltic motion. The advantage of both these techniques is that no additional software or particular technical expertise is needed to implement them.

2.8.2.4 Hardware Refinements

A rather complex method is to restrict the field of view (FOV)\textsuperscript{44}. This can be achieved by the use of surface coils and image strips. If the FOV is restricted to a part of the body not exhibiting motion then the acquired image should be artifact free.

2.8.2.5 Imaging Sequences

A particular imaging sequence that will reduce the effect of motion artifacts is STIR (short-tau-IR)\textsuperscript{50}. In a sequence with a short $\tau$ the fat gives little or no image intensity and so the ghosts due to moving fat are eliminated. The drawback of this is the resulting low contrast of the image. Also its limitation to a specific ghosting problem.

2.8.2.6 Averaging

Another method of data manipulation is averaging\textsuperscript{45,46,51}. It is a method usually employed to reduce random noise but ghosts can be
removed if each acquisition is taken at a different place. As mentioned before, for different phase encoding steps the phase of the ghosts are different. Averaging gives the opportunity to achieve destructive interference of the ghosts. There is maximum separation of ghosts when the respiratory rate is equal to twice the product of the repetition rate and the number of averages or put another way, when the interval between phase encoding increments are half the respiratory period. The result of maximum separation is that the ghosts will be off the image. The requirement for minimum separation of ghosts is for one cycle of displacement to be spread over the phase encoded sequence. The result of this is that the ghost is folded back onto the original image. This requires twice as much imaging time as maximum separation however. Generally the intensity of ghosts decrease as an inverse function of the number of averages (NSA), though it depends on the mode of motion and the sequence. Also the displacement of the ghosts increases with increasing NSA. Ghosts are reduced additionally due to the reduction of noise.

Disadvantages of averaging are that it does not reduce blurring, the resulting increased imaging time makes it suitable for short TR but this negates the effect of lower image intensity. For T2 weighted images the technique is not practical because of long TR. A short TE gives a better signal-to-noise ratio (unless the sampling time is too short) and reduces the intensity of ghosts.
2.8.2.7 Pre-Saturation Pulses

Another method of reducing flow artifacts and improving the depiction of vascular anatomy is *spatial presaturation*. Errors due to unsaturated spins entering the imaging volume are eliminated by the addition of spectrally shaped r.f. pulses which selectively saturate these regions. Spatial presaturation has the advantage that it is compatible with most pulse sequences and imaging hardware. Disadvantages of this include the fact that a small amount of extra time is required for the presaturation pulses.

2.8.2.8 Gradient Moment Nulling

One of the most frequently used methods of motion artifact reduction to be considered here is MAST or *gradient moment nulling*. This method is unique in that rather than trying to keep the dephasing due to motion constant from view to view it attempts to rephase all the spins at the echo *regardless* of the type of motion which caused the dephasing. It achieves this by the addition of various gradients to the sequence. Motion can be considered as a Taylor expansion of position as a function of time

\[
x(t) = x_0 + vt + \frac{1}{2}at^2 + \frac{1}{3}pt^3 + \text{higher order terms}
\]

(2.16)
where \( x_0 \) is the original position, \( v \) is velocity, \( a \) is acceleration and \( p \) is pulsatility.

Higher orders of motion contribute insignificantly to the effect. The phase is given by

\[
\phi = \gamma \int_0^t G(t') \cdot x(t') \, dt'
\]

(2.17)

The idea of MAST is that equation (2.17) is set to zero and (2.16) is solved for \( G(t) \). This is done independently for the read gradient and the slice select gradient. There is negligible effect from the phase encoding gradient for a number of reasons. It is only on once for each signal acquisition and then for a relatively short time. Further it introduces the least amount of phase shift around the central views of the data area which corresponds to the majority of the signal.

Multiple echo sequences allow different orders of motion to be compensated for in different echoes of the sequence as required.

In general the order of MAST correction depends on the shortest TE required since the higher the order of correction the larger the number of additional gradient pulses are needed.

The technique works best at high fields due to the fact that artifacts are most prominent at high field strengths.

There are problems associated with MAST. Blurring due to motion is not compensated for, small calibration errors can lead to significant phase effects when the velocity is large, there are problems of finite gradient rise times and associated eddy currents and the problem of limited gradient power output may
limit the number of slices allowed in a multislice sequence.

MAST is not helpful if you actually want to see motion but this can be overcome to some extent by designing the sequence so that incomplete rephasing occurs but enough signal remains to give information of the velocity present.

2.8.2.9 Additional R.F. and Gradients

Finally there are techniques which use additional pulses or gradients to give information on the motion occurring within the scan and so either discard the data or use it to modify the reconstruction. One technique is to place a small object (which will produce an NMR signal) next to the patient in such a way that patient motion will obscure its signal. If the signal is below a certain threshold then ideally the sequence would be aborted, but this is not possible in practice, so a predetermined number of acquisitions at each phase encoding step are taken, and the data from the one which provides the greatest signal is kept. Obviously this increases imaging time dramatically so an alternative would be to detect in which data acquisition cycle the patient moved (by looking at the signal from the object) and either redoing that acquisition or extrapolating the data from either side. A non-NMR method of doing this would be to use an external triggering mechanism such as a light beam.

The other technique is to look at the projection data which is a line integral along the direction of the frequency encoding gradient. The magnitude of the projection data varies according
to the cardiac cycle and the boundary of the projection data varies according to the respiratory cycle. Applications of this are made to cardiac and abdominal imaging respectively.

Cine mode imaging was used for cardiac imaging (employing an SSFP sequence rather than a gradient echo), with additional gradients which cause a ‘projection’ signal before the conventional NMR signal. The cardiac cycle can be derived from the projection data, so the data can be arranged according to this rather than to a conventionally measured cardiac cycle.

Abdominal imaging used a technique called POPE (projection ordered phase encoding). It is similar to ROPE in that the state of the motion determines the phase encoding gradient to be applied. After each data acquisition the projection data is examined to determine the state of the motion. This is used to select the next phase encoding step from a previously compiled look-up table.
3.1 MRI SYSTEM

The MRI system used for this programme of research was a complete overhaul of a home built system which had been established between 1983 and 1989. The only components retained were the gradient power amplifiers which were reconditioned. The block diagram below in Figure 3.1 shows the basic elements of the system.

Figure 3.1 Schematic diagram of basic elements of MRI system.
The author built an r.f. coil, an insert gradient, phantoms and also wrote a number of pulse sequences and other software.

3.1.1 Multiprocessor Unit

Figure 3.2 illustrates the components of the multiprocessor unit.

The computer (hardware and software), data processing cards, and pulse sequence controller form the multiprocessor unit supplied by S.M.I.S. Ltd (Guildford, U.K.). The 386 host computer runs under Microsoft Windows. The package enables pulse programs to be written using a C-like language and then compiled. Input parameters are chosen and the program can then be run in either set-up mode where the user can view the signal and change parameters, or in acquisition mode where data is acquired. The software enables subsequent images to be reconstructed, and spectra to be analysed. There is also control over the IP2000 image display board which enables data processing and manipulation.
The pulse sequence controller consists of a pulse processor and a waveform generator. The pulse processor controls output from the waveform generator which stores user defined r.f. and gradient waveforms. These waveforms are called as appropriate during sequence execution.

The data processing cards consist of data acquisition: two ADCs running at either 16bit 100kHz or 12bit 400kHz, and the array processor which allows rapid data processing.

### 3.1.2 R.F. Sub-System

Figure 3.3 below illustrates the r.f. sub-system.

![RF Sub-System Diagram](image)

The system can be separated into three functional systems: transmit, receive and probe.
3.1.2.1 Transmitter System

Figure 3.4 shows the basic elements of the transmitter system.

The PTS frequency synthesizer generates a continuous waveform of the required frequency (21.24MHz for a 0.5T operating field strength). The signal is modulated by an appropriate waveform from the waveform generator board, and gated then attenuated or amplified interactively by the user before entering the power amplifier (ANALOGIC AN8061 1kW solid state). To cut down on noise transmission the amplifier is also gated. What comes out of the transmit system is an appropriately modulated, gated and amplified r.f. signal.

3.1.2.2 R.F. Coil System

Figure 3.5 overleaf shows the components of the coil system.
The purpose of this system is to allow transmission and reception using just one r.f. coil. Built into the design is protection for the pre-amplifier and reduction of noise from the main transmit amplifier.

The system consists of three $\lambda/4$ transmission lines where $\lambda$ is the wavelength of the r.f. radiation in the cable. Transmission lines are essentially transformers which transform impedance and voltages. A line of length $\lambda/4$ will transform a low impedance to a high impedance and vice versa. A $\lambda/2$ line will transmit exactly the impedance (or voltage) at one end to the other.

In transmit mode the r.f. at A has two choices: either into the
coil at C, or along to B. The diodes at B are switched into conductance by around 0.5V which is much less than the size of the transmitted pulse, so acting as an open circuit. This open circuit will be transformed to very high impedance at A, λ/4 away. Therefore the transmitted signal power primarily goes to the coil. The residual 0.5V across the diodes at B however leads to a temporary saturation of the transistors in the pre-amplifier (which are sensitive to operating voltages of the order of microvolts) and a ‘dead-time’ of the receiver.

In receive mode there is a choice of path for the r.f. signal: a λ/2 path along to the transmitter, or a λ/2 path to the pre-amplifier. The transmitted r.f. is not large enough to operate the diodes along either of the paths, so the only route available is direct to the pre-amplifier.

The r.f. transmit amplifier should be blanked in receive mode, but some noise still gets through. An additional purpose of the diodes at A' is to reduce noise from the transmitter.

3.1.2.3 Receiver System

Figure 3.6 overleaf illustrates the basic components of the receiver system.

The signal from the pre-amplifier undergoes full amplification on entering the receiver. The frequency is usually of the order of tens of megahertz which quite apart from being a high frequency can have a large range e.g. 10-300MHz.
For a 7T (300MHz) magnet resonance frequencies of $^{13}\text{C}$, $^{19}\text{F}$ and $^{31}\text{P}$ are 75, 235 and 121MHz respectively.

The r.f. signal can have a bandwidth of 250kHz centred on the resonance frequency. It is desirable for signal processing reasons to have the NMR signal being carried on a fixed frequency which is called the intermediate frequency or IF. This is accomplished using a mixer. It takes in the resonance frequency ($f_r$) plus signal (S) and 'mixes' it with the difference between $f_r$ and the IF (which is supplied by a frequency synthesizer). The output of the mixer is the sum and the difference of the two inputs i.e.,

\begin{align}
\text{IF } &\pm S \tag{3.1} \\
2f_r - \text{IF } &\pm S \tag{3.2}
\end{align}

$f_r$ is typically 300MHz, and the IF is 2MHz for this system. Therefore, with a low pass filter, the higher frequency signal is taken out leaving the IF and the signal.

In order to analyse the NMR signal it is desired to have phase information on the signal and it is also necessary to bring the
frequency down to the audio range i.e., kHz.

This is achieved by the following arrangement shown in Figure 3.7.

\[ B \sin(\omega_r t) \]

\[ \longrightarrow \]

\[ A \sin(\omega_s t + \phi) \]

\[ \longrightarrow \]

\[ A B \sin[(\omega_s - \omega_r) t + \phi] \]

\[ B \cos(\omega_r t) \]

\[ \longrightarrow \]

\[ A \sin(\omega_s t + \phi) \]

\[ \longrightarrow \]

\[ A B \cos[(\omega_s - \omega_r) t + \phi] \]

\[ \longrightarrow \]

\[ \text{Phase sensitive detection.} \]

The signal is split up into two channels and enters a phase sensitive detector (PSD). A mixer is again used. This time the mixing frequency is at the IF (2MHz). This leads to 2IF+/-S and +/-S. The higher frequency is again eliminated by a low pass filter. The IF is provided by a 2MHz oscillator and puts a 90° phase shift on the IF entering channel 2.

The result is two signals in the correct frequency range with a 90° phase shift between them.

The digitizer samples the discrete points at a frequency which fulfills the Nyquist theorem i.e., sampling must be done at least twice per wavelength cycle in order to resolve the actual frequency.
of the signal.

3.1.3 Probe

The specifications for the probe were that it should have a good signal-to-noise ratio, the ability to be tuned over a wide range of loads (to encompass phantoms and human extremities) and to fit within the insert gradient (see 3.1.4.1). The type of coil most near to fitting these specifications is a birdcage coil which consists of a 'ladder' of copper tape around a cylindrical former as in Figure 3.8 below.

![Diagram of birdcage coil](image)

*Figure 3.8* Icematic diagram of birdcage coil.

The resonant frequency of the birdcage coil is determined by the capacitance and inductance by a relationship *approximately* given by

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The inductance depends upon the structure of the coil, and the capacitance is dependent upon capacitors soldered between the ends of the 'legs' and one of the end rings. Two variable capacitors are soldered onto opposite sides of the coil, one for tuning, one for matching.

The coil works along the same lines as transmission lines. When correctly tuned a standing wave is set up along the end rings which causes nodes and antinodes in the current flow. Where there is maximum current - in 2 legs opposite from each other there is maximum magnetic field generated. In the centre of the coil there will be a uniform field. Each of the legs will also produce magnetic fields with the net effect of a homogeneous magnetic field in a large volume of the coil. The coil tuned well and proved to be the most stable of the existing coils.

3.1.4 Gradient System

The gradient waveforms that are produced by the pulse sequence generator travel through a pre-emphasis unit on their way to the gradient amplifiers. A pre-emphasis unit is required because the gradient coils produce time dependent gradients which then generate eddy currents in the body of the magnet. Inside the unit there is circuitry designed to produce exponentials and other offsets which when added to the gradient waveforms will produce a shape capable of compensating for the effects of the eddy currents (more detail
in 5.3.1).

The modulated waveforms then go to the gradient amplifiers. These are Amcron amplifiers designed to be used as audio amplifiers. There are two per gradient axis, each capable of delivering a peak current of 38A for 5-10msec, and an RMS current of 16A. The amplified gradient waveforms go to the gradients via shielded coaxial cables (to shield out r.f and other extraneous noise) and filter boxes (one for each axis) containing low pass filters designed to eliminate extraneous signal.

The gradients are a saddle coil design with 19 turns per gradient axis. This combination of amplifiers and gradients produced a maximum gradient strength of 6mT/m.

3.1.4.1 Insert Gradient

A maximum gradient strength of only 6mT/m would probably be enough for some standard diffusion work, but not nearly enough for quantitative perfusion measurements. An example calculation in a later chapter (6.2.1.) shows the requirement to deliver gradients of 32.8mT/m. (This requirement would only be for one imaging axis for the author’s applications). The z-axis would be most useful because flow along the longitudinal axis of the body can be most readily observed. A z gradient is also the easiest of the three to construct since it is essentially just a Helmholtz coil i.e. two counter-wound coils separated by a distance which produces optimum field gradient uniformity.

The author must acknowledge Fred Goldie (S.M.I.S.) as supplying
the expertise in the design of this gradient coil. A specification of 114mT/m for a half-sine gradient of duration 10ms was the target for the design which went as follows. The length (l) of the coil was 40cm to allow enough room such that the gradient was uniform in the region of the brain given that the gradient set would sit on the shoulders of a human subject. The radius of the coil was 17.5cm which does not fulfill the optimum separation of length = \sqrt{3} \times \text{radius}, but it is within reasonable range. Sixty turns of wire were required to produce a gradient strength in the region of 114mT/m given these dimensions and the capability of the gradient amplifiers. All of the calculations had to be done with the resulting inductance in mind, which with these parameters was estimated to be about 4.5mH. The gauge of copper wire was 2.75mm - the limiting factor on this was the RMS current density of the wire. Also, with this gauge of wire the heat dissipation is of the order of 300W, which is tolerable for a scan with a low gradient duty cycle.

Soft 99% pure copper was carefully wound around a wooden former of the correct dimensions to fulfill the above criteria and also to allow a birdcage r.f. coil to fit snugly in place within it. Wood was the most readily available material although it should be pointed out that bakolite would probably be the most suitable material for the job due to its strength and ability to dissipate heat. The wire was held in place by smearing quick-set epoxy adhesive in between the layers.

Figure 3.9 overleaf is a photograph of the insert gradient and r.f coil.
3.1.4.1.1 Testing of the Insert Gradient

The testing of the gradient was two-fold. As a quick test, there was an examination of the gradient produced from a plot of the magnetic field measured at various points using a Hall probe and Gauss-meter. The readings were only accurate to +/-0.2 Gauss but the Figures 3.10 and 3.11 (overleaf) - longitudinal and radial plots - indicate consistent measurements.
Figure 3.10 Longitudinal plot of field strength in Gauss.

Figure 3.11 Radial plot of field strength in Gauss at 4cm and 45° intervals.

All of these readings were taken with a voltage of 1.6V and a current of 4A.
A much more rigorous testing was then undertaken. The gradient was calibrated by running a program which uses the gradient under analysis as a frequency encoding gradient i.e., it is applied during data acquisition. The size of the resulting profile in frequency space enables the actual applied gradient to be calculated.

The program allows the user to specify values 0 to 2047 representing the current in the gradient.

Figure 3.12 below is a plot of the calculated gradient strength versus applied current.

![Figure 3.12 Plot of gradient strength with increasing voltage.](image)

The linearity of the gradient is very good but there was a problem with the maximum strength achieved. It is only 64mT/m as opposed to the 114mT/m required. There are a couple of contributory factors. Firstly, the calculations were done assuming the gradient amplifiers could produce 70A (peak current) whereas in fact their
measured peak turned out to be 54A. Secondly the pre-emphasis box had a DC offset which reduced the maximum voltage obtainable.

One major problem which came to light when calibrating the gradient was the limitation of an inductance of 4.5mH. The high inductance manifested itself in the current monitors of the gradient amplifiers registering a much higher current than had been applied i.e., large overshoot. The only solution to this problem was to ramp the gradients at a much slower rate - 4ms as opposed to 1ms (for the whole body gradients). This long ramp time was to prove a severe limitation in the experimental work.

3.1.4.1.2 Interaction Between Insert Gradient and R.F. Coil

The manner in which the r.f. coil is inserted into the gradient set, with the turns of the gradient coil being physically very close to the outer copper strips of the r.f. coil, may suggest problems of interaction. Fortunately this proved not to be the case other than a slight (10%) decrease in the Q factor of the r.f. coil which is acceptable.
3.1.5 Magnet

The magnet is a 0.5T 850mm super-conducting and actively shielded Oxford magnet. Cooling is via recycled liquid helium which has a boil off rate of 0.25l/hr necessitating refilling at approximately three weekly intervals. The shimmed magnet peak to peak homogeneity using Oxford passive shims was better than 5ppm over a 30cm diameter.

3.2 PHANTOMS

A number of different phantoms have been used by other investigators to demonstrate diffusion and perfusion imaging. Diffusion phantoms are usually very simple - a small container of liquid most usually water or acetone.

Perfusion phantoms are a little more varied and depend upon what sort of sequence is being undertaken. For anisotropic flow a dialysis filter was used. For coherent but isotropic flow Ahn used a ball made from winding a 1mm diameter plastic tube through which flow was driven by gravity. For isotropic flow at smaller scales Duewell used an anion-exchange resin which consists of small beads with an average size of 450µm. Another increasingly common phantom is made from Sephadex - used by chemists in chromatography tubes. It consists of tiny beads which when wetted expand and form a gel. Sephadex is relatively inexpensive and easy to obtain and so was used in the construction of the phantom.

The body of the phantom consisted of a perspex tube of diameter
38.5mm and length 70mm with push on nylon ends. See Figure 3.13 below.

![Image](image.jpg)

**Figure 3.13 Sephadex perfusion phantom.**

Into the nylon ends were screwed nylon connectors for the fluid to travel in and out of. The beads of the Sephadex can easily be squashed, ruining their uniformity and tissue ‘equivalence’ so great care had to taken in transferring the wetted beads into the phantom.

Over the ends of the perspex tube inside the nylon ends was stuck disks of nylon fabric of such a gauge that would allow fluid flow but not the transferance of the beads.

Sealing the nylon to the perspex proved to be a significant problem when fluid was flowing at the higher flow rates and resulted in the phantom being reconstructed three times - with unavoidably different amounts of Sephadex.

Initially the seal was made with PTFE tape (Mk I), then epoxy adhesive was used (Mk II), and finally and most successfully with copious amounts of aquarium sealant (Mk III).
A Pye Unicham pump was used to drive the fluid through the flow phantom. It had a range of flow rates from 0 to 9.9mls/min in increments of 0.1mls/min which is within the range of flow rates that have been used by other investigators.

3.3 PRESSURE CUFF

For some of the in-vivo work of Chapter Six it was necessary to use a pressure cuff of the type used to measure blood pressure. It was initially attached to a pressure gauge but because it was ferromagnetic, it was removed and the appropriate air holes sealed.

3.4 PULSE SEQUENCES

The experiments carried out for this research used standard pulse sequences: single and double spin echoes - the only slight variation being for the in-vivo work which used orthogonal slice selection. The greatest problem encountered in designing the pulse sequences was the limitation of a 4ms 'ramp up to' and 'down from' the z-gradient waveform. Short echo times were out of the question with this limitation and so led to some quite significant problems with the signal-to-noise ratio compounded by the 50Hz effect (see 3.4.1).

The requirement that the second echo of the double echo sequence be concurrent with the echo of the single echo sequence (6.1.1) meant that time available was twice as limited for the double echo
sequence. The timing diagram in Figure 3.14 below shows the r.f. and gradients for a double echo flow encoding sequence.

![Figure 3.14 Double echo flow encoding sequence.](image)

In this sequence the slice is in the z-plane which is what is desired and the 90°-pulse does the slice selection. However, it takes more valuable time for the slice gradient to come down and form the rephase lobe than it would do if the slice was done on the 180-pulse, as in Figure 3.15 below.

![Figure 3.15 Selective 180° pulse.](image)

The time required for this was still too long, and so it was decided to combine the flow encoding and the slice selection giving Figure 3.16 overleaf.
This was relatively easy to incorporate into the sequence although some of the experiments required a variation in the size of the flow encoding gradients. This could not be done in isolation from the slice selection gradient and so different gradient waveforms needed to be inserted so that the slice select gradient was kept at the same strength whilst the flow encoding gradient increased in magnitude.

For the in-vivo work where it was desired to select a column there needed to be slice selection on both the $90^\circ$ and $180^\circ$-pulses which lead inevitably to a longer echo time and hence poorer signal-to-noise.

3.4.1 50Hz Effect

It was noticed that in images where the half echo time (in msecs) was not divisible by 20 there was significant ghosting. For echo times of 40 and 80 msecs there was no apparent problem.

It was deduced that the sequence was being adversely affected by the 50Hz mains cycle. For ‘problem’ echo times the 90- and 180-pulses would occur at different points along the mains cycle.
See Figure 3.17 below.

Figure 3.17 Occurrence of 90° and 180° pulses with respect to mains cycle.

It does not matter how long the repetition rate is, just that the 90° and 180°-pulses are at the same phase. This problem was intermittent and it was possible to have a half echo time of 22 msec before the problem became too obvious.

With the SMIS console it was possible to gate the start of the sequence to an external reference which in this case needed to be the mains signal. A number of home built circuits were included into the electronics to do this. They basically took a stepped down part of the mains signal, rectified it and formed a square wave from it. Lines of code were inserted into the sequence which required a short loop to be executed until a falling edge of the signal was detected - upon detection of this the r.f. pulse was triggered. This was done for both pulses which ensured that they were both at the same phase.

The exercise was not entirely successful because it could take a
while for the 180-pulse to be triggered if the falling edge was missed so there could be a timing error which would again lead to a phase error, and ghosting on an image.
CHAPTER FOUR

COMPUTER SIMULATION
4.1 INTRODUCTION

A number of simulations have been written. Most are simple and designed for a specific purpose such as analysing signal-to-noise requirements (5.3.2). There are some simulations that are more complex and written in a similar way to the one described in this chapter. One at least is available for purchase, generally for teaching purposes. None however offer the range of flow and motion variables that this one does.

The main objective of writing this simulation was to build a tool for theoretical analysis of flow experiments and hence to assess their viability. There are numerous advantages in running a computer simulation over carrying out any sort of experiments in the lab.

Probably the most important advantage is the reproducibility inherent in a simulation. With so many factors that could change in a lab situation from day to day such as gradient matching, pulse lengths, coil tuning and flow rate, it would be hard to make a perfect comparison of techniques or to repeat a technique changing just one parameter without repeating the experiment many times. The simulation only needs to be run once - the results would always be the same.

Following on from this, there are no hardware limitations to the simulation. For example in a standard diffusion experiment large gradients are used which lower the signal-to-noise ratio so a number of averages are required which increases the imaging time. In the simulation multiple averaging does not have to be done unless the user wants to investigate the effects of averaging.
sequence which contains simulated noise.

The situation in a real system under investigation is never simple. For example in a perfusion phantom (see 3.2) there will be diffusion and ‘perfusion’ and perhaps a degree of macroscopic motion. These factors will be present in different amounts along different axes. The simulation allows the user to specify exactly the model that they desire with no unknowns.

Finally, modelling various flow effects in the simulation increases understanding of how these will affect the MRI experiment in the lab environment, hence it compliments the practical work.
4.2 THE BLOCH EQUATIONS

The Bloch equations² form the basis of the simulation because they describe the motion of the magnetization and any NMR imaging sequence can be broken down into the effect that various components of the equations have on the net magnetization of the nuclei.

4.2.1 Solution to the Bloch Equations

To solve the Bloch equation two assumptions are made about what happens during the r.f. pulse⁶¹:
(a). $B_t \approx B_o - \omega/\gamma$ and
(b). Relaxation effects are negligible.

The equation is then solved for two different situations: during the r.f. pulse and between the r.f. pulses. During the r.f. pulse the resultant magnetization can be written in terms of a rotation matrix $P$, and the initial magnetization $M(0)$

$$M(t) = P(t)M(0)$$  \hspace{1cm} (4.1)

where

$$P(t) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\beta & \sin\beta \\ 0 & -\sin\beta & \cos\beta \end{bmatrix}$$  \hspace{1cm} (4.2)

and where $\beta = \gamma B_t t_p$ is the angle through which the magnetization is
tipped through about the x-axis by a pulse of length $t_p$.
(See Appendix 1).

Between pulses, the solution of the Bloch equation is

$$M(t) = R(t)M(0) + M_0[1 - \exp(-t/T_1)]k$$  \hspace{1cm} (4.3)

where the relaxation operator $R(t)$ is given by

$$R(t) = \begin{bmatrix}
\exp(-t/T_2)\cos\delta\omega t & -\exp(-t/T_2)\sin\delta\omega t & 0 \\
\exp(-t/T_2)\sin\delta\omega t & \exp(-t/T_2)\cos\delta\omega t & 0 \\
0 & 0 & \exp(-t/T_1)
\end{bmatrix}$$  \hspace{1cm} (4.4)

and where $\delta\omega = \omega - \omega_0$ and $\omega_0 = \gamma B_0$. (See Appendix 2).

From (4.1) and (4.3) it is possible to calculate the effect of any pulse sequence on the magnetization.

For example, one "pulse cycle" (illustrated in Figure 4.1) i.e., a time interval of $T$ followed by an r.f. pulse of length $\tau$ can be broken into two steps:

![Figure 4.1. One "pulse cycle".](image)
After relaxation of $T$ :

$$
\bar{M}^- = R(T)M(0) + M_o [1 - \exp(-T/T_1)]^k
$$

(4.5)

After pulse $\tau$ :

$$
\bar{M}^+ = P(\tau)R(T)M(0) + M_o (1 - E_1^p) P(\tau)^k
$$

(4.6)

where $E_1^p = \exp(-T/T_1)$ $M_o$ is the magnetization at the start of the pulse cycle and other variables are those indicated in Figure 4.1.

If a steady state is achieved, i.e., the time that an identical train of pulses is maintained is large compared to $T_1$ so that the magnetization from pulse cycle to pulse cycle is the same, then $\bar{M}(0) = \bar{M}^+$. Substituting this into the previous equation we obtain

$$
\bar{M}^+ = M_o (1 - E_1^p) [P^+(\tau) - R(T)]^k
$$

(4.7)

4.2.2 Derivation of Bloch equations modified by gradients and flow

In equation (1.53) it was stated that

$$
B_{eff} = (B_0 - \omega/\gamma)\hat{k} + B_1\hat{z}
$$

However, if a gradient is present then this becomes

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where \( G_{rk} = (G_x + G_y + G_z)k \)

Macroscopic flow can then also be incorporated by a Taylor expansion i.e.,

\[
r(t) = r_0 + vt + \frac{at^2}{2} + \text{higher order terms} \tag{4.9}
\]

Therefore equation (4.8) becomes

\[
B_{\text{eff}} = B_i + (B_0 - \omega/\gamma)k + G.rk \tag{4.10}
\]

for the case when flow is present.

### 4.2.3 Solution to Modified Bloch Equations

It is assumed that there are no gradients applied during the r.f. pulses, therefore there will be no detected flow during these times and the rotation (or pulse) matrix \( P(t) \) will not be affected.

The relaxation operator \( R \) retains its form as below

\[
R(t) = \begin{bmatrix}
\exp(-t/T_2)\cos(*) & -\exp(-t/T_2)\sin(*) & 0 \\
\exp(-t/T_2)\sin(*) & \exp(-t/T_2)\cos(*) & 0 \\
0 & 0 & \exp(-t/T_1)
\end{bmatrix}
\tag{4.11}
\]
but the asterisks become the following for different circumstances:

(i). For no gradient and no flow:
\[ \delta \omega t \text{ (as before)} \]  
\[ (4.12) \]

(ii). For a gradient but no flow:
\[ \delta \omega t - \gamma G_r t \]  
\[ (4.13) \]

(iii). For a gradient and velocity:
\[ \delta \omega t - \gamma G_r t - \gamma G_v v t^2/2 \]  
\[ (4.14) \]

(iv). For a gradient, velocity and acceleration:
\[ \delta \omega t - \gamma G_r t - \gamma G_v v t^2/2 - \gamma G_a a t^3/3 \]  
\[ (4.15) \]

(See Appendix 3).

4.2.4. Numerical Solution to the Bloch Equations

For a 3D simulation i.e., simulated 3D object, providing a 2D image, a slice selective pulse may be required. This will involve the simultaneous application of a gradient and an r.f. pulse. Therefore the assumption made that \( B_1 > B_o - \omega t / \gamma + G_r t \) is no longer valid, necessitating the need for a numerical solution to the Bloch equations. (See Appendix 4). Magnetizations \( M_x, M_y \) and \( M_z \) are given overleaf.
\[ M_x(\Delta t) = M_x(0) \]

\[ + \frac{\gamma \Delta t(B_0 - \omega / \gamma + G.r)(-M_x(0)\gamma \Delta t(B_0 - \omega / \gamma + G.r) + M_y(0) + M_z(0)\gamma \Delta t B_1(\Delta t))}{(1 + \gamma^2 \Delta t^2((B_0 - \omega / \gamma + G.r)^2 + B_1(\Delta t)^2)} \]

\[ (4.16) \]

\[ M_y(\Delta t) = \frac{-M_x(0)\gamma \Delta t(B_0 - \omega / \gamma + G.r) + M_y(0) + M_z(0)\gamma \Delta t B_1(\Delta t))}{(1 + \gamma^2 \Delta t^2((B_0 - \omega / \gamma + G.r)^2 + B_1(\Delta t)^2)} \]

\[ (4.17) \]

\[ M_z(\Delta t) = M_z(0) \]

\[ + \frac{\gamma \Delta t B_1(\Delta t)(-M_x(0)\gamma \Delta t(B_0 - \omega / \gamma + G.r) + M_y(0) + M_z(0)\gamma \Delta t B_1(\Delta t))}{(1 + \gamma^2 \Delta t^2((B_0 - \omega / \gamma + G.r)^2 + B_1(\Delta t)^2)} \]

\[ (4.18) \]

They need to be solved for a large number of time increments which inevitably increases the duration of the simulation.

### 4.3 FACTORS INCORPORATED INTO THE SIMULATION

This simulation will be used to analyse current diffusion and perfusion MRI techniques and will incorporate such things as eddy currents and motion artifacts. All these factors must therefore be included.
4.3.1 Macroscopic Flow

Velocity, acceleration or any order of macroscopic flow can be incorporated into the simulation by the appropriate inclusion of (i) to (iv) from section 4.2.4 into the relaxation operator.

4.3.2 Diffusion

In order to input diffusion into the relaxation operators it is necessary to build a model for this flow phenomenon. The mathematical model of the diffusion process was first proposed back in the 1950s - in the early days of NMR. The following is a derivation which comes from Stejskal\textsuperscript{62} (which in turn came from Torrey\textsuperscript{63}). The derivation considers the change in magnetic moment in a volume element $\Delta V$ and the axes are oriented arbitrarily with respect to the field direction. The nuclear spins are quantized along the $z$ axis initially. Diffusion current densities $j$ representing flux of spins are given by

$$j = D \nabla n$$  \hspace{1cm} (4.19)

where the positive and negative signs represent the direction of flux, $n$ the densities of either the positively or negatively oriented spins and $D$ the diffusion tensor. The diffusion current density of magnetization is written as
\[ \mu(j \cdot j) = -D \cdot \nabla M_z \quad (4.20) \]

where \( \mu \) represents the magnetic moment of a single spin and \( M_z \) the 
z component of the magnetic moment per unit volume.

Consider the flux through the element of volume \( \Delta V \):

\[
(\partial M_z / \partial t)_D = -1/\Delta V \int \mu(j \cdot j) \, d\sigma = 1/\Delta V \int \nabla \cdot D \cdot \nabla M_z \, d\sigma
= \nabla \cdot D \cdot \nabla M_z \quad (4.21)
\]

(By Divergence Theorem - see Appendix 5)

The other two components of the nuclear magnetization are derived in the same way, giving the modified Bloch Equation:

\[
\frac{\partial M}{\partial t} = \gamma M \times B - \left( M_x i + M_y j \right)/T_2 + \left( M_o - M_z \right)k/T_1 + \nabla \cdot D \cdot \nabla M \quad (4.22)
\]

However, it is not possible to solve this equation in the same way as in Appendices 1 and 2. Le Bihan et al. \(^64\) found a way around this and the following is a brief summary of the analysis.

The relevant operator in the rotating frame can be thought of in general terms as

\[
R(t) = \begin{pmatrix}
\exp(-t/T_2) \cos\Phi(r,t) & \exp(-t/T_2) \sin\Phi(r,t) & 0 \\
\exp(-t/T_2) \sin\Phi(r,t) & \exp(-t/T_2) \cos\Phi(r,t) & 0 \\
0 & 0 & \exp(-t/T_1)
\end{pmatrix}
\]

(4.23)
where $\Phi(r,t)$ is the dephasing acquired by isochromatic spins at location $r$.

In the presence of incoherent spins there is a distribution of dephasings in each voxel and $R(t)$ must be averaged in each voxel according to the Theorem of the Central Limit (Appendix 6):

$$<D(t)> = \begin{pmatrix}
\exp(-t/T_2)\langle\cos\Phi(r,t)\rangle & \exp(-t/T_2)\langle\sin\Phi(r,t)\rangle & 0 \\
-\exp(-t/T_2)\langle\sin\Phi(r,t)\rangle & \exp(-t/T_2)\langle\cos\Phi(r,t)\rangle & 0 \\
0 & 0 & \exp(-t/T_1)
\end{pmatrix}
$$

(4.24)

The position of the spins in the diffusion process can be described by

$$r(t) = r_0 + u(t) \quad \text{with } u^2 \ll r^2
$$

(4.25)

where $r_0$ is the fixed voxel location and $u(t)$ the instantaneous displacement in the voxel.

The dephasing $\Phi(r,t)$ can then be written as

$$\Phi(r,t) = \Phi_{r_0}(t) + \Phi_u(t)
$$

(4.26)

with

$$\Phi_{r_0}(t) = \gamma \int_0^t G(r,t_0) dt
$$

(4.27)
\[ \Phi_u(t) = \gamma \int_0^t G_u \, dt \]  

(4.28)

where it is assumed that the field inhomogeneities described by an instantaneous linear gradient \( G \).

Now, averaged quantities \( D(t) \) may be written:

\[
\langle \cos \Phi(r,t) \rangle = \cos \Phi_r(t) \langle \cos \Phi(t) \rangle - \sin \Phi_r(t) \langle \sin \Phi(t) \rangle \\
(4.29)
\]

\[
\langle \sin \Phi(r,t) \rangle = \cos \Phi_r(t) \langle \sin \Phi(t) \rangle + \sin \Phi_r(t) \langle \cos \Phi(t) \rangle \\
(4.30)
\]

Since diffusion is a pure random motion, parity considerations require that

\[ \langle \sin \Phi_u(t) \rangle = 0 \]  

(4.31)

and taking into account the normalized phase distribution in the voxel \( p(\Phi_u,t) \)

\[
\langle \cos \Phi(t) \rangle = \int_0^{2\pi} \cos \Phi(t) p(\Phi_u,t) \, d\Phi_u \equiv A(t) \\
(4.32)
\]

Since \( A(t) \leq 1 \), the effect of diffusion will be an attenuation of the signal. Putting this altogether the averaged relaxation operator is given by
A(t) can be deduced by the following

Diffusion may be described by the probability $P(u,t)$ that molecules will have displacement $u$ during a time interval $t$. In the case of the free Brownian diffusion this probability is

$$P(u,t) \, du = (4\pi Dt)^{-3/2} \exp\left[-u^2/(4Dt)\right] \, du$$

(4.34)

In a given direction i.e., the direction of the gradient $G$

$$P(u,t) \, du = (4\pi Dt)^{-3/2} \exp\left[-u^2/(4Dt)\right] \, du$$

(4.35)

The relationship between displacements and dephasings is given by equation (4.28). An equation may now be derived using the phase angle as the independent variable. From this it is easily shown that the distribution of dephasings $p(\Phi_u,t)$ will also be a Gaussian distribution,

$$p(\Phi_u,t) = (2\pi\sigma_u^2)^{-1/2} \exp\left[-\Phi_u^2/(2\sigma_u^2)\right] \, d\Phi_u,$$

(4.36)

with a variance

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where

\[ k = \gamma \int_0^t G \, dt \]  

(4.38)

In the case of a Gaussian distribution centred at 0 it is generally true that \( <\cos(x)> = \exp(-\sigma^2/2) \). Thus we obtain for molecular diffusion

\[ A = \exp(-bD), \]  

(4.39)

where \( D \) is the diffusion coefficient and \( b \) a gradient factor defined by

\[ b = \int_0^t k^2 \, dt \]  

(4.40)

The variable \( b \) must be calculated for each time that the relaxation matrix is used (with the appropriate time variables).

4.3.3 Pseudo-Diffusion Model

The pseudo-diffusion model of perfusion is the same as that of
diffusion i.e., a series of random walks of average length $\frac{1}{v}$ and velocity $v$. However, these ‘walks’ are on a slightly different scale - reduced by a factor of about ten. Therefore, pseudo-diffusion can be incorporated into the simulation in a manner exactly analogous to diffusion with the user inputting the appropriate variable.

4.3.4 Coherent Perfusion Model

The coherent model of perfusion is basically flow that may go in different directions, but will not change direction during the measurement time. Ahn$^{41}$ and Le Bihan$^{66}$ have both modelled this phenomena in similar ways and the following is a compilation of the two derivations.

The dephasing $\delta \Phi_j$ of the transverse magnetization of a population $j$ of spins moving within a voxel during a time interval $T$ is given by

$$\delta \Phi_j = \gamma \int_0^T \mathbf{v}_j(t) \cdot G(t) \, dt$$

(4.41)

where $\mathbf{v}_j$ is the instantaneous velocity and $G$ is the gradient vector.

If the perfusion is coherent then the above equation simplifies to
\[ \delta \Phi_j = v_j (\gamma \int_0^T G(t) \, dt) = v_j c \]  

(4.42)

where

\[ c = \gamma \int_0^T G(t) t \, dt \]  

(4.43)

If \( \theta_j \) is the angle between the direction of the capillary segment and the gradient direction, then

\[ \delta \Phi_j = c v_j \cos \theta_j \]  

(4.44)

The overall magnitude of the transverse magnetization \( M \) and the dephasing are dependent upon the population distribution of the dephasing within each voxel according to

\[ M \exp(i\Phi) = \sum_j \exp(i\delta \Phi_j)p(\delta \Phi_j) \]  

(4.45)

Now, taking into account the distribution of dephasing in the voxel the above equation can be written as

\[ M \exp(i\Phi) = \int_0^\infty \int_0^\pi p(\theta)p(v) \exp(ic.v \cos(\theta)) \sin \theta \, d\theta \, dv \]  

(4.46)

where \( \theta \) and \( v \) are independent variables with population distributions of \( p(\theta) \) and \( p(v) \) respectively. The capillaries are
assumed to be oriented isotropically therefore

\[
p(\theta) = \begin{cases} 
\sin(\theta)/2 & 0 \leq \theta \leq \pi, \\
0 & \text{otherwise.} 
\end{cases} \tag{4.47}
\]

(in spherical coordinates).

Substituting this into equation (4.46) gives

\[
F = \int_0^\infty p(v) \left[ \int_0^\pi p(\theta).\sin(\theta).\exp(ic.v.cos(\theta)) \, d\theta \right] \, dv
\]

\[
= \int_0^\infty p(v).\text{sinc}(cv/c) \, dv \tag{4.49}
\]

(a standard integral)

where \( F \) replaces \( M \) as an attenuation factor.

This is a real-valued function i.e., the phase is zero.

The distribution of velocities has been solved for a Gaussian velocity profile and plug flow giving

\[
\text{GAUSSIAN} \quad F = \text{sinc}(cv_0/\pi) \tag{4.50}
\]

where \( v_0 \) is the average velocity of the flow and

\[
\text{PLUG} \quad F = \text{Si}(2cv_0)/(2cv_0) \tag{4.51}
\]

where
\[ Si(x) = \int_{0}^{x} \text{sinc}(x'/\pi) \, dx' \] (4.52)

and \( v_0 \) is the velocity of the plug of flow.

These are input into the relaxation matrix in the same way as attenuation due to diffusion. The variable \( c \) must be calculated at each time point that the matrix is used.

### 4.3.5 Motion Artifacts

As mentioned in 2.8 motion of any object (body) being imaged will cause artifacts on any image. This can be incorporated into the simulation by adding time varying positions to the position variables. However this complicates the sequence because rather than having the same relaxation matrix \( R(t) \) for the duration of a gradient, this time the position will change with real time along the length of the gradient. Therefore the gradient duration needs to be divided up into small time intervals (generally 1ms for long echo times). For each of the time intervals there will then be different offset positions approximating the shape of the motion.

Any sort of motion may be simulated, but those which are most likely to be relevant would be momentary jog, respiratory or cardiac motion. The last two can be made up from a number of simple sine waves using Fourier Analysis. The motion that is presently incorporated is a simple sine wave since this is sufficient to
illustrate the basic properties of motion artifacts.

4.3.6 Noise

Noise was included into the simulation using a Microsoft C library function which generated random numbers. The random numbers are scaled to the appropriate size according to the signal-to-noise requirements.

4.3.7 Eddy Currents

The phenomenon of eddy currents is described in some detail in 5.2.1 but essentially their effect is a reduction in the resultant applied gradient, and a modification of a trapezoidal gradient waveform to that shown in Figure 4.2.

![Figure 4.2 Gradient waveform modified by eddy currents.](image_url)

The way that eddy currents are incorporated into the simulation is
by including a time varying gradient waveform in place of a constant one. The user can specify the size of the eddy current and the time constant of the decay seen on the falling slope of the waveform.

4.3.8 Summary

For any given sequence the appropriate relaxation operator (the old one with the added flow and motion terms) can be used in the combination of matrices to obtain the effect on the magnetization.
4.4 PROGRAM CAPABILITY

A number of programs have been written. All are based on either a single or double echo sequence. The variety is in the number of pixels, phase encoding steps, sample points and the number of dimensions - from a 1-D experiment in the x- or y-plane or a 2D xy-plane experiment to a 3D experiment with a slice selective pulse.

All flow and motion effects are included in the simulation: constant velocity, constant acceleration, diffusion, incoherent and coherent perfusion, sinusoidal motion meant to simulate tissue pulsations from cardiac and respiratory functions, eddy currents and noise.

The user must input values for the above parameters (if required) in addition to the standard NMR parameters of T₁, T₂, r.f. pulse lengths, gradient strengths etc.

The data output is entirely analogous to that of a real NMR imaging experiment i.e., following a 2DFT (for the 2- or 3D experiment) a real and imaginary image are obtained from which a magnitude and phase image can be calculated.
4.5 PROGRAM DESCRIPTION

As mentioned there are several different programs, but these all have the same basic structure. The simulation is written in C, is approximately 4,500 lines of code long and needs 97,840 Bytes of memory to run. It is divided up into 7 or more modules, each with a specific task in the imaging experiment - see Figure 4.3.

![Diagram of simulation program](https://via.placeholder.com/150)

*Figure 4.3 Schematic diagram of simulation program.*
MODULE 1: Calls up all the functions within the different modules and controls the incrementing loops.

MODULE 2: Asks the user for information about the sequence such as gradient strengths and timings and relaxation times.

MODULE 3: Assigns the input parameters to the variables used in the pulse and relaxation matrices.

MODULE 4: Called when a 3D simulation is required, solving the Bloch Equations numerically at small time increments through the slice select gradient (see 4.2.4).

MODULE 5: Performs a calculation based on the solution to the Bloch equations outlined in section 4.2.2. The calculation is done many times for all the different resolvable positions of the phantom, the sampling points of the NMR signal and the phase encoding gradient increments. The simple calculation (equation (4.19)) is made vastly more complicated by the inclusion of relaxation matrices containing gradients and flow which are repeatedly multiplied together.

MODULE 6: This is almost identical to MODULE 5 but it is
called when motion artifacts are required. For a number of points along any imaging or flow encoding gradient the position is varied sinusoidally to simulate pulsatile tissue motion.

MODULE 7: This module takes the raw data and produces the final image. It is instructive to see what steps are gone through in order to obtain the final image.

In a manner analogous to that of a real MRI experiment, a signal obtained from an object undergoes a 2DFT. However, in the simulation this signal must be made up from \( nx \times ny \times nz \) different signals corresponding to all the x-, y- and z-components of position in the phantom - this is the purpose of the x, y and z loops. The summation of these signals is then sampled to provide a discrete signal just as would happen experimentally. The different time points that the signal is sampled at is controlled by the time loop. The final loop controls the level of the phase encoding gradient that is stepped through to obtain a data set which is required to undergo the 2DFT.

MODULE 8: Displays the data in image form using some basic graphics.
MODULE 9: This module writes the image data and the input parameters to files in floating point format.
4.6 LIMITATIONS OF THE SIMULATION

The only real limitation of the simulation is the time it takes to run. This puts a limit on the resolution of the final image to 16×16 pixels. A simulation which consists of an object filling the field of view would take about 2 hours to run with this time increasing if the motion artifact or eddy current modules are used. Obtaining a 256×256 image would take of the order of 100 years to run!

A significant factor in this is the speed of the processor. If a faster processor was installed matters would be improved greatly. The low resolution images that result do not prove to be too much of a problem since the simulation is not intended to provide perfect images - more an accurate representation of the effect of NMR sequences. Having said this care must be taken that the input parameters for such a small image (e.g., sample frequency and gradient strengths) are scaled down such that they are realistic for the low resolution.
4.7 TESTING THE SIMULATION

The importance of thoroughly testing the simulation cannot be over-estimated. Unless it is certain that the simulation produces reliable data the whole of the work done with it will be undermined.

The behaviour of the simulation has been tested for a variety of different characteristics. As mentioned previously the NMR image is influenced by a variety of characteristics which include relaxation times, flow, motion etc. Under certain conditions each of these variables can be considered independent and their effect predictable. They can therefore be used to test the reliability of the simulation.

In addition to these characteristics, for the 3D simulation, the selective pulse module needs to be tested to make sure that the correct slice profile is obtained.

4.7.1 Longitudinal Relaxation $T_1$

$T_1$ can be calculated from the spin echo sequence by varying the repetition rate and comparing it to an image with a very long repetition rate.

For the first sequence 'a' with a repetition rate of the order of $T_1$, the magnetization is given by:

$$M_a(te) = M_o \exp(-te/T2)[1-\exp(-T/T1)]$$

(4.53)
where $t_e$ is the echo time and $T$ is the repetition rate.

For sequence ‘b’ if $T > T_1$, the magnetization is given by

$$M_b(t_e) = M_o \exp(-t_e/T_2)$$  (4.54)

Substitution equation (4.53) into (4.54)

$$M_a(t_e) = M_b(t_e)(1-\exp(-T/T_1))$$  (4.55)

Rearranging this gives

$$\ln[1-M_a(t_e)/M_b(t_e)] = -T/T_1$$  (4.56)

Therefore by varying the repetition rate $T$, the value of $T_1$ is obtained. Results for this are shown in Figure 4.4.

![Figure 4.4 Plot of $\ln(1-M_a/M_b)$ against repetition rate $T$.](image)
Plot A represents an input parameter of $T_1=500\,\text{ms}$ and plot B $T_1=300\,\text{ms}$. The graph yields values of $500 \pm 2\,\text{ms}$ and $300 \pm 1\,\text{ms}$ respectively.

4.7.2 Transverse Relaxation $T_2$

If long repetition rates are used then equation (4.24) is valid. Rearranging it gives

$$\ln[M_a(te)] = -\frac{te}{T_2} + \ln[M_o] \quad (4.57)$$

By varying the echo $T_2$ can be obtained. Results for this are shown in Figure 4.5.

![Figure 4.5 Plot of $\ln(M(te))$ against echo time $te$.](image)

Plot A represents an input parameter of $50\,\text{ms}$ and Plot B $100\,\text{ms}$. 

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The graphs yield values of 50ms and 100ms to within a small fraction of a percent.

4.7.3 Macroscopic Flow

In a NMR experiment when there is no flow present all of the signal occurs in the real image. When there is flow, some of the signal will occur in the imaginary image. The amount of signal in the imaginary image is governed by the fact that the signal in the phase image should equal

$$\phi = \gamma g v \delta \Delta$$  \hspace{1cm} (4.58)

where $\gamma$ is the gyromagnetic ratio, $g$ is the strength of the flow encoding gradient in the direction of flow, $v$ is the velocity, $\delta$ is the duration of the gradient and $\Delta$ is the time between the leading edges of the flow encoding gradients.

The phase will not be exact because of the assumptions that are made in solving the Bloch equations during an r.f. pulse i.e. relaxation effects are negligible. The error due to this can be minimized by making the pulses as short as possible.

Also corrections have to be made to the areas of the image beyond the phantom i.e., where the signals in the real and imaginary channels are about the same size and nearly zero, the calculated phase from these two will probably not be nearly zero. The solution to this is to assign to all pixels in the imaginary image below a certain threshold the value zero.
Care must be taken that sampling of the echo is done from the correct position in time. If only the second half of the echo is sampled then this will result in a phase variation across the image.

Figure 4.6 below shows the simulated data versus the simple calculation data.

![Graph showing simulated data versus calculated data.](image)

*Figure 4.6 Simulated data versus calculated data.*

It can be seen that there is excellent agreement between the two.

### 4.7.4 Microcirculatory Flow

Diffusion and both types of perfusion (coherent and incoherent) merely attenuate the signal. The result of adding these terms would be an exact reflection of the input value but for the gradient factors that they are multiplied by i.e., the \( b \) (or \( c \))
factors. These gradient factors are worked out numerically and there will therefore be some inaccuracy - the degree depending upon how many fine steps the time is broken down into. The equation describing the b factor (2.11)

\[ b_n = \gamma^2 \sum_{k=1}^{n} \sum_{l=x,y,z} G_{kl}^2 \delta_{kl}^2 (\Delta_{kl} - \delta_{kl}/3) \]

For \( G = 30 \text{mT/m}, \delta = 40 \text{ms} \) and \( \Delta = 68 \text{ms} \) the above equation gives a b factor of \( 9.45998 \times 10^7 \text{m}^2/\text{s} \). The numerical solution to this used in the simulation gives a value of \( 9.46144 \times 10^7 \text{m}^2/\text{s} \). This value is to within 0.02\%.

4.7.5 Slice Selection

To see whether a rectangular slice profile is obtained from the selective pulse, the magnetization as a function of position in the selection direction (z) can be viewed following the pulse. Fig.4.7 overleaf illustrates what should happen for the three components Mx, My and Mz.
Figure 4.7 Theoretical components of magnetization following slice selection.

Figure 4.8 below shows the simulated data.

Figure 4.8 Simulated components of magnetization following slice selection.
4.7.6 Motion Artifacts

It was seen in section 2.8 that there exists a relationship between sequence parameters and motion characteristics

\[ \text{SEP} = Y_{\text{TOT}} \times n_{av} \times \frac{\text{TR}}{T} \]

where SEP is the separation of the ghosts on the image, \( Y_{\text{TOT}} \) is the total number of capillaries across the field of view, \( n_{av} \) is the number of acquisitions averaged before each new phase encoding step, TR is the repetition rate and T is the period of the motion.

Therefore, for a given T, TR and number of averages, the deduced separation of the ghosts ought to be the same as that given by the simulation.

N.B. Care must be taken to ensure that the amplitude of the motion is much smaller than the field of view otherwise there will be a 'wrap around' of the object and ghost leading to a distorted image.

Figures 4.9 and 4.10 overleaf show images for TR = 5sec, T = 16sec, \( Y_{\text{TOT}} = 16 \), \( n_{av} = 1 \) and motion amplitude = 0.5mm for motion in the x and y direction respectively. The separation is 5 pixels which is what would be expected from the above equation.

N.B. The x-direction is horizontal and the y-direction vertical on the simulated images.
4.7.7 Noise

The random number that is added on to the real and imaginary signals is very straightforward and merely manifests itself as lack
of uniformity of the image.

### 4.7.8 Eddy Currents

Eddy currents have no effect if they have decayed away in time before any imaging gradients are applied. This was seen in the analysis of 5.3.1 for eddy current constants of 1ms in images 5.17 and 5.18.
4.8 EXAMPLE SIMULATED IMAGE

An example experiment was carried out with the simulation. A $T_1$ variation was incorporated as illustrated below in Figure 4.11.

![Diagram of $T_1$ variation across the image.]

Parameters used were

- TR (repetition rate) = 4sec
- TE (echo time) = 20msec
- $T_2 = 200$ms
- $g_x$ (frequency encoding gradient) = 0.313168mT/m
- $d_gy$ (phase encoding gradient increment) = 0.0391461mT/m
- FOV = 20cm
- Sampling rate = 0.375msec

The simulation took just under an hour to run and the resulting image is shown in Figure 4.12 overleaf.
This appears to give very good agreement with the input data. Figure 4.13 shows profiles through A and B to give more accurate information.

![Figure 4.12 Simulated image from data of Fig 4.11.](image)

![Figure 4.13 Profiles through the simulated image.](image)
The writing of the computer simulation provided excellent insight into the theoretical side of the MRI experiment. It also gave understanding of the perfusion and diffusion models since they had to be incorporated into the simulation.

The end result of the simulation provided a powerful analytical tool. Due to the modularity of the design the simulation will be relatively easy to modify to incorporate any further effects.

The only drawback of the simulation was the time taken to run the experiment and the necessary resulting low resolution (16×16 pixels). Having said this the low resolution of the images did not prove to be a problem. The running time can be greatly reduced by running the program on a faster processor.
CHAPTER V

ANALYSIS OF DIFFUSION AND PERFUSION IMAGING TECHNIQUES
5.1 INTRODUCTION

The diffusion and perfusion imaging techniques detailed in Chapter Two were all borne out of theories and mathematics that assumed ideal systems. 'Ideal' in this context may refer to a completely isotropic orientation of capillaries, or a complete absence of eddy currents, or negligible background noise.

The intention of this chapter is to take the three main perfusion imaging categories: IVIM imaging, phase display and rephasing techniques, and analyse them in terms of all factors which could affect measurement and interpretation of diffusion and perfusion values. The IVIM imaging and phase display techniques were described in sections 2.7.3.1 and 2.7.3.3 respectively. There are a number of rephasing techniques with the standard ones described in 2.7.3.2. However none of these give quantitative information about flow and so in general they do not aid this analysis. Chapter Six describes a new method of perfusion measurement based on the rephasing phenomenon of even echoes which does provide quantitative information and is therefore frequently used in this chapter. Two sequences are executed: the first is a standard single echo sequence with strong additional flow encoding gradients, the second is a double echo sequence with matching gradient factors to the first sequence. By dividing the single echo sequence by the double echo sequence one can obtain quantitative information in the form of a perfusion fraction. For more information see 6.2.1.

All of the techniques use the same sequence parameters that have been reported by the appropriate experimentors.
These factors affecting flow measurement fall into three groups:

1. Flow models - transitions between anisotropic and isotropic capillary orientations, and between coherent and incoherent flow regimes.

2. Hardware - presence of eddy currents, signal-to-noise requirements and gradient balancing.

3. Flow and motion effects - presence of motion artifacts and changing flow during measurement.

The analysis will be done where appropriate using the simulation described in Chapter Four. Otherwise relevant mathematical treatments will be given.
5.2 FLOW MODELS

5.2.1 Analysis of the Anisotropic/Isotropic Transition

In Chapter Two the body was described in terms of different flow systems. In the microcirculation, the arrangement of capillaries depends upon the organ in which they are situated - but can be anything from parallel (anisotropic) to completely randomly oriented (isotropic). Each of the diffusion/perfusion imaging techniques assume a model of the microcirculation - if that model is not an accurate representation of the true physiology then the results obtained using that technique would not be valid. For example, some investigators have used the IVIM imaging technique (which assumes an isotropic orientation of capillaries) to measure perfusion in the limb muscles where the capillaries are clearly not in a random orientation.

This section attempts to follow the transition between the anisotropic and isotropic models of the microcirculation - and analyse the results that different diffusion and perfusion techniques would give.

It was seen in 4.3.4 that there is an attenuation factor $F$ due to microcirculation - it's form depends upon whether the flow is incoherent (changes direction during measurement time) or coherent (remains constant in speed and direction during measurement time). For incoherent flow,

$$F_{\text{incoherent}} = \exp(-bD)$$  \hfill (5.1)
where $b$ is the gradient factor and $D^*$ is the pseudo-diffusion coefficient. For coherent flow

$$F_{\text{coherent}} = \int_0^\infty \int_0^{\pi} p(\theta) p(v) \exp(i c v \cos \theta) \sin \theta \, d\theta \, dv$$

where $\theta$ is the angle between the direction of the capillary segment and the gradient direction, $v$ is the instantaneous velocity and $p(\theta)$ and $p(v)$ their respective population distributions.

When the capillaries are oriented other than isotropically the incoherent attenuation factor can be expressed in terms of orthogonal components $x, y, z$, and becomes

$$\exp(-b_x D_x - b_y D_y - b_z D_z)$$

The only real effect that this will have is that there will be a greater signal attenuation if the flow encoding gradient is applied along the same direction of the elevated pseudo-diffusion.

For anisotropic coherent flow instead of summing $p(\theta)$ from 0 to $\pi$, it is summed to a value of less than $\pi$ (to simulate a bunching of capillaries rather than an even distribution on the surface of a sphere.)

Equation 5.2. is solved numerically for two different flow models plug flow

$$p(v) = \delta(v - v_0)$$
where $v_0$ is the velocity of the plug flow, and laminar flow

$$p(v) = \begin{cases} \frac{1}{2v_0} & \text{if } 0 \leq v \leq 2v_0 \\ 0 & \text{otherwise} \end{cases}$$ (5.5)

where $v_0 = \frac{v_{\text{max}}}{2}$.

Figure 5.1 below is the solution to equation (5.2) solved for a range of angles, for both plug and laminar flow - with $v_0=2\text{mm/s}$ and $c=2829\text{s/m}$.

Figure 5.1 Theoretical attenuation curves from anisotropic to isotropic flow for the plug and laminar flow models for $c=2829\text{s/m}$.

N.B All the following techniques use $D=1.25\times10^{-9}\text{m}^2/\text{s}$, $D^* = 2\times10^{-8}\text{m}^2/\text{s}$, $f = 5\%$ and $v=2\text{mm/s}$.

IVIM Imaging

The parameters used were $b_0=0$, $b_1=94.6\times10^7\text{ s/m}^2$, $b_2=1.799\times10^8\text{ s/m}^2$. 

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c_0 = 0, c_1 = 2829 s/m, c_2 = 3901 s/m.

**Diffusion Coefficient.** Figure 5.2 below shows that the plug flow model is accurate at the beginning and end of the curve, but in between has rather wild fluctuations (these come from the sinc 'wiggles' from Figure 5.1). Measurements vary by as much as 16% on these dips.

![Diffusion Coefficient Graph](image)

*Figure 5.2 Theoretical prediction of diffusion coefficients for plug and laminar flow models varying with degree of anisotropy.*

The laminar flow model only varies by about 5% along the curve - very accurate for anisotropic flow, over-estimating by ~2% at the end.

*Perfusion Fraction.** For the plug flow model, at more anisotropic flow regimes there will be no measured perfusion fraction as can be seen in Figure 5.3 overleaf. It then climbs dramatically to a point at around θ = π/2 when the measurement would be 6% - 30%
higher than the value of 4.6% measured at complete isotropy.

![Graph showing perfusion fraction vs. degree of anisotropy for laminar and plug flow models.]

**Figure 5.3** Theoretical predictions of perfusion fractions for plug and laminar flow models varying with degree of anisotropy.

For the laminar flow model the measured perfusion fraction remains roughly constant with a few oscillations along the curve, but it is always on the low side.

For the pseudo-diffusion model of perfusion, if there was a higher pseudo-diffusion coefficient this would result in a more accurate measurement of \( f \), because the IVIM technique is based on the fact that \( e^{-bD} = 0 \) for \( b_1 \) and \( b_2 \). Likewise, if \( D^* \) was smaller along that axis, \( f \) would be measured less accurately.

Different conclusions may be arrived at depending upon whether the flow in the capillaries is best described by the plug or laminar flow model. The plug flow model suggested that at anything
other than complete anisotropy, spurious results for both the diffusion coefficient and perfusion fraction would result, rendering the IVIM technique useless. Results using the laminar flow model - which may in actual fact be closer to the physiological reality - are much better. There is certainly a departure from the true values, but by far less than when using the plug flow model. The greatest inaccuracy would be when measuring the perfusion fraction in an intermediate orientation. In conclusion then, in order to get the most accurate measurements it is important that the technique used is appropriate to the capillary arrangement. However, the departure from ‘true’ values are not in fact that great.

N.B. This analysis uses only a simple model to see the effect of changes in the orientation of the capillaries on the measured diffusion coefficient and perfusion fraction. It should be noted that if the capillaries are oriented other than isotropically then this will have a direct effect on the measured diffusion coefficient since the capillaries will form a barrier to diffusion in a particular direction.\textsuperscript{67}

Phase Display

Equation (5.2) was solved using $c=8186\text{ s/m}$ which is calculated from typical phase display experiments. Figure 5.4 overleaf shows the results for plug and laminar flow, for the transition from anisotropic to isotropic flow.
Figure 5.4 *Attenuation curves from anisotropic to isotropic flow* for the plug and laminar flow models for $c=8186\text{o/m}$.

The phase display technique assumes anisotropic flow so that an overall phase measurement will be assigned to each pixel. Figure 5.5 overleaf shows the effect of the changing degree of anisotropy on the measured phase ($\Phi_m$) calculated from phase of the flowing spins ($\phi_v$) according to

$$\Phi_m = \tan^{-1}\left(\frac{\sin(\Phi_v)}{(1-f)+f\cos(\Phi_v)}\right)$$

(From section 2.7.3.3.)
The measured phase oscillates wildly for both the laminar and plug flow models. This is due to phase wrap around i.e., if the value of $\phi_m$ in radians exceeds $+2\pi$, then the phase will be given a value starting 'again' at $-2\pi$. For anisotropic flow (where the model is appropriate) there is a sensible value of phase, but after this it would be difficult to get an accurate measurement, whether using the plug or the laminar flow model. At complete isotropy there is no detectable phase which is what would be expected since there can be no overall phase measurement when the capillaries are oriented isotropically.

Therefore measured phases are not reliable at anything other than complete anisotropy.
Rephasing Techniques

This group of techniques rely on the fact that the flow is coherent so that by the addition of flow rephasing gradients, or another 180° pulse, the flow will be rephased. Whether the coherent flow is isotropically or anisotropically oriented makes no difference.
5.2.2 Analysis of the Coherent/Incoherent Transition

As mentioned in 5.2.1, there exist different models of microcirculation. This section analyses not the arrangement of the capillaries but the ‘regime’ of the flow i.e., whether it is coherent or incoherent. The different diffusion/perfusion imaging techniques are appropriate to particular flow regimes usually one or the other but the IVIM imaging technique is suitable for both. It is important therefore to gain an understanding of the flow regime but this is difficult and the interpretation of the available physiological data varies considerably from group to group. The seminal research into the tomography of capillaries in the brain (where most diffusion/perfusion work is done) was consulted\textsuperscript{14}. With this information this section attempts to unravel how suitable each of the imaging methods are, assuming there own interpretation of the data and then the suitability assuming the author’s interpretation and mathematical analysis.

The key research paper on the subject of microcirculation in the brain was by Pawlik et al\textsuperscript{14}. They visualized the microcirculation in the cerebral cortex of the cat brain in vivo using a technique called microtransillumination and documented it by high-speed microcinephotography. The data most relevant to this analysis is the velocity of the flow through the capillaries and the length of the capillary segments. The lengths of capillary segments were found to follow most closely the Weibull distribution\textsuperscript{68} which has a frequency distribution given by

\[
f(t) = m \lambda t^{m-1} \exp(-\lambda t^m)
\]  

(5.7)
and a cumulative density function given by

$$F(t) = 1 - \exp(-\lambda t^m)$$  \hspace{1cm} (5.8)

Pawlik determined a cumulative density function

$$F(X \leq x) = 1 - \exp(-x/150.33)^{123}$$  \hspace{1cm} (5.9)

from which $\lambda$ and $m$ can be deduced.

The lengths of capillary segments varied widely from 12 to 302\,\mu m with 50% being up to 108\,\mu m. From this data a plot can be obtained of the frequency of capillary lengths. This is shown in Figure 5.6 below.

![Figure 5.6 Frequency distribution of capillary lengths.](image)

From Figure 5.6 the fraction of coherent and incoherent flow can be deduced. The length that a plug of flow has travelled during the measurement time is given by $l_1$ and is governed by the velocity of
the flow and the measurement time. Figure 5.7 below shows this travel length on the axis of the frequency distribution of capillary segment lengths.

![Image of Frequency Distribution of Lengths](image)

**Figure 5.7 Travel length in relation to frequency distribution.**

The flow on the left of the intersecting line will be incoherent since the fluid will all have gone further than $l_i$. There will also be a contribution from the right hand side - those plugs of flow which by virtue of their distance down a capillary segment will change direction during the measurement time. The coherent flow fraction is given by the remainder. Expressing this mathematically

$$ f_{\text{inc}} = \int_{l_2}^{l_1} f(l) \, dl + \int_{l_1}^{302} f(l) \cdot \frac{l}{l} \, dl $$

(5.10)

$$ f_{\text{coh}} = 1 - f_{\text{inc}} $$

(5.11)

where $f(l)$ is the frequency distribution of capillary segment...
lengths, and is given by

\[
0.02583.(l-12)^{0.23}.\exp(-0.021.(l-12)^{1.23})
\]  \hspace{1cm} (5.12)

Figure 5.8 below illustrates how the fractions of coherent and incoherent flow change as a function of \( l \).

![Graph showing fractions of coherent and incoherent flow](image)

**Figure 5.8** Fractions of coherent and incoherent varying with travel length \( l \).

**IVIM Imaging**

A simple definition of the NMR signal (ignoring the effects of T1 and T2) is given by

\[
S = \exp(-b.D).((1-f) + f.F))
\]  \hspace{1cm} (5.13)
where $b$ is the gradient factor, $D$ is the diffusion coefficient, $f$ is the flowing fraction of spins and $F$ gives an attenuation due to the perfusion i.e., there is a small fraction of perfusing and diffusing spins, and a remainder of diffusing only spins. This $F$ factor is different depending upon whether the flow is coherent or incoherent.

$$F_{\text{coherent}} = \frac{\sin(c.v)}{c.v} \quad (5.14)$$

(assuming plug flow)

$$F_{\text{incoherent}} = \exp(-b.D^*) \quad (5.15)$$

where $c$ is another gradient factor, $v$ is the velocity of the flow and $D^*$ is the pseudo-diffusion coefficient. It is assumed that the flow is completely isotropic for this analysis.

Equation (5.13) becomes

$$S = \exp(-b.D).((1-f) + f.(f_{\text{incoherent}} + f_{\text{coherent}})) \quad (5.16)$$

Using this equation for the three different values of flow encoding gradients the diffusion coefficients and perfusion fractions can be determined. Figure 5.9 overleaf illustrates the results.
Figure 5.9 Diffusion coefficients and perfusion fractions varying with degree of coherence as a function of travel length.

The diffusion coefficient is initially below the correct value and increases to an over-estimate, varying by a maximum of about 20%. The perfusion fraction increases exponentially to the most accurate estimate at complete coherence.

It is interesting to note that although the IVIM technique is supposedly suitable for both flow regimes, it provides more accurate results for incoherent flow.

Phase Display

Generally, the phase from a perfusion imaging experiment is given by
where \( f \) is the fraction of perfused capillaries (see 2.7.3.3).

The experimental set-up should involve varying the gradient to maximise \( \Phi_m \) (i.e., \( \Phi_v \pi/2 \)). Therefore,

\[
\Phi_m = \tan^{-1}(f/(1-f))
\]

(5.18)

\( f \) is more accurately described as the fraction of coherent flow capillaries and so the fraction of coherent flow can be normalised to a maximum of 5%, and substituted into equation (5.18).

\[
\Phi_m = \tan^{-1}(\text{frac}_{\text{coherent}} / (1-\text{frac}_{\text{coherent}}))
\]

(5.19)

The graph of this is shown below in Figure 5.10 and is identical to Figure 5.6 since \( \tan^{-1}(x) \approx x \).

\textbf{Figure 5.10} Measured phase varying with degree of coherence as a function of travel length.

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Therefore as might be expected accurate phase measurements will only be possible when the flow is coherent.

Rephasing Techniques

These techniques are again difficult to evaluate because they do not give qualitative results except for the new technique proposed in Chapter Six. An analysis will be done for this technique. Equation 5.16 is solved for two cases: \( c=0 \) and \( c=5000\text{s/m} \) with \( b=4.79\times10^8\text{m}^2/\text{s} \) for both sequences. The resulting signals are plotted on Figure 5.11 below.

![Travel Length (\( \mu \text{m} \))](image)

Figure 5.11 Solution to equation 5.13 for \( c=0 \) and \( c=5000\text{s/m} \), varying with degree of coherence as a function of travel length.

It can be seen in Figure 5.11 that as the flow becomes more
incoherent the difference between the two signals becomes less and less leading to an under-estimate of the perfusion fraction since the difference is given by 1-f.

Therefore for this particular technique at least it is important to have a coherent flow regime.
5.3 HARDWARE

5.3.1 Effect of Eddy Currents

Eddy currents have long been known to cause problems in MRI, and have potentially serious effects in diffusion/perfusion imaging where the additional gradients are often very large.

Eddy currents exist due to the design of a magnet. In a superconducting magnet there exist at least two conducting cylinders between the room-temperature bore and the magnet windings. The gradient coils inductively couple to the first conductive cylinder that they 'see' in the magnet - usually the 77K radiation shield, which is typically of pure (high electrical and thermal conductivity) aluminium. The coils induce currents of the same symmetry but opposite sense in the shield, creating a current distribution that is like a smoothed out version of the gradient.

For example, a waveform of the shape shown in Figure 5.12

![Figure 5.12 Example square gradient waveform.](image)

would induce a waveform of the type in Figure 5.13 overleaf.
This leads to a combined waveform of that shown in Figure 5.14.

\[ 
\text{Figure 5.13 Induced current waveform.} 
\]

\[ 
\text{Figure 5.14 Resulting gradient waveform.} 
\]

i.e., the maximum gradient is not achieved immediately and it decays slowly away.

Commonly eddy currents are corrected for by using pre-emphasis which adds one or more exponentials to the gradient waveform. For example a current waveform similar to that shown in Figure 5.15 overleaf.
would be added to the square output waveform to produce the waveform below in Figure 5.16

which when added to the eddy waveform would produce the original desired rectangular waveform.

Alternatively, self-shielded gradients can be used which work by deducing the induced current pathways and building coils to negate their effect. These have the disadvantages that they take up more physical space hence reducing bore size, they are difficult to build and are expensive to buy.

The following analysis will assume that neither of the two
methods of elimination have been used which is a little unrealistic but still instructive. Eddy currents originating only from the large additional flow encoding gradients will be considered.

The effects that eddy currents have on an image are numerous and depend upon which of the imaging axes the flow encoding gradient is applied and also the time domain of the eddy current. There are three time domains that can be considered:

(i). Long (>20ms). These will typically be small - of the order of a few percent of the original gradient, and can be considered to be constant over a short time scale.

(ii). Intermediate (1-20ms). These are probably most typical and will cause the greatest problems. They are also the most difficult to model because they vary with time.

(iii). Very short (<1ms). Provided that the different gradients are not very close to each other these will have no adverse effects on the image, and so will not be considered.

Gradient Parallel
The effect that the additional gradient has on subsequent imaging gradients along the same axis is analysed in the following.

*Frequency Encoding.* Referring back to equation (1.64), the signal
during the frequency encoding gradient is given by

$$S_m = D(x).\exp(it_m (\gamma G \cdot x))$$  \hspace{1cm} (5.20)$$

The effect of a residual eddy current on during acquisition can be modeled by adding another term to (5.20).

$$S_m = D(x).\exp(it_m (\gamma G \cdot x)).\exp(it_m (-\gamma G_e(x,y,z,t)x))$$

$$= D(x).\exp(it_m (\gamma(G - G_e(x,y,z,t))x))$$  \hspace{1cm} (5.21)$$

where \( G_e(x,y,z) \) is the initial magnitude of the eddy current induced gradient waveform.

For a long term eddy current \( G_e(x,y,z,t) \) can be approximated to \( G_e(x,y,z) \) i.e., a constant in time. The effect of this is to decrease the overall gradient (since eddies oppose), so reducing the frequency spread which manifests itself as a contraction of the object.

For intermediate eddies \( G(x,y,z,t) \) will be an exponential function with a time constant roughly of the order of half the echo time.

$$S_m = D(x).\exp(it_m \gamma G \cdot x).\exp(it_m (\gamma(-\exp(t /T))x))$$

$$= D(x).\exp(it_m \gamma x(G - \exp(t /T)))$$  \hspace{1cm} (5.22)$$

It is not easy to envisage what effect this will have on the
It can however be solved analytically using the computer simulation described in Chapter Four.

Three time ‘constants’ (T) were used 100, 10 and 1 secs. The initial magnitude of the eddy induced gradient waveform was given to sizes corresponding to 5% and 25% of the frequency encoding gradient i.e., $1.56584 \times 10^{-5}$ and $7.8292 \times 10^{-5}$ T/m.

Resulting images are shown in Figures 5.17 and 5.18.
Figure 5.17 Effect of eddy currents on an image for $B_e = 1.56584 \times 10^{-5}$ T/m, and $T = (a) 100$, (b) 10 and (c) 1msecs.
Figure 5.18 Effect of eddy currents on an image for $B = 7.8292 \times 10^5 \text{T/m}$, and $T = (a) 100$, (b) 10 and (c) 1msecs.
It is immediately apparent that for eddies with shorter time constants their is no apparent effect on the image which is what would be expected because they would decay away very quickly. For longer time constants however their is considerable variation in intensity across the image. This is seen most visually in Figure 5.18 for \( T = 1 \text{msec} \) where there appear to be ripples in the intensity. For a large eddy current effect i.e., 25% of the frequency encoding gradient there is also a contraction of the image which again would be expected given that the frequency encoding gradient would be reduced.

For short term eddies (<1ms) there will be no problems because they will decay away before they can interfere with the frequency encoding gradient.

The effect of eddies on the frequency encoding gradient depend entirely on the time domain of the eddies. For intermediate and long term eddy currents the effects are serious and will undoubtedly affect accuracy of quantitative measurements to due poor linearity of the image intensity and change in shape of the object.

**Phase Encoding.** In an analogous manner, refer back to equation (1.68) where the signal due to the phase encoding gradient is given by

\[
S_n = D(y).\exp(i\gamma G^n_y y)
\]  

(5.23)
The effect of an eddy induced gradient which is on during phase encoding is given by

\[
S_n = D(y).\exp(i\gamma T G^n_y).\exp(\int_0^T G_B(x,y,z,t) \, dt).y
\]

(5.24)

The additional term is constant from scan to scan (if the eddy current is always the same size) and so the signal can be written

\[
S_n = D(y).\exp(i\gamma T G^n_y).\exp(i\phi)
\]

(5.25)

When Fourier Transformed the eddy current term will come out as a constant which will merely shift the object within the field of view. This is the case for either long term or intermediate eddies because \(\phi\) depends on the integral of the gradient waveform and not its shape. This also applies to short term eddies but is not relevant because they will have died away already.

Therefore, if the eddy currents remain constant there will be no consequence for quantitative flow measurements because all the images will be shifted.

**Slice Selection.** From equation (1.63) it can be seen that the gradient strength is proportional to the size of the selected slice. If there are eddy induced gradient waveforms which oppose
the slice selection gradient then this will lead to thicker slices being selected. However this is for uniform gradients. If the gradients are decaying away exponentially this may have some additional effect on the selected slice.

This was analysed with a one dimensional version of the computer simulation of Chapter Four.

Figure 5.19 overleaf shows the effect on the selected slice for a variety of eddy current time constants. The slice select gradient was on for a duration of 1.5ms. The profile shown is actually that of the z-component of the magnetization and can be compared with that shown in 4.7.5.

![Diagram showing the effect of eddy currents on the slice shape.](image)

**Figure 5.19 Effect of eddy currents on the slice shape.**

Whilst the slice thickness is increased for eddies with longer time constants (because there is a larger gradient still on, hence smaller residual gradient) there appears to be no distortion of the
slice profile.

In conclusion, if the eddy currents are constant then although the thickness of the slice will not be as expected, there will again be no serious consequences for flow measurements.

**Gradient Perpendicular**

*Frequency Encoding.* If the flow encoding gradient causes eddy currents in a direction orthogonal to the frequency encoding gradient the signal will be given by

$$S_m = D(x) \cdot \exp(it \gamma G_x) \cdot \exp(it (-G(x,y,z,t) \cdot r))$$  \hspace{1cm} (5.26)

For long term eddies the additional gradient can be considered to be constant and the effect is that the combined gradient is directed along a different direction: the displacement from the x axis depending upon the magnitude of the eddy current and the axis along which the eddy induced waveform lies.

For intermediate eddies the case is once again non-trivial because of the gradient amplitude changing during acquisition. However the effect would be the same as that shown in Figures 5.17 and 5.18 but with the image plane skewed. Due to the small number of pixels used in the simulation this could not be illustrated effectively.

*Phase Encoding.* For flow encoding on an axis orthogonal to the
phase encoding gradient, the resulting signal is given by

\[ S_n = D(y).\exp(i\gamma T G^n_\gamma y).\exp\left(i\gamma \int_0^t G_e(x,y,z,t) \, dt\right) \]

\[ = D(y).\exp(i\gamma T G^n_\gamma y).\exp(i\phi(r)) \] (5.27)

As in the 'gradients parallel' case the eddy current term will come out as a constant phase. This time however there is also a skew due to the gradient not being along the y axis.

**Slice Selection.** For the case of a constant additional gradient the selected slice would merely be rotated by an amount governed by the strength of the additional gradient in comparison to that of the slice select gradient. For shorter term eddies, profiles like those in Figure 5.19 would be expected but with the additional skew due to the presence of a simultaneous gradient along another axis.

General conclusions that can be reached are that if the eddy currents are constant form scan to scan then only if they are along the frequency encoding axis will they cause any major problem affecting quantitative diffusion and perfusion measurements.
5.3.2 Signal-to-Noise Requirements

Noise proves to be one of the most serious problems in perfusion imaging. This is because the level of noise which is generally of the order of a few percent is at the same level as the perfusion fraction.

IVIM Technique

Madden and Leach\(^6^9\) modelled the imaging process, creating a 2D complex object. The effects of perfusion and other flow effects were introduced into the image and the impacts of various motions and imaging parameters investigated. The SNR of the perfusing and static fractions was investigated for a number of sequence parameters reported by other groups, with a noise level estimated using the groups own values.

They found that after adjusting the signal for T\(_2\) effects and the intravoxel blood fraction the perfusion contribution was comparable to the noise level, preventing accurate measurements. The effect of noise was further accentuated by division of the data sets (for the IVIM technique). They deduced that a factor of ten improvement in the blood signal is required for perfusion quantification to become feasible.

In another study\(^7^0\) computer simulations were used to estimate the SNR requirements for accurate measurements of the diffusion coefficient (D) and the perfusion fraction (f). Simulated IVIM data
was generated using $f = 5\%$, $D = 1 \times 10^{-9} \text{m}^2/\text{s}$ and $D^* = 1 \times 10^{-8} \text{m}^2/\text{s}$ ($D^*$ is the pseudo-diffusion coefficient). The data was contaminated with noise and the minimum SNR requirement for estimation of IVIM parameters within the desired accuracy was determined. They discovered that for an accuracy of $\pm 5\%$ in $D$ (with a $b$ factor of $3 \times 10^8 \text{s/m}^2$), a SNR of 61 is required. However a SNR of 313 would be required to determine $f$ to within $\pm 20\%$ at $b=3 \times 10^8 \text{ s/m}^2$.

Another published study\textsuperscript{71} on the subject concludes that to estimate diffusion coefficients to within 20\% a SNR of 40:1 is required. However, for 20\% accuracy of perfusion fraction this requirement becomes 400:1.

This is a very tough criteria to meet. Clinical systems at 0.5T and 1.5T commonly have SNR of around 40 and 120:1 respectively. Therefore in order to obtain accurate perfusion measurements large numbers of averages would need to be obtained which would be a problem in a clinical environment unless rapid imaging techniques such as EPI are available.

Phase Display

The necessary SNR for accurate phase measurements was calculated by adding noise in the guise of a random number generated by a mathematical function as illustrated in Figure 5.20.
The measured phase was then calculated from

$$\Phi_m = \tan^{-1}(f \sin \Phi_y / (1-f) + f \cos \Phi_y))$$

(5.28)

The result of this analysis was that for an accuracy in the phase of 20%, can be achieved with a noise level equivalent to 50% of the signal size. This is surprisingly low.

Rephasing Techniques

The rephasing techniques do not give quantitative information, except for the new perfusion imaging technique detailed in Chapter Four. Therefore most will suffer little apart from degradation of the image quality. The new technique described in Chapter Six can be evaluated in terms of the require SNR by looking at the attenuation with the flow encoding gradients.
Typically the b factor for the new technique is $4.79 \times 10^8 \text{s}^2/\text{m}$. Therefore the required SNR will be

$$\text{SNR}_{\text{rephase}} = \frac{(\exp(-b_{\text{rephase}} D)/\exp(-b_{\text{IVIM}} D)) \cdot \text{SNR}_{\text{IVIM}}}{\exp(-b_{\text{IVIM}} D)} = 397 : 1,$$

where $b_{\text{rephase}} = 3 \times 10^8 \text{s}^2/\text{m}$, $\text{SNR}_{\text{IVIM}} = 313 : 1$, for example. The calculated $\text{SNR}_{\text{rephase}} = 397 : 1$, which is an even tougher criteria to meet.
5.3.3 Balancing of Flow Encoding Gradients

One of the most difficult but crucial steps in diffusion/perfusion imaging is the balancing of the large flow encoding gradients. The analysis below illustrates the extent to which they must be matched in order to get reliable measurements of the diffusion coefficient and perfusion fraction.

The phase that an isochromat of spins acquire along a given axis is given by

\[ \phi = \int_{0}^{1} \int_{-1}^{1} \gamma g_z(t) \cdot z \cdot t \, dt \, dz' \]  \hspace{1cm} (5.30)

In this analysis \( g_z \) is given typical IVIM imaging flow encoding gradient values i.e.,

\[ g_1 = 3.88762 \times 10^{-3} \text{T/m} \]

and \( g_2 = 5.611 \times 10^{-3} \text{T/m} \)

Reasonable values for \( z_1 \) and \( t \) are 0.01m and \( t = 0.04\text{secs} \) respectively.

If the gradients were perfectly balanced then the phase acquired during the first half of the spin echo would be canceled out by that from the second half. (This is assuming no net motion).

However, if there is an imbalance between the two lobes of the gradients there would be a resultant phase shift leading to a
reduction in the signal size.

Figure 5.21 below illustrates the effect of a poor second gradient on the measured signal.

![Graph showing signal reduction due to poorly balanced gradients.](image)

**Figure 5.21 Signal reduction due to poorly balanced gradients.**

There is an exponential increase in the signal level as the gradients become better matched.

**IVIM Technique**

The reduction in amplitude causes enormous errors in the measured D and f which can be seen in Figure 5.22 overleaf.
The theoretical prediction of diffusion coefficients and perfusion fractions for poorly balanced gradients.

\( \delta = 40\text{ms}, \Delta = 68\text{ms}, \text{TE} = 140\text{ms}, b_0 = 0, b_1 = 9.46 \times 10^7, b_2 = 17.99 \times 10^7 \) c.f. Le Bihan.

The diffusion coefficient is over-estimated for badly matched gradients, for a mismatch as small as 4%.

The perfusion fraction is under-estimated for badly matched gradients.

It is crucial therefore at set-up to carefully adjust the flow encoding gradients for maximum signal (see 6.2.2).
Phase Display

It can be seen from Figure 5.23 that there is a linear increase to the correct phase. If the gradients are not properly balanced then the measured phase will be under-estimated.

![Graph showing linear increase in measured phase]

Figure 5.23 Theoretical prediction of measured phase for poorly balanced gradients.

Rephasing Techniques

These techniques are reliant on the fact that the coherent flow is rephased. However, if the gradients are not balanced there will not be complete rephasing. There will be a variety of effects depending upon the particular technique. For the technique described in Chapter Six the effect will be a reduced signal intensity for both sequences. Therefore although the perfusion
fraction will not be directly affected, there will be a reduction in the signal intensities and therefore a decrease in the SNR, hence reducing the accuracy.
5.4 FLOW AND MOTION EFFECTS

5.4.1 Simulated Effect of Motion Artifacts on Measurements

Section 2.8 describes the effects that motion artifacts have upon a reconstructed NMR image, in particular how the spacing of the resulting ghosts are determined by the number of pixels ($Y_{\text{TOT}}$), averages ($n_{av}$), the period of the motion ($T$) and the repetition rate ($TR$). The formula is given by equation (2.14)

$$\text{separation} = Y_{\text{TOT}} \times n_{av} \times \frac{TR}{T} \quad (5.31)$$

Also it was noted that the intensity of the ghosts are proportional to the amplitude of the motion and the intensity of the originating body.

This section seeks to examine what effect flow encoding gradients have upon motion artifacts, and the subsequent effects on diffusion and perfusion measurements.

All results come from the simulation described in Chapter Four with parameters chosen such that the object was only one pixel in size in the centre of a 16x16 pixel FOV - the ghosts spaced at 5 pixel intervals.

The effect that varying the magnitude of the gradient has on the original object and ghosts can be seen in Figure 5.24 overleaf.
Figure 5.24 Effect on motion artifacts of increasing gradient strength with a motion amplitude of 0.2mm in a FOV of 200mm.

[Parameters : $T_1 = 500\,\text{ms}$, $T_2 = 200\,\text{ms}$, $te = 140\,\text{ms}$, $TR = 5\,\text{s}$, $\delta = 40\,\text{ms}$, $\Delta = 68\,\text{ms}$, FOV = 200mm and amplitude of motion = 0.2mm].

It is apparent that there is a dramatic reduction in the signal from the object even with a small motion amplitude of 0.2mm.

Figure 5.25 overleaf shows the effect of varying the motion amplitude on the object and ghost - all with a gradient strength of 5mT/m.
Again there is serious reduction in signal form the object as motion amplitudes increase, eventually falling below the level of the ghosts for motion amplitudes above 1mm.

It is interesting to examine whether it is the strength of the gradient or its duration which is the prominent cause of the problem. In order to investigate this the IVIM experiment was repeated at 0.5mm motion amplitude for the same b factors but varying δ between 5 and 65ms, changing the gradient strength to compensate. Figure 5.26 overleaf illustrates the results.
Figure 5.26 Effect of varying $\delta$ on the motion artifacts.

It shows that the ghosts have greater intensity for a longer duration of gradient rather than for a larger gradient strength. The effect is not a large one however - the ghosts vary by about 20% over the range, the object by less than one percent.

The following is an analysis of how the amplitude of the motion affects the measured diffusion coefficients and perfusion measurements using the three main types of sequence.

**IVIM Technique**

Parameters used were identical to those overleaf. For sequence 0 there was no flow encoding gradient, for sequence 1 $g_1 = 3.88762$ mT/m and for sequence 2 $g_2 = 5.3611$ mT/m. This gave the same $b$ factors as used by Le Bihan. The diffusion coefficient was given a value of
1.25 \times 10^{-9} \text{ m}^2/\text{s} and the perfusion fraction was 5%.

Figures 5.27 and 5.28 illustrate the calculated diffusion coefficients and perfusion fractions for increasing motion amplitudes from the resulting images.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diffusion_coefficient.png}
\caption{Theoretical prediction of diffusion coefficients varying for increasing motion amplitudes.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{perfusion_fraction.png}
\caption{Theoretical prediction of perfusion fractions varying for increasing motion amplitudes.}
\end{figure}

The results are quite dramatic, and indicate that for motion of
as little as 0.6mm the diffusion coefficient is considerably over-estimated. The perfusion fraction becomes very inaccurate beyond 1.8mm.

Phase Display

It is interesting to see the effect that motion artifacts have on the phase of the signal. The simulation was run with the following parameters: $t_e = 80\text{ms}$, $TR = 5\text{s}$, $\delta = 34\text{ms}$, $\Delta = 40\text{ms}$ and $g = 22.5\text{mT/m}$. These are identical to those used by Young et al for phase display imaging of the brain.

The measured phase of the signal is shown in Figure 5.29 below.

![Figure 5.29 Theoretical prediction of measured phase varying with increasing motion amplitudes.](image)

Again, this is a dramatic effect, and shows that if the amplitude
of the motion is above about 0.3mm then the measured phase will be greatly over-estimated.

Rephasing Techniques

The oscillating position which represents motion can be broken down into its frequency components by Fourier Analysis. The components will either be odd or even functions as illustrated simply in Figure 5.30.

\[
\begin{align*}
\text{90} & \quad \text{180} & \quad \text{180} \\
\text{odd} & \quad \text{even}
\end{align*}
\]

*Figure 5.30* Odd and even frequency components in relation to even echo sequence.

For an odd frequency component there will be rephasing on the second echo (the even echo rephasing phenomenon). For even frequency components the phase offset will be double that of a single echo and therefore the artifacts will be twice as bad.

The combined effect will depend entirely on the nature of the oscillation, but it would be between zero and twice as bad.

The nature of the increase of the ghosts with increasing gradient strength and motion amplitude would however be the same.
For a rephasing technique which provides quantitative information (the one described in Chapter Six), the problem of ghosts would be virtually identical in both sequences since the b factors are the same for both sequence. (It was seen that it did not matter to any great extent whether δ or g was changed as long as the gradient factor remained the same). Therefore there will be no problems obtaining good results in the presence of motion artifacts, as long as the motion remains constant.

In conclusion it has been seen that the motion artifacts are greatly increased when additional gradients are applied. The amplitude of the motion when these effects are very noticeable (1/10ths of millimeters) are within the range that would be expected from pulsatile tissue. Therefore it can be deduced that diffusion and perfusion imaging techniques will generally suffer from elevated measurements when the object under investigation undergoes motion - be it pulsatile tissue in the brain or organs affected by respiratory flow.
5.4.2 Effect of Flow Changes During Measurement

Recently, experiments have been set up to detect changes in flow as a result of some external stimulus. This section analyses how the various techniques cope with both changing velocity (v) of capillary flow and fraction (f) of perfusing spins since what happens during stimulation is not clear.

**IVIM Imaging**

The following is an analysis of the effect of changes in the perfusion fraction (f) and flow rate on the measured perfusion fraction (f\textsubscript{m}) and diffusion coefficient.

*Effect of Changing f on f\textsubscript{m}.* In general, changes in the perfusion fraction cause no problem. For plug flow, measurements were 4.6%, 9.2% and 1.8% for input perfusion fractions of 5, 10 and 2% respectively - all under-estimates by up to 10% . For laminar flow measurements are 4.1%, 8.3% and 1.7% for the same respective perfusion fractions - up to 18% under-estimation.

*Effect of Changing the Flow Rate on f\textsubscript{m}.* For plug flow, doubling the flow rate to 4mm/s reduces the perfusion fraction a little - from 4.6% to 4.1%. Whilst for laminar flow the same change increases it a little from 4.1% to 4.5% .

Reducing the flow rate to 0.8mm/s causes problems for both flow models. For plug flow the perfusion fraction is measured at 1.4% -
for an input value of 5%. For laminar flow, it is measured at 2.4% for the same value.

The reason why a change in flow rate causes a change in the measured perfusion fraction is due to the gradient factors not being suitable for a different flow rates. In the situation of a substantial change in the flow rate (illustrated by the change from 2mm/s to 0.8mm/s) it may prove prudent to chose b-factors suitable for a mid-point flow rate as a compromise. This will probably lead to a less severe change in the measured perfusion fraction.

Effect of Changing $f$ on the Diffusion Coefficient. The diffusion coefficients are determined most accurately for both flow models when the perfusion fractions are smallest which is what would be expected from the theory.

For plug flow, the measured values for an input diffusion coefficient of $1.25 \times 10^{-9} m^2/s$ are $1.235 \times 10^{-9} m^2/s$, $1.219 \times 10^{-9} m^2/s$ and $1.244 \times 10^{-9} m^2/s$ for perfusion fractions of 5, 10 and 2% respectively - all under-estimates. For laminar flow the respective values are $1.27 \times 10^{-9} m^2/s$, $1.292 \times 10^{-9} m^2/s$ and $1.258 \times 10^{-9} m^2/s$ - all over-estimates.

Effect of Changing the Flow Rate on the Diffusion Coefficient. The effect of changing the velocity for plug flow is predictable in that for a velocity of 0.8mm/s the value is $1.454 \times 10^{-2} m^2/s$ - an error of 16%. This is the velocity that caused problems because it was so different from the assumed value when calculating the gradient factors. For a velocity of 4mm/s the diffusion coefficient is slightly less accurate at $1.298 \times 10^{-2} m^2/s$ than the
1.235×10⁻² m²/s measured for 2mm/s.

For laminar flow the picture is similar - 1.333×10⁻² m²/s for a velocity of 0.8mm/s, but now 4mm/s being more accurate at 1.263×10⁻² m²/s than 1.27×10⁻² m²/s for 2mm/s.

A couple of conclusions may be arrived at. Most importantly, since sequence parameters are chosen with a particular flow rate or perfusion fraction in mind, when this changes it can severely affect measurements particularly if the flow rate is decreased (2mm/s to 0.8mm/s). Another important point to note is that it would appear that for a substantial increase in the flow rate, there is barely any change in the measured perfusion fraction. This has some serious implications for functional studies that measure \( f_m \), if the flow that accompanies stimulation increases its rate rather than occupying resting capillaries i.e., the flow rate increases rather than \( f \) changing.

**Phase Display**

The measured phase is given by

\[
\Phi_m = \tan^{-1} \left( \frac{f \sin \Phi \sqrt{(1-f)+f \cos \Phi}}{(1-f)+f \cos \Phi} \right)
\]  

(5.32)

If the fraction of perfusing spins \( f \) is changed this will merely result in a different measured phase which will accurately reflect the change occurring. However, if the velocity is changed this will
affect the measured phase since the gradient strength was chosen such that maximum \( \phi_v \) was obtained and hence largest measurable value of \( \phi_m \). This will mean that at less accurate measured phase will be obtained.

Rephasing Techniques

Since most rephasing techniques do not give quantitative information they would probably not be used for these types of studies. However for the rephasing technique proposed in Chapter Six, if the velocity was changed this would affect the attenuation factor \( F \). For an increase in \( v \), \( F \) would decrease and the technique would prove more accurate. For a decrease in \( v \), \( F \) would increase and result in less accuracy.

Changing the perfusion fraction would result in an accurate change in the measured fraction.
5.5 CONCLUSIONS

The matrix attached is a brief summary of the effects that different factors have on the various diffusion and perfusion imaging techniques.

General conclusions are that before undertaking an experiment, the investigator must be sure about the structure of the tissue (isotropic/isotropic) and the flow regime (coherent/incoherent) otherwise an inappropriate measuring technique may be chosen which may or may not give results which reflect the true situation. Having said this even if a perfusion imaging technique is appropriate to the tissue under investigation there exist many factors which can undermine the accuracy of the results including noise, motion artifacts and eddy currents.

Taking all of these factors into account it is in fact remarkable that there have been any consistent perfusion measurements.
Changing Dependent upon magnitude
Changing f will reduce A_s for phase display.

How of change, for changed f accuracy, changing
not critical. f motion
consistent. Phase over-estimate.

Flow
Motion
Motion Effects
Flow and Motion

Flow
Motion
Motion Effects
Flow and Motion

Complex - dependent upon nature of the eddy currents and the orientation of the flow encoding gradients.

Decompose
Measured pump

time

Flow
Model
Experimental
Factors
Techniques
CHAPTER VI

A NEW METHOD OF PERFUSION MEASUREMENT
6.1 INTRODUCTION

In a summary of the available perfusion imaging sequences Le Bihan categorized them into three different groups: (i). Intravoxel Incoherent Motion Imaging - which relies on amplitude attenuation due to incoherent intravoxel motions, (ii). Refocusing Imaging Techniques which separate out the capillary blood flow that is coherent by either flow compensation gradients or even echo rephasing and (iii). Intravoxel Coherent Motion Imaging which looks at macroscopic coherence and detects phase information.

The methods in the second category - Refocusing Techniques - at present do not give a measurable quantity that could be called 'perfusion' since the calculated images contain other information besides microcirculatory flow ($T_1$, $T_2$ etc.). A new technique is described which falls into the refocusing technique category (for coherent flow) and which does give quantitative information. This information is the form of a perfusion fraction analogous to that used by Le Bihan.

6.1.1 Description of Model

Consider a simple model of a voxel of tissue which consists mainly of diffusing only intra- and extra-cellular fluid, and a small fraction of diffusing and flowing fluid. It is this small fraction of flow that is of interest and represents the capillary blood flow. Only coherent flow is included in this model which is reasonable for short echo times, and relatively long capillary
There are a variety of contributory factors determining the signal from a voxel of tissue. These include diffusion coefficients, attenuation due to perfusion and relaxation times. The contributions of each of these factors depends upon the ratio of the amount of flowing spins to stationary spins. Two assumptions are also made: the relaxation times and diffusion coefficients of the stationary tissue and moving fluid the same. This is a standard assumption (c.f. Le Bihan) and is not unreasonable. The signal from a voxel in the tissue can then be described mathematically by

$$S = [(1-f) + f.A(C)]A(D).A(T_1).A(T_2)$$  \hspace{1cm} (6.1)

where attenuations due to coherent perfusion, diffusion, $T_1$ and $T_2$ are represented by $A(C)$, $A(D)$, $A(T_1)$ and $A(T_2)$ respectively and $f$ is the small fraction of perfusing spins. It should be emphasized that an appropriate area of tissue needs to be selected such that
the assumptions hold (i.e., small f) and the tissue is uniform throughout the field of view selected.

It was seen in 4.2.4.3 that the attenuation due to coherent perfusion is given by either \( \text{sinc}(cv_0/\pi) \) or \( \text{Si}(2cv_0)/(2cv_0) \) for plug and laminar flow respectively. For a first sequence if the c factor (which is representative of the gradient strength and duration) is very large then the attenuation due to coherent perfusion, \( A(C) \approx 0 \) and therefore

\[
S_1 = (1-f)A(D).A(T_1).A(T_2)
\]  

(6.2)

In a second sequence, since the flow is coherent it can be rephased on even echoes, then \( A(C) = 1 \) for even echoes hence

\[
S_2 = A(D).A(T_1).A(T_2)
\]  

(6.3)

If the b factors (which determine attenuation due to diffusion and are also representative of gradient strength and duration) are the same for both sequences, and the second echo of sequence 2 is concurrent with the echo from sequence 1 then dividing the two signals will give

\[
\frac{S_1}{S_2} = 1-f
\]  

(6.4)

Therefore from the combination of just two sequences : a single and double echo, it is possible to obtain a quantitative measurement of the perfusion fraction.

In order to satisfy the condition of \( A(C)=0 \) for the first
sequence, very large gradients are required. This poses problems: a requirement for very high gradient strengths and a resulting low signal due to diffusion attenuation.

### 6.1.2 Example Calculation

For the plug flow model i.e., \( A(C) = \sin(cv_0/(c\nu_c)) \), a reasonable approximation to zero would be an attenuation to 10% of the original signal size. Figure 6.2 below shows timing diagrams for sequences 1 and 2.

![Timing diagrams for single and double echo sequences](image)

Figure 6.2 Timing diagram for the single and double echo sequences.

For a velocity of 2mm/s, attenuation to 10% would correspond to a necessary c factor of 5000s/m. The gradient factor is given by
\[ c = \gamma g \delta \Delta \]  
\text{(6.5)}

where \( \delta \) is the duration of the gradient pulses and \( \Delta \) the time between the start of the two pulses. For \( c_1 = 5000 \text{s/m} \), \( \delta_1 = 20 \text{ms} \) and \( \Delta_1 = 40 \text{ms} \), the gradient strength \( g_1 \) needs to be 23.4 mT/m.

The \( b \) factor is given by

\[ b = \gamma^2 g^2 \delta^2 (\Delta - \delta/3) \]  
\text{(6.6)}

and the corresponding \( b \) factor for \( c=5000 \text{s/m} \) and the appropriate timings is \( 5.21 \times 10^8 \text{s/m}^2 \).

The \( b \) factor from this sequence has to be matched with that for sequence two to give identical attenuation due to diffusion. For \( \delta_2 = 15 \text{ms} \) and \( \Delta_2 = 20 \text{ms} \), \( g_2 \) must be 32.8 mT/m. A number of computer programs were written to allow easy computation of the \( b \) and \( c \) factors. An example is included in Appendix 7.

The values for \( g_1 \) and \( g_2 \) of 23.4 and 32.8 mT/m respectively are large and would be beyond the range of most standard whole body gradients. However the insert gradient constructed for this programme of work is capable of delivering up to 64 mT/m so this should not be a problem. However, the \( b \) factor of \( 5.21 \times 10^8 \text{s/m}^2 \) produces an attenuation of 73\% for a diffusion coefficient of \( 2.5 \times 10^{-9} \text{m}^2/\text{s} \) (diffusion coefficient of water). This low level of signal needs to be compensated for by taking a lot of averages, which is not a great problem for the phantom experiments but is more problematic for in-vivo experiments.
6.2 PHANTOM EXPERIMENTS

The main aim of this section is to analyse the new technique in the controlled environment of a phantom before using it the human body where conditions are less well defined.

The standard method of diffusion/perfusion imaging, IVIM was also carried out in order to validate the general set-up, and to provide data for comparison with the novel technique.

6.2.1 Procedure

A number of different experiments were undertaken using the equipment described in Chapter 3 and with the IVIM experiments being carried out concurrently with the novel technique experiments.

The importance of a high signal-to-noise (SNR) was detailed in 5.2.2. The SNR is already compromised to a certain extent by carrying out the experiments on a 0.5T magnet. There is the additional serious problem of using the insert gradient which has a high inductance and therefore very slow ramp times leading to long echo times. This is further exacibated by the '50Hz effect' (3.4.1) which limits the echo time to multiples of 40ms. Everything possible had to be done to achieve the best SNR given the above limitations. This basically came down to using long repetition rates (to minimize $T_1$ relaxation effects), using several averages and only acquiring low resolution images ($64\times64$ pixels).

Initially the phantom work was carried out using distilled water
because it was desirable to have the attenuation due to $T_2$ relaxation considerably different from that due to diffusion. After conducting several experiments it was decided to change to water doped with CuSO$_4$ since this reduced the value of $T_1$ and hence allowed faster repetition rates to be used. (The time taken to acquire a data set for the novel technique was as much as 9 hours using distilled water).

The r.f. coil used (3.1.3) had an intrinsically high Q factor which would have lead to excessively high voltages in the coil and breakdown of capacitors. In order to reduce the Q factor a loading phantom was used which was simply a large saline filled bottle.

In the initial experiments the IVIM experiment and novel experiment were run concurrently to facilitate comparison (within the obvious constraints that IVIM detects incoherent flow and the novel technique only coherent flow).

**Maths of the IVIM Imaging Technique**

The following summarises the steps to go through in order to obtain the diffusion coefficient and the perfusion fraction using the IVIM imaging technique$^{41}$.

A number of sequences are used. The first one has no additional gradients except for the imaging gradients which are chosen to be of a scale where they do not cause significant attenuation due to diffusion. Additional gradients of different strengths are applied in subsequent sequences.

The signal at the centre of the echo obtained from any of the sequences can be described by
\[ S(TE) = S(0) \cdot \exp(-TE/2) \cdot \exp(-bD)[(1-f) + fF] \]  \hspace{1cm} (6.7)

where \( F \) is the attenuation due to microcirculation given by \( \exp(-bD^*) \) where \( D^* \) is the pseudo-diffusion coefficient. For the first sequence with no additional gradients \( \exp(-b_0D) = 1 \) and \( F = 1 \) i.e.,

\[ S(TE) = S(0) \cdot \exp(-TE/T2) \]  \hspace{1cm} (6.8)

For the other sequences the additional gradients are large enough to make \( F = 0 \) i.e.,

\[ S(TE) = S(0) \cdot \exp(-TE/T2) \cdot \exp(-bD)(1 - f) \]  \hspace{1cm} (6.9)

From equation (2.12) it is possible to deduce an apparent diffusion coefficient

\[ ADC = \log(S_0/S)/(b-b_0) \]  \hspace{1cm} (6.10)

Combining equations (6.8) and (6.9) as in (6.10) gives

\[ ADC = D + \log[1/(1-f)]/(b-b_0) \]  \hspace{1cm} (6.11)

or since \( f \ll 1 \)

\[ ADC \approx D + f/(b-b_0) \]  \hspace{1cm} (6.12)

From equation (6.10) and (6.12)
\[
\log\left(\frac{S_0}{S}\right) / (b - b_0) = D + f / (b - b_0)
\]  
(6.13)

or rearranging gives

\[
\log\left(\frac{S_0}{S}\right) = (b - b_0)D + f
\]  
(6.14)

i.e., plot \(\log\left(\frac{S_0}{S}\right)\) against \(b - b_0\) and the diffusion coefficient will be the gradient of the slope and the perfusion fraction \(f\) will be the intercept.

### 6.2.2 Results - IVIM Technique

**Experiment 1 - IVIM Imaging (I)**

Gradient factors of between 0 and \(3.53 \times 10^9 \text{m}^2/\text{s}\) were used to determine the diffusion coefficients of water and acetone, and the perfusion fraction of the flow phantom.

A flow rate of 6mls/min was established in the phantom using the pump. Imaging parameters for the experiment were: \(t_e = 160\text{ms}, TR = 3\text{s}, \delta = 40\text{ms}\) and \(\Delta = 68\text{ms}\) (see Figure 6.2 for timing diagram). Four averages were taken for each image.

Figure 6.3 overleaf shows the image obtained for a gradient factor of zero.
Figure 6.3 Image of water, acetone, perfusion and loading phantom.

From the top going clockwise the phantoms are perfusion, loading, acetone and water.

There was a large loading phantom (filled with a salt solution) in order to adequately load the coil which had an intrinsically high Q factor.

The diffusion coefficient of the static and flowing water should be the same.

Figure 6.4 overleaf is a plot of $\ln(S_0/S)$ versus b factor where $S$ is the signal intensity obtained from a ROI average (using software on the IP2000) and $S_0$ is that intensity obtained for a b factor of zero.
This experiment gave diffusion coefficients of $6.7 \times 10^{-9}$, $4.68 \times 10^{-9}$ and $4.23 \times 10^{-9}$ m$^2$/s for acetone, static water and flowing water respectively and a perfusion fraction of the flow phantom was measured at about 25%.

The figures for the diffusion coefficients are much too large. Acetone and water diffusion coefficients are given as $4.5-4.8 \times 10^{-9}$ m$^2$/s and $2.25-2.51 \times 10^{-9}$ m$^2$/s respectively in the literature. From equation (2.12) this implies that either the gradient factor was larger than that calculated or $S$ was too small i.e., there was too much attenuation of the signal when the diffusion gradient was applied. The gradient was re-calibrated at a appropriate value and the gradient factor calculation checked but
there was no obvious problem. In section 5.3.3 it was illustrated how unbalanced diffusion gradients can cause substantial signal attenuation with resulting over-estimation of the diffusion coefficient and perfusion fraction. This was the most likely source of error.

As a result of this the sequence was modified so that the gradient balancing could be finely tuned by varying the lengths of the gradients by as little as a microsecond.

Experiment 2 - IVIM Imaging (II)

With the adjustments made to the sequence (and leaving out the glass water and acetone phantoms in case of any susceptibility effects) the experiment was repeated. The parameters were the same as before. Figure 6.5 illustrates the results.

![Figure 6.5](image-url)  
*Figure 6.5 Experiment II: Plot of \( \ln(S_0/S) \) versus \( b \) to obtain diffusion coefficient and perfusion fraction.*
Measured diffusion coefficients for the water of the loading phantom and flow phantom were now 2.2 and \(2.35 \times 10^{-9} \times 10^{-9} \text{m}^2/\text{s}\) respectively. These diffusion coefficients are in good agreement with the literature values.

It was not however possible to detect a perfusion fraction.

Experiment 3 - IVIM Imaging (III)

The experiment was repeated with phantom Mark II and doped water. This time 8 averages were taken and the range of b factors went up to \(6 \times 10^8 \text{m}^2/\text{s}\). The imaging parameters were: \(t_e = 80 \text{ms}, TR = 1 \text{s}, \delta = 20 \text{ms}\) and \(\Delta = 42 \text{ms}\). Repeat readings were taken at several points - the results are shown on Figure 6.6 below.

![Figure 6.6 Experiment III: Plot of \(\ln(S_0/S)\) versus \(b\) to obtain diffusion coefficient and perfusion fraction.](image)

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The diffusion coefficients for the loading and flow phantom are 2.49 and $2.31 \times 10^9 m^2/s$ respectively, with a perfusion fraction of about 20%.

6.2.3 Results - Novel Technique

6.2.3.1 Investigation 1 - Changing the Flow Rate

The new technique is based on the phenomenon of even echo rephasing which means that on even echoes of a spin echo sequence the flowing spins are rephased. Thus the attenuation factor $A(C)$ due to perfusion (see 6.1.1) is equal to one. However, this is only the case if the perfusion is coherent (flow does not change direction) during the measurement time. If the flow is incoherent there will be no rephasing of this flow and hence the attenuation factor $F$ will no longer be equal to one.

This transition from coherent to incoherent flow and it's effect on the technique can be investigated using the phantom by varying the likelihood of the flow changing direction. This could be achieved by either changing the measurement (echo) time or varying the flow rate. Lengthening the echo time would compromise the signal-to-noise ratio which would not be acceptable for this perfusion imaging experiment, so the flow rate was varied.

Figure 6.7 overleaf gives an indication of what would be expected for a variation in the flow rate.
When there is no flow the normalized images from the single and double echoes would be the same. Then there would be a time whilst the flow was generally coherent because of the low flow rate when the perfusion fraction would tend to a maximum measurable value. The reason why it tends to this value is because for the single echo, the attenuation factor $A(C)$ (which must be approximately zero for the single echo sequence) approaches zero as the velocity increases.

At the turning point of the curve the velocity of the flow causes maximum attenuation in the single echo image and at the same time the flow reaches the transition between the two flow regimes. The graph should then tend towards one. This is because a more full description of the signal than that given in equation (6.1) is
\[ S = [(1-f_{\text{incoh}}) + f_{\text{incoh}} A(\text{IC}) + (1-f_{\text{coh}}) + f_{\text{coh}} A(\text{C})] \]  

(6.15)

where \( A(\text{IC}) \) (attenuation due to incoherent perfusion) is given by \( \exp(-bD^*) \). Since the \( b \) factors are the same for both sequences, (i.e., \( A(\text{IC}) \) is the same) and \( f_{\text{coh}} \to 0 \), the signal from both sequences will be identical, and their ratio one.

**Experiment 1 - Effect of Changing the Flow Rate (I)**

Flow rates of between 0 and 10mls/min were used. At each point images were acquired using the single and double echo sequence with echo times of 80 and 40ms respectively so that the effect of \( T_2 \) attenuation would be the same for both sequences. The \( c \) factor was 5000s/m for the single echo sequence which is equivalent to a \( b \) factor of \( 4.9\times10^8 \text{m}^2/\text{s} \) (the \( b \) factor was the same for both sequences to ensure attenuation due to diffusion was the same). The large value of the gradient factor leads to considerable signal attenuation and therefore 8 averages were taken to improve the signal-to-noise ratio.

Figure 6.6 overleaf is a plot of \( 1-f \) against flow rate obtained by dividing the single echo image by the normalized even echo image.

N.B. The term *normalised* here means that the level of signal from the single and double echo sequence should be the same for the case of no flow. This was achieved by comparing the image.
intensity of the loading phantom for both sequences.

![Graph](image)

*Figure 6.8 Experiment 1: \((1-\ell)\) versus the flow rate.*

The origin does not go through 1 and the graph tails off at high flow rates pointing possibly to badly balanced gradients and inaccurate measurements at higher flow rates.

**Experiment 2 - Effect of Changing the Flow Rate (II)**

The experiment was repeated with the same imaging parameters. This time the results gave the curve illustrated in Figure 6.9 overleaf.
Again the origin of the graph does not go through 1, but the curve is a similar shape and it does tend towards 1 at high flow rates.

It was realized that not enough time had been left between different flow rates in order to establish a steady rate of flow. In experiment 1 the results had been obtained in descending values of flow rate, in experiment 2 in ascending values. Therefore one would expect a dip at a lower flow rate in experiment 1 since the real flow rate was probably higher than was realized. A delay of 30 minutes between each flow rate change was decided upon to establish a steady rate of flow.
Experiment 3 - Effect of Changing the Flow Rate (III)

At this time it became clear in the IVIM experiments that the balancing of the diffusion gradients was critical in the set-up. This addition was made to both the single and double echo sequences.

The experiment was repeated again with the same parameters as before and the results obtained are shown in Figure 6.10.

![Figure 6.10 Experiment III : (1-f) versus the flow rate.](image)

This time the origin is very nearly at 1. The dip is at 6mls/min and the graph could well be tending to 1 at high flow rates. A perfusion fraction of 4.6% can be deduced from this data.
Experiment 4 - Effect of Changing the Flow Rate (IV)

This final experiment used doped water and hence a faster repetition rate. This enabled more points on the graph to be obtained in one day. The experient also used phantom Mark III which inadvertently contained slightly less Sephadex. Figure 6.11 shows the results.

![Graph showing the results of Experiment IV](image)

*Figure 6.11 Experiment IV :$(1-f)$ versus the flow rate.*

Repeat readings were taken at the zero flow rate. They were all accurate to within 1.5%. A measurement was also repeated at 6mls/min - it varied by 3% It should be expected that the errors would increase for higher flow rates because the level of signal gets smaller. The reason for this can be speculated as being due to the fact that as the flow rate increases the flow becomes more incoherent and mimics diffusion - this 'pseudo-diffusion'
coefficient becomes greater as the flow rate increases and hence there is more attenuation of the signal.

The perfusion fraction deduced from this graph is between 12 and 15%. The reason why it is so much higher than for experiment 3 is probably due to the fact that there was a smaller amount of Sephadex and hence a larger amount of perfusing water.

6.2.3.2 Investigation 2 - Changing the Gradient Factors

As mentioned in 6.2.3.1, the changing velocity causes a change in the attenuation factor A(C) of the single echo sequence. Changing the c factor with all other factors held the same will also cause a change in F. As the c factor increases F gets smaller and the measured perfusion fraction should tend to a maximum as illustrated in theoretical curves in Figures 6.12 and 6.13.

![Figure 6.12 Attenuation factor versus increasing c factor.](image)
Figure 6.12 shows the attenuation factor $F$ for increasing $c$ factor (for two different flow models). Figure 6.13 shows the resultant signal intensity from $(1-f)+fF$ which tends to a value of $1-f$ from above i.e., the perfusion fraction tends towards $f$ from below.

The experiment was carried out on the flow phantom with $c$ factors ranging from 0 to 3795 s/m with a constant flow rate.

Figure 6.14 below shows the results.
This appears to agree very well with the theory with increasing $f$ at higher $c$ factors. The ‘blip’ in the curve may be due to a sinc ‘wiggle’ from Figure 6.12, or may just be indicative of the margin of error. Repeat readings were taken at two different points, and measurements were to within one percent of each other. If the repeat readings had been taken at the highest $c$ factors the margins of error would have been greater since the standard deviation of the regions of interest was larger for these scans due to lower signal intensity with larger gradient factors.

A collection of theoretical curves may be obtained for different velocities, and by finding the closest of these to the phantom results, an average velocity may be determined for the phantom flow.
6.3 IN-VIVO FLOW EXPERIMENTS

In this section an in-vivo application of the new technique is described. The work is broken down into sections on choice of tissue, choice of dimensionality of the experiment, setting up of the single and double echo sequences and results. Also included at the end are several experiments using the IVIM technique which tie in with the theoretical work of 5.2.1.

6.3.1 Choice of In-Vivo Flow System

It is necessary to use the new technique in an environment where there is coherent flow since it is a rephasing technique. Also, in order to thoroughly investigate the technique it is useful to choose a flow system that can exhibit a change in the flow rate.

It was decided to measure flow in the calf muscle since capillaries in the muscle are arranged essentially parallel and therefore the flow would be coherent. (The flow would also be anisotropic but the technique should still work (see 5.2.1)). The flow in the calf muscle is easily reduced by applying a pressure cuff (see 3.3) and this reduction can be monitored.
6.3.2 Initial Choice of Dimensionality

Section 6.2.1 re-iterated the importance of having the very best signal-to-noise ratio possible and the requirement of having a large number of averages. In the phantom experiments eight averages were taken (which took over eight minutes to acquire). It would be very likely that a leg (which will load the coil more hence reducing the Q factor) will have a greater intrinsic noise associated with it. Therefore an experiment which uses the calf muscle will require many more than eight averages. Also, the echo time was 160ms due to timing restrictions (see 3.4) which is long and therefore results in a reduced signal-to-noise ratio, again requiring more averages.

The restriction of flow to the calf muscle by applying a pressure cuff above the knee can only be sustained for 2 or 3 minutes - this is much less than the time required for even eight averages. A shorter repetition rate may help matters but there is a limit to this governed by the duty cycle of the gradient set. Therefore 2D imaging of flow changes in the calf muscle was not a feasible option at the magnetic field strength available.

The alternative is to lose a spatial dimension and look at a profile of the leg. This can either be done by selecting a column using two orthogonal slice select gradients (which provides more localized information) or by merely selecting a slice, and reading along the length of it (providing a profile of the whole slice of the leg). For both these techniques an initial image would be needed in order to determine the position of bone and major blood vessels which need to be avoided. A low resolution image of the
calf muscle typical of the type obtained before a flow experiment is shown in Figure 6.15. It illustrates the presence of vessels and bone, and the areas free from structure.

![Figure 6.15 Low resolution transverse image of calf muscle.](image)

For an average size leg it is be possible to select an area free from bone and vessels.

A low resolution image was taken before each scan so that the input parameters would be the same as for the flow sequences so that setting up time could be kept to a minimum.

(The requirement for low resolution images hence improved SNR was even more critical for the in-vivo work).

### 6.3.3 Setting up the Single Echo Sequence

**Problems of Pulse Timings and Gradient Balancing.**

Initially it was decided to use a sequence that selected a column of tissue using orthogonal slice select gradients. The sequence was identical to that used by Feinberg et al, except for the addition of flow gradients in the z direction. See Figure 6.16 overleaf.
There were a couple of practical difficulties in the setting up of this pulse sequence. Firstly, because both the 90° and 180° pulses were selective it was difficult finding a systematic method of setting the pulse lengths and gradient durations such that all pulse timings were optimized, and all gradients properly balanced. This problem was solved to a certain extent by writing a pulse sequence which consisted solely of a selective 90° pulse. The pulse length and gradient compensation could then be set up in isolation, and the values then inserted into the full spin echo sequence.

Another problem was due to the profile of the insert gradient waveform. Pre-emphasis of the gradients was optimized for the whole body gradients and so was not appropriate to the insert gradient. The profile had an overshoot on the rising edge of the waveform. This was overcome by putting a delay of 2ms after the rise of the gradient so that the r.f. pulse was on during a reasonably flat part
of the waveform.

The combined effect of these two problems was a tedious set-up procedure in which the signal became more unstable when flow encoding gradients were added - the instability increasing for increasing gradient strengths.

During the initial experimental work there were great problems in setting up the sequence which were thought to be due to badly balanced gradients. It transpired that the problem was actually due to breakdown of the r.f. coil at larger pulse angles. (This was a saddle coil chosen for it's good SNR, but which was then replaced by the birdcage coil described in 3.1.3 and used for the phantom experiments).

Problems of Motion

In a paper by Chenevert et al\textsuperscript{72} the problem of macroscopic motion in imaging was discussed. They showed that for 2DFT imaging unwanted motion would be a problem if averaging was carried out before the Fourier Transform of the 1D sequence. Software was therefore written so that data from different acquisitions was stored sequentially in different 'frames', then Fourier transformed \textit{then} averaged. (It was in fact necessary to obtain two averages for each frame in order to correct for a DC offset that existed).

Truncation Artifacts

The profile of a column through a phantom using the single echo sequence is shown in Figure 6.17 overleaf. The particular permutation of the slice selection gradients for this sequence was $90^\circ_z$ and $180^\circ_y$. 

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The phantom was a 20cm diameter, 4cm length cylinder filled with a CuSO₄ solution. This profile is obviously not an accurate representation of the column that was selected. A clue to the origin of the ripples is the frequency of the oscillation. The period of the oscillation in the frequency domain is about 300Hz. The reciprocal of this is about 3ms which is half the total length of the frequency encoding gradient. It was therefore deduced that the ripples were due to truncation of the echo signal because the Fourier transform of a rectangle (the truncated echo) is a sinc shape. A program employing a cosine squared filter was written in order to smooth out the edges of the echo. The profile resulting from filtering is shown in Figure 6.18 overleaf.
This is obviously much better. The root cause of this problem was background noise on the acquired echo which came from a variety of different sources (poor connections on gradient filters, interference from the gradient amplifiers on the received signal and problem of mains synchronization). These were dealt with as they became apparent and when they could be located.

### 6.3.4 Setting up the Double Echo Sequence

The double echo sequence is shown in Figure 6.19 overleaf.
Referring back to 3.4 it was seen that the only reasonable way of fitting in all the gradient profiles (bearing in mind a ramp time of 4ms for the z-gradient) was to ramp the flow encoding gradients down to slice selection.

It would be expected that with the same gradient factors the level of signal from the double echo sequence would be the same as for the single echo sequence. (This had been true for the 2D sequences used in the phantom work). However, this turned out not to be the case. The level of signal from the double echo sequence was much lower hence leading to a much poorer SNR. The lone selective 90° pulse set-up program was run to obtain appropriate values for the first part of the double echo sequence and values for the 180° pulse lengths were taken from the set-up of the single echo sequence, but values for the balancing of the flow encoding gradients came from trial and error. There was no systematic method of balancing the gradients. The two pairs could not be set up in isolation from one another because of the profile of the flow encoding gradient being used in slice selection.
It was decided to give up a degree of localization and instead obtain a simple profile of the leg using just one gradient axis. If the read gradient was in the correct direction enough of the leg which contained muscle tissue only could be seen. This eased problems in setting up of the double echo sequence and also made for a simpler set up of the single echo sequence.

6.3.5 Results

Using the simple profile acquisition of the single and double echo sequences results for the new technique were then obtained. In order to properly calibrate the perfusion fraction, a small bottle of doped water was placed alongside the leg in a manner analogous to that in 6.2.3.

6.3.5.1 Investigation 1 - Changing the Gradient Factor

As in 6.2.3.2 the effect of changing the c factor is investigated. Six profiles were obtained - a single and double echo sequence for each of three different c factors - 0, 2000s/m and 5000s/m. These profiles are shown in Figure 6.20 overleaf. The object on the left side of the graph is the normalization phantom required for this technique.
Figure 6.20 Investigation I(i) : Profiles of the flow phantom for varying c factors.

A plot of the perfusion fractions with an expanded horizontal scale for the relevant points is shown in Figure 6.21 below.

Figure 6.21 Investigation I(i) : Perfusion fraction of the calf muscle for varying c factors.
These plots are in agreement with that be predicted by theory and was seen in the phantom experiments with increasing perfusion fractions for increasing c factors. The experiment was repeated and similar results were obtained. The perfusion fractions for the relevant points are shown in Figure 6.20 below.

![Perfusion Fraction vs Pixel Number](image)

**Figure 6.22** Investigation I(ii): Perfusion fraction of the calf muscle for varying c factors.

Again the fractions showed a gradual increase for increasing c factors but a smaller increase than in the previous experiment.

N.B. It should be noted that when the sequence was run with the largest gradient factor the signal was unstable due to the decrease in the SNR and therefore much more difficult to critically balance the additional gradients.

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6.3.5.2 Investigation 2 - Changing the Flow Rate

The changing flow rate experiment was then undertaken. For this experiment the largest gradient factor was used in order to obtain the most accurate perfusion fraction. The experiment was carried out for flow before, during and after flow restriction. The first experiment yielded results shown in Figure 6.23 below.

![Perfusion Fraction Graph](image)

**Figure 6.23 Investigation 2(ii): Perfusion fraction of the calf muscle for varying flow rates.**

These are quite promising results with some decrease in $f$ during restriction (pixels 25 and 26) and then an increase in the fraction again, but to levels less than pre-restriction.

The change in the measured perfusion fraction is small however and it may be that they all fall within a margin of error.

The experiment was repeated but produced different results.
as shown in Figure 6.24.

![Graph showing perfusion fraction of the calf muscle for varying flow rates.]

**Figure 6.24** Investigation 39(ii): Perfusion fraction of the calf muscle for varying flow rates.

This time, before restriction the measured perfusion fraction is negative which could presumably just be the margin of error of the measurement. During restriction the perfusion fraction increases slightly for a couple of pixels, decreases for the others, and after the restriction is removed, the fraction goes much higher.

It was very clear from the set-up of these experiments that because it was necessary to use the highest $c$ factor ($c=5000\text{s/m}$) there were problems of stability as mentioned in Investigation 1 and this undoubtedly had very serious consequences in the resulting accuracy of the measurements.
6.3.6 IVIM Technique

The IVIM technique is supposed to be applicable to *incoherent* motions i.e., that flow which changes direction during measurement time. However, it was shown in 5.2.2 that it was possible to obtain apparently sensible results with the technique in the regime of *coherent* flow. In this section the IVIM technique is used in the calf muscle to investigate what happens in practice.

The technique requires only a single echo. A column was selected using two orthogonal gradients and the perfusion fraction calculated before, during and after restriction. The experiment used gradient factors of 0, $7.7 \times 10^7$ and $17.3 \times 10^7$ s/m². The perfusion fractions are plotted in Figure 6.25 below.

![Perfusion Fraction Graph](image)

**Figure 6.25** IVIM technique (9) : Perfusion fraction of the calf muscle with varying flow rates.

Remarkably these perfusion fractions show a consistency with what would be expected from the experiment: a lowering of the perfusion fraction during restriction of the flow, then an
increases again after the pressure is released. Averaged over the relevant data points (i.e., those not containing bone or large vessels) the values were 49%, 1% and 20% for before during and after restriction respectively. The experiment was repeated but the results this time were quite different as can be seen in Figure 6.26.

![Graph](image)

**Figure 6.25 IVIM technique** (33) : Perfusion fraction of the calf muscle with varying flow rates.

This time, averaged results were 1.6%, 0.7% and 0.8% for before, during and after which makes no sense at all.

No firm conclusions can be drawn from this since the two sets of results differ so wildly. It does however show how it could be possible for other investigators to get apparently sensible results when applied to an appropriate tissue model.
In this chapter the basic principles of a new method of obtaining quantitative perfusion measurements has been demonstrated. The major problems of the hardware in the successful implementation have been identified as being an inherently low SNR at 0.5T and a long ramp time of the insert gradient leading to long echo times and hence further degradation of the SNR.

The technique proved successful in the phantom work with reproducible results and clear agreement with the proposed theory. This technique could be used in phantom work where quantitative measurements of small fractions of flow are required e.g. in the study of oil and water in rocks for the oil industry.

Unfortunately the poor SNR severely affected the in-vivo work and it was not thought constructive to pursue the work with the hardware that was available.

In order to take this technique further actively shielded (and low inductance) gradients and a high field (2T) magnet would be required. These hardware requirements are not beyond the limits of many clinical systems available now.

In a clinical environment with the appropriate hardware (high strength, low inductance gradients and high field magnet) the technique could be used to investigate any coherent microscopic flow in the body. For example one could do a time course study of a muscle strain injury, where there would be elevated capillary flow due to tissue damage. Quantitative measurements could be made to assess the degree of injury.
APPENDIX 1

The Bloch equation may be given as

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

where \( B_{\text{eff}} = (B_0 - \omega/\gamma) k + B_1 i \).

During pulse

\[ B_1 > (B_0 - \omega/\gamma) \]

\[ \therefore B_{\text{eff}} = B_1 i \]

Also relaxation effects are negligible so ignore \( T_1, T_2 \) terms.

\[ \therefore \frac{dM}{dt} = \gamma M \times B_1 i = \gamma \begin{vmatrix} i & j & k \\ M_x & M_y & M_z \\ B_1 & 0 & 0 \end{vmatrix} \]

\[ = \gamma \{ iM B_{1 z} - kM B_{1 y} \} \]

\[ \therefore \frac{dM_x}{dt} = 0 \Rightarrow M_x(t) = \text{constant}, M_x(0) = \text{constant} \]

\[ \Rightarrow \text{constant} = M_x(0) \]

\[ \therefore M_x(t) = M_x(0) \]

\[ \frac{dM_y}{dt} = \gamma M B_{1 y} \]
\[
dM_z/dt = -\gamma M_y B_1
\]

To solve these, doubly differentiate:

\[
d^2M_y/dt^2 = \gamma dM_y/dt \times B_1 = -\gamma^2 M_y B_1^2 = -\omega^2 M_y
\]

\[
=> d^2M_y/dt^2 + \omega^2 M_y = 0 \tag{A1.1}
\]

\[
d^2M_z/dt^2 = -\gamma dM_z/dt \times B_1 = -\gamma^2 M_z B_1^2 = -\omega^2 M_z
\]

\[
=> d^2M_z/dt^2 + \omega^2 M_z = 0 \tag{A1.2}
\]

Solution to (A1.1)

\[
M_y(t) = A\cos(\omega t) + B\sin(\omega t)
\]

Solution to (A1.2)

\[
M_z(t) = C\cos(\omega t) + D\sin(\omega t)
\]

To find constants

\[
dM_y/dt = \omega B\cos(\omega t) - \omega A\sin(\omega t) = \omega M_z
\]

\[
= \omega C\cos(\omega t) + \omega D\sin(\omega t)
\]

\[
=> B = C \text{ and } A = -D
\]

\[
M_y(t) = A\cos(\omega t) + B\sin(\omega t)
\]

\[
M_z(t) = B\cos(\omega t) - A\sin(\omega t)
\]

Also, \( M_y(0) = A.1 + 0 \) \( \Rightarrow A = M_y(0) \)

and \( M_z(0) = B.1 - 0 \) \( \Rightarrow B = M_z(0) \)

\[
\therefore M_y(t) = M_y(0)\cos(\omega t) + M_z(0)\sin(\omega t) \tag{A1.3}
\]
\[ M_z(t) = M_z(0)\cos(\omega t) - M_y(0)\sin(\omega t) \quad (A1.4) \]

\[ M_x(t) = M_x(0) \quad (A1.5) \]

In order to put this into a matrix write out

\[
\begin{pmatrix}
  M_x(t) \\
  M_y(t) \\
  M_z(t)
\end{pmatrix} =
\begin{pmatrix}
  P_{11} & P_{12} & P_{13} \\
  P_{21} & P_{22} & P_{23} \\
  P_{31} & P_{32} & P_{33}
\end{pmatrix}
\begin{pmatrix}
  M_x(0) \\
  M_y(0) \\
  M_z(0)
\end{pmatrix}
\]

\[
\therefore M_x(t) = P_{11}M_x(0) + P_{12}M_y(0) + P_{13}M_z(0) \quad \text{c.f. (A1.5)}
\]

\[ P_{11} = 1, \ P_{12} = 0 \text{ and } P_{13} = 0 \]

\[
\therefore M_y(t) = P_{21}M_x(0) + P_{22}M_y(0) + P_{23}M_z(0) \quad \text{c.f. (A1.3)}
\]

\[ P_{21} = 0, \ P_{22} = \cos(\omega t) \text{ and } P_{23} = \sin(\omega t) \]

\[
\therefore M_z(t) = P_{31}M_x(0) + P_{32}M_y(0) + P_{33}M_z(0) \quad \text{c.f. (A1.4)}
\]

\[ P_{31} = 0, \ P_{32} = \sin(\omega t) \text{ and } P_{33} = \cos(\omega t) \]

\[
\therefore P(t) =
\begin{pmatrix}
  1 & 0 & 0 \\
  0 & \cos(\omega t) & \sin(\omega t) \\
  0 & -\sin(\omega t) & \cos(\omega t)
\end{pmatrix}
\]

**APPENDIX 2**

Between pulses there is no \( B_1 \), so \( B_{\text{eff}} = (B_0 - \omega/\gamma)k \)
\[ \begin{vmatrix} i & j & k \\ M_x & M_y & M_z \\ 0 & 0 & (B_o - \omega/\gamma) \end{vmatrix} = - (M_x i + M_y j) / T_2 - (M_z - M_0) k / T_1 \]

\[ \begin{align*}
\frac{dM_x}{dt} &= M_y (B_o - \omega/\gamma) - M_x / T_2 \\
\frac{dM_y}{dt} &= -M_x (B_o - \omega/\gamma) - M_y / T_2 \\
\frac{dM_z}{dt} &= -(M_z - M_0) / T_1
\end{align*} \tag{A2.1, A2.2, A2.3} \]

Solving (A2.3) first

\[ \int \frac{dM_z}{(M_z - M_0)} = - \int \frac{1}{T_1} dt \]

\[ \left[ \ln(M_z - M_0) \right] - \left[ \ln(-M_0 - M_0) \right] = - \left[ \frac{t}{T_1} \right] \]

\[ \ln \left( \frac{M_z - M_0}{-2M_0} \right) = - \frac{t}{T_1} \]

\[ M_z = M_0 (1 - 2e^{-t/T_1}) \tag{A2.4} \]

Solve equations (A2.1) and (A2.2) simultaneously

\[ \begin{align*}
\frac{dM_x}{dt} &= \gamma M_y (B_o - \omega/\gamma) - M_x / T_2 \\
\frac{dM_y}{dt} &= -\gamma M_x (B_o - \omega/\gamma) - M_y / T_2
\end{align*} \]

Substitute to simplify: \( M_x = X, M_y = Y, \alpha = -\gamma (B_o - \omega/\gamma) \) and \( \beta = 1 / T_2 \)

and rearranging

\[ \frac{dX}{dt} + \alpha Y + \beta X = 0 \]

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\[ \frac{dY}{dt} - \alpha X + \beta Y = 0 \]

First write operator \( \frac{d}{dt} \) as \( D \) to give

\[
(D + \beta)X + \alpha Y = 0 \quad (A2.5)
\]
\[
(D + \beta)Y - \alpha X = 0 \quad (A2.6)
\]

To eliminate \( X \), multiply (A2.5) by \( \alpha \) and (A2.6) by \( (D + \beta) \)

\[
\alpha (D + \beta)X + \alpha^2 Y = 0 \quad (A2.7)
\]
\[
-\alpha (D + \beta)X + (D + \beta)^2 = 0 \quad (A2.8)
\]

Adding (A2.7) to (A2.8) gives

\[
\alpha^2 Y + (D + \beta)^2 Y = 0 \quad (A2.9)
\]

Rearranging (A2.9) gives

\[
(D^2 + 2D\beta + \beta^2 + \alpha^2)Y = 0 \quad (A2.10)
\]

To solve this use the quadratic formula

\[
D = -\beta \pm i\alpha \quad (A2.11)
\]

i.e (A2.10) can be written

\[
(D + (\beta-i\alpha))(D + (\beta+i\alpha))Y = 0 \quad (A2.12)
\]

First bracket, \((D + (\beta-i\alpha))Y = 0 \quad \Rightarrow \frac{dY}{dt} = -(\beta-i\alpha)Y\)

Solution is

\[
Y = Ae^{-(\beta-i\alpha)t} \quad (A2.13)
\]

\( \beta \) and \( \alpha \) are both independent of \( t \) so
\[ Y = Ae^{-\beta t}e^{i\alpha t} \]  
(A2.14)

\[ = e^{-\beta t}(B\cos(\alpha t) + iC\sin(\alpha t)) \]  
(A2.15)

Second bracket, \((D + (\beta + i\alpha))Y = 0 \implies dY/dt = -(\beta + i\alpha)Y\)

Solution is

\[ Y = De^{-\beta t}e^{i\alpha t} \]  
(A2.16)

\[ = e^{-\beta t}(E\cos(\alpha t) - iF\sin(\alpha t)) \]  
(A2.17)

Final solution is a combination of these solutions:

\[ Y = e^{-\beta t}(B\cos(\alpha t) + E\cos(\alpha t) + iC\sin(\alpha t) - iF\sin(\alpha t)) \]

\[ = e^{-\beta t}(E\cos(\alpha t) + H\sin(\alpha t)) = M_y(t) \]

What are \(G\) and \(H\) ?

At \(t=0\), \(M_y(0) = 1.\) \(G = M_y(0)\)

To find \(H\) need to find \(M_x(t)\). Substitute for \(Y\) in (A2.6)

\[ \alpha X = dY/dt + \beta Y \]

\[ = -\beta Y + e^{-\beta t}(-\alpha G\sin(\alpha t) + \alpha H\cos(\alpha t)) + \beta Y \]

\[ \therefore X = e^{-\beta t}(-G\sin(\alpha t) + H\cos(\alpha t)) = M_x(t) \]

At \(t=0\), \(M_x(0) = 1.\) \(H = M_x(0)\)

\[ \therefore M_x(t) = e^{-\beta t}(M_x(0)\cos(\delta \omega t) - M_y(0)\sin(\delta \omega t)) \]  
(A2.18)

and \(M_y(t) = e^{-\beta t}(M_x(0)\sin(\delta \omega t) + M_y(0)\cos(\delta \omega t)) \)  
(A2.19)

Putting the solution into matrices
\[
\begin{pmatrix}
M_x(t) \\
M_y(t) \\
M_z(t)
\end{pmatrix} =
\begin{pmatrix}
R_{11} & R_{12} & R_{13} \\
R_{21} & R_{22} & R_{23} \\
R_{31} & R_{32} & R_{33}
\end{pmatrix}
\begin{pmatrix}
M_x(0) \\
M_y(0) \\
M_z(0)
\end{pmatrix}
\]

\[M_x(t) = R_{11}M_x(0) + R_{12}M_y(0) + R_{13}M_z(0)\]
c.f (A2.18)
\[R_{11} = e^{-\frac{T_2}{T}}\cos(\delta \omega t), R_{12} = -e^{-\frac{T_2}{T}}\sin(\delta \omega t)\text{ and } R_{13} = 0\]

\[M_y(t) = R_{21}M_x(0) + R_{22}M_y(0) + R_{23}M_z(0)\]
c.f (A2.19)
\[R_{21} = e^{-\frac{T_2}{T}}\sin(\delta \omega t), R_{22} = e^{-\frac{T_2}{T}}\cos(\delta \omega t)\text{ and } R_{23} = 0\]

\[M_z(t) = R_{31}M_x(0) + R_{32}M_y(0) + R_{33}M_z(0)\]
c.f (A2.4)
\[R_{31} = 0, R_{32} = 0\text{ and } R_{33} = (1-2e^{-\frac{T_1}{T}})\]

or \[R_{33} = e^{-\frac{T_1}{T}}\text{ and add } M_z(0)(1-e^{-\frac{T_1}{T}})\]

\[R(t_p) = \begin{pmatrix}
e^{-\frac{T_2}{T}}\cos(\delta \omega t) & -e^{-\frac{T_2}{T}}\sin(\delta \omega t) & 0 \\
e^{-\frac{T_2}{T}}\sin(\delta \omega t) & e^{-\frac{T_2}{T}}\cos(\delta \omega t) & 0 \\
0 & 0 & e^{-\frac{T_1}{T}}
\end{pmatrix}\]

\[\therefore \text{APPENDIX 3}\]

For gradients and flow.

\[B_{\text{eff}} = B_1 - (B_0 - \omega \gamma)k + (G_x + G_y + G_z)k\]

where \[G_x = (G_x + G_y + G_z)k\]

Between pulses there is no \(B_1\)

\[\therefore \frac{dM}{dt} = \gamma \begin{pmatrix}
i \\
j \\
k
\end{pmatrix} \begin{pmatrix}
M_x \\
M_y \\
M_z
\end{pmatrix}
\]

\[0 0 (B_0 - \omega \gamma + G_x + G_v t + G_w t^2/2)\]
(A2.1) and (A2.2) this time with $\alpha = \delta \omega - \gamma G.r - \gamma G.v.t - \gamma G.a.t^2/2$. However the assumption made that $\alpha$ is independent of $t$ is not valid in the case of flow so the first bracket of (A2.12) gives

$$ Y = e^{\beta t}(B\cos(\int \alpha dt) + iC\sin(\int \alpha dt)) \quad (A3.5) $$

The second bracket gives

$$ Y = e^{\beta t}(E\cos(\int \alpha dt) - iF\sin(\int \alpha dt)) \quad (A3.6) $$

The complete solution is a combination of (A3.5) and (A3.6)

$$ Y = e^{\beta t}(G\cos(\int \alpha dt) + H\sin(\int \alpha dt)) \quad (A3.7) $$

The derivation continues as for Appendix 2 but with $(\int \alpha dt)$ replacing $\alpha t$.

So

$$ M_x(t) = e^{-\nu t_2}(M_x(0)\cos(\int \alpha dt) - M_y(0)\sin(\int \alpha dt)) $$

$$ M_y(t) = e^{-\nu t_2}(M_x(0)\sin(\int \alpha dt) + M_y(0)\cos(\int \alpha dt)) $$

and therefore

$$ D(t) = \begin{bmatrix} e^{-\nu t_2}\cos(\int \alpha dt) & -e^{-\nu t_2}\sin(\int \alpha dt) & 0 \\ e^{-\nu t_2}\sin(\int \alpha dt) & e^{-\nu t_2}\cos(\int \alpha dt) & 0 \\ 0 & 0 & e^{-\nu t_1} \end{bmatrix} $$

where $\int \alpha dt = \delta \omega - \gamma G.r.t - \gamma G.v.t^2/2 - \gamma G.a.t^3/6$
APPENDIX 4

The assumption that $B_1 \gg G_r$ is not valid when the 90°-pulse is on at the same time as the slice select gradient. This makes the calculation impossible to do unless an analytical solution is used.

Bloch equation for a variable $B_1$

$$\frac{dM}{dt} = \gamma M \times B_{\text{eff}}$$

where $B_{\text{eff}} = (B_o - \omega/\gamma)k + B_1(t)i + G.rk$

During pulse:

$$\therefore \frac{dM}{dt} = \gamma \begin{vmatrix} i & j & k \\ M_x & M_y & M_z \\ B_1(t) & 0 & (B_o - \omega/\gamma + G.r) \end{vmatrix}$$

$$= \gamma \left[ iM_y(B_o - \omega/\gamma + G.r) \\
+ j(-M_x(B_o - \omega/\gamma + G.r) + M_zB_1(t)) \\
- kM_zB_1(t) \right]h$$

$$\frac{dM_x}{dt} = \gamma M_y(B_o - \omega/\gamma + G.r)$$

$$\frac{dM_y}{dt} = \gamma \left[ -M_x(B_o - \omega/\gamma + G.r) + M_zB_1(t) \right]$$

$$\frac{dM_z}{dt} = -\gamma M_yB_1(t)$$

Locher\textsuperscript{73}:

$$\Delta M = (M \times \gamma B_{\text{eff}}) \Delta t$$

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\[ \Delta M_x = \gamma M_y ( B_o - \omega/\gamma + G.r ) \Delta t \]

\[ \Delta M_y = \gamma \{ -M_x ( B_o - \omega/\gamma + G.r ) + M_B(t) \} \Delta t \]

\[ \Delta M_z = -\gamma M_B(t) \Delta t \]

Also

\[ M(\Delta t) = M(0) + \Delta M \]

so that

\[ M_x(\Delta t) = M_x(0) + \Delta M_x \]

\[ = M_x(0) + \gamma M_y(\Delta t)( B_o - \omega/\gamma + G.r ) \Delta t \quad (A4.1) \]

\[ M_y(\Delta t) = M_y(0) + \Delta M_y \]

\[ = M_y(0) + \gamma \{ -M_x(\Delta t)( B_o - \omega/\gamma + G.r ) \]

\[ + M_B(t) \} \Delta t \quad (A4.2) \]

\[ M_z(\Delta t) = M_z(0) + \Delta M_z \]

\[ = -\gamma M_y(\Delta t)B_1(t) \Delta t \quad (A4.3) \]

Substitute for \( M_x(\Delta t) \) in equation (A4.2) :

\[ M_y(\Delta t) = M_y(0) \]

\[ + \gamma \{ -M_x(0) + \gamma M_y(\Delta t)( B_o - \omega/\gamma + G.r ) \]

\[ \times \Delta t( B_o - \omega/\gamma + G.r ) + M_B(t) \} \Delta t \quad (A4.4) \]

Substitute for \( M_x(\Delta t) \) in equation (A4.4) :
\[
M_y(\Delta t) = M_y(0) + \gamma \Delta t \left\{ \gamma M_y \Delta t \left( B_o - \omega/\gamma + G.r \right)^2 + B_1(\Delta t)^2 - M_y(0) \left( B_o - \omega/\gamma + G.r \right) \right\} = M_z(0)B_1(\Delta t) \]  
\text{(A4.5)}
\]

Rearranging (A4.5):

\[
M_y(\Delta t) = -M_x(0)\gamma \Delta t \left( B_o - \omega/\gamma + G.r \right) + M_y(0) + M_z(0)\gamma \Delta t B_1(\Delta t) \\
\left( 1 + \gamma^2 \Delta t^2 \left( B_o - \omega/\gamma + G.r \right)^2 + B_1(\Delta t)^2 \right) 
\]  
\text{(A4.6)}

Substitute (A4.6) into (A4.1)

\[
M_x(\Delta t) = M_x(0) \\
+ \gamma \Delta t \left( B_o - \omega/\gamma + G.r \right) \left( -M_x(0)\gamma \Delta t \left( B_o - \omega/\gamma + G.r \right) + M_y(0) + M_z(0)\gamma \Delta t B_1(\Delta t) \right) \\
\left( 1 + \gamma^2 \Delta t^2 \left( B_o - \omega/\gamma + G.r \right)^2 + B_1(\Delta t)^2 \right) 
\]  
\text{(A4.7)}

Substitute (A4.6) into (A4.2)

\[
M_z(\Delta t) = M_z(0) \\
+ \gamma \Delta t B_1(\Delta t) \left( -M_x(0)\gamma \Delta t \left( B_o - \omega/\gamma + G.r \right) + M_y(0) + M_z(0)\gamma \Delta t B_1(\Delta t) \right) \\
\left( 1 + \gamma^2 \Delta t^2 \left( B_o - \omega/\gamma + G.r \right)^2 + B_1(\Delta t)^2 \right) 
\]  
\text{(A4.8)}

These solutions are iterative: so the components of magnetization can be calculated for any number of time increments.

Flow can also be incorporated into the solution.
APPENDIX 5

Divergence Theorem\textsuperscript{74}

\[ \int \int \int_{\tau} \text{div} \, \mathbf{V} \, \, d\tau = \int \int \mathbf{V} \cdot n \, \, d\sigma \]

where \( \tau \) represents a volume, \( \partial \tau \) means the closed surface of \( \tau \), \( \mathbf{V} \) a vector and \( n \) a unit vector.

APPENDIX 6

Theorem of the Central Limit\textsuperscript{75}

Provided the sample size is sufficiently large, the mean of only one random sample \( X_n \) can be considered to be a score from a normal distribution that is centred on \( \mu \) and that has a standard error equal to \( \sigma/\sqrt{n} \). Where \( \mu \) is the mean value, \( \sigma \) is the variance and \( n \) is the number of samples.
APPENDIX 7

The following computer program is an example of one used to calculate gradient factors for a sequence.

```c
#include <stdio.h>
#include <math.lib>
#define gamma 2.6751e+8
#define pi 3.1415927

int te_int, dur_int, start_int[20], ramp_time[20];
float start_float[20], dur_float[20], ramp_time_float[20];
float ramp_time[20];
int i, j, t, no_pulses;
float dur[20], start[20];
float f_ar[16002], f, SUMf2, SUMff, te;
float gradient[61002], gval[20];
float b[3], btot;
float gmax[20];
char ch;
int ax;

main()
{
    printf("This program calculates the b-factor");
    printf("\nenter the number of pulses ");
    scanf("%d", &no_pulses);
    ...
```
printf("enter echo time (in msecs) ");
scanf("%f", &te);
te_int=te*80;
for (ax=0; ax<3; ax++)
{
    for (i=0; i<no_pulses; i++)
    {
        printf("Is the gradient a half-sine shape ?");
        printf("(y or n) ");
        scanf("%ls", &ch);
        if (ch==y)
            printf("Enter maximum gradient strength");
        printf(" (in T/m) ");
        scanf("%f", &gmax[i]);

        printf("Enter start time (in msecs) ");
        scanf("%f", &start[i]);
        start_int[i]=start[i]*80;
        start_float[i]=start_int[i];

        printf("Enter duration (in msecs) ");
        scanf("%f", &dur[i]);
        dur_int[i]=dur[i]*80;
        dur_float[i]=dur_int[i];

        for (j=0; j<dur_int[i]-1; j++)
        {
            t=j+start_int[i]+1;
            gradient[t]=gmax[i]*sin
(pi*((t-start_float[i])/dur_float[i]));
}
}
else if (ch=='n')
{
    printf("Enter gradient strength (in T/m ) ");
    scanf("%f", &gmax[i]);

    printf("Enter start time (in msecs ) ");
    scanf("%f", &start[i]);
    start_int[i]=start[i]*80;

    printf("Enter duration of ramp (in ms ) ");
    scanf("%f", &ramp_time[i]);
    ramp_time_int[i]=ramp_time[i]*80;

    printf("Enter duration of g (in msecs ) ");
    scanf("%f", &dur[i]);
    dur_float[i]=dur_int[i];

    start_float[i]=start_int[i];
    dur_float[i]=dur_int[i];
    ramp_time_float[i]=ramp_time_int[i];

    for (j=0; j<ramp_time_int[i]; j++)
    {
        t=j+start_int[i]+1;
    
}
gradient[t] = gmax[i] * j/ramp_time_float[i];

for (j=0; j<dur_int[i]; j++)
{
    t = j + start_int[i] + ramp_time_int[i] + 1;
    gradient[t] = gmax[i];
}

for (j=0; j<ramp_time_int[i]; j++)
{
    t = j + start_int[i] + ramp_time_int[i] + dur_int[i] + 1;
    gradient[t] = (-gmax[i] * j/ramp_time_float[i]) + gmax[i];
}

f_ar[0] = 0;
SUMf2 = 0;
for (i=0; i<te_int; i++)
{
    t = i + 1;
    f_ar[t] = f_ar[t-1] + gradient[t];
    gradient[t] = 0;
    SUMf2 = SUMf2 + (f_ar[t] * f_ar[t]);
}

255
if (t==te_int/2)
{
    f_f_ar[t];
}

SUMff=0;
for (i=0; i<te_int/2; i++)
{
    t=i+(te_int/2; i++)
    SUMff=SUMff+f_ar[t];
}

b[ax]=gamma*gamma*(SUMf2-4*f*SUMff+2*f*f*te_int)
    /512e+12;
}

btot=b[0]+b[1]+b[2];
printf("b is %g (in s/m2)\n", btot);
}
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