Influence of Diffusion on Contrast and Sensitivity in MRI of Gases

Diplomarbeit

dem
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vorgelegt von

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Mainz 2004
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In the 1930’s Rabi and co-workers, based on the papers of Stern and Gerlach from ten years before, studied the interaction of the spin of a proton with a magnetic field. These quantum mechanical concepts were extended in 1946 by Bloch and Purcell to the measurement of the precession of nuclear spins in magnetic fields. They were awarded the Nobel Prize in Physics in 1952 for this work. These first steps of the Nuclear Magnetic Resonance (NMR) were extended in 1973 by Lauterbur and Mansfield by the development of MRI, which allows acquiring 3D images and tomography. The idea was simple, since spins precess with a frequency (Larmor frequency) that depends on the magnetic field, the magnetic field has to be made spatially dependent to result in a frequency representation of the sample’s geometry. They were awarded the Nobel Prize in Physiology or Medicine in 2003 for this work, [Man,Lau].

MRI has several advantages when compared to other clinical imaging techniques (e.g. CAT, PET). Firstly no ionizing radiation has to be used, so that the health risk for the patient is greatly minimized. Actually so far any damaging effect on the human body has been found, when the experiment is kept with certain limits for the magnetic and r.f.-fields used. Secondly the method allows obtaining images from arbitrary directions through the body with varying thickness and resolution. Finally the most important advantage is that soft tissues can be studied with unique resolution and contrast. For the latter, a variety of parameters (spin density, relaxation times, diffusion coefficients, velocities etc.) exists, which can be used to emphasize certain disease patterns.

However, highly resolved images can only be obtained from parts of the body, which are rich in a sensitive NMR-isotope (e.g. protons) in highly mobile environments (e.g. liquids). Therefore, rigid tissues (e.g. bones) and hollow structures (e.g. lungs) do not contribute to the MR-image. While bones can be nicely resolved by X-ray techniques the
diagnostic imaging techniques for pulmonary diseases were very limited\(^1\) until MRI with hyperpolarized gases was introduced by Albert et al. [Alb].

“Hyperpolarization” means that the NMR-signal is increased by up to five orders of magnitude due to optical pumping with polarized LASER-light. This idea bases on the research of Alfred Kastler, who facilitated the study of atomic structures by means of the radiation that atoms emit under excitation by light and radio waves. He was awarded the Nobel Prize in Physics in 1966 for these works. Since then the technique of optical pumping (i.e. generating alignment of spins by transferring angular momentum to the spins from polarized light) has been studied extensively and developed by several groups [Bou, Sche, Col, Gam]. Recently, the field has expanded rapidly with the advent of inexpensive, high-power diode laser arrays. Liters quantities of \(^3\)He or \(^{129}\)Xe can now be routinely produced in a matter of hours, with absolute nuclear polarizations of unity order.

It only happened within the last decade that all these techniques reached a level of perfection that they could be introduced in clinical research. However, the effects on the MRI quality which arise from the use of gases rather than liquids have not been discussed in great detail yet.

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\(^1\) Essentially only scintigraphy of gaseous radio isotopes (\(^{99m}\)Tc, \(^{127}\)Xe, \(^{133}\)Xe, \(^{181}\)Kr) can be used. Because the radioactive dosage is limited the concentration of such isotopes has to be kept relatively low, which results in poorly resolved images.
II Motivation.

Magnetic Resonance Imaging (MRI) is a tool for measuring the spatial distribution of a certain isotope, which possesses a nuclear spin, where medical applications of MRI typically use $^1$H NMR [Cal,Tal]. This is primarily because biological systems contain a big amount of water; for instance the human body is composed to 70% of water (i.e. a very high density (63 %) of hydrogen nuclei (100 mol/L) with sufficiently narrow resonance lines). However, this does not permit to image the air filled parts of the body, as for instance the lungs. This is because gases at 1 atm have densities (and nuclear spin densities) about $10^{-3}$ of liquid water; hence there are simply too few spins to give sufficient signal using ordinary NMR techniques. Recently the development of hyperpolarized gases artificially increase the signal by $10^5$ and high quality MRI of gases can be achieved this way [Goo,Bec]. The increase in sensitivity and acquisition time is in principle of a great advantage compared to water [Cha,Gla]. Thus, in the last decade MRI of hyperpolarized gases have been introduced for imaging of voids in porous systems, as foams, granular systems and of course lungs [Blü,App]. The most interesting question in spatially resolved experiments is of course the achievable resolution and contrast by controlling the diffusivity.

However, gases have a high diffusivity which strongly influences the NMR signal strength, hence the resolution and appearance of the images. The influence of such diffusive processes scales with the diffusion coefficient of the gas, the strength of the magnetic field gradients and timing used in the experiment. Diffusion may not only limit the MRI resolution, but also distort the line shape of MR images for samples, which contain boundaries or diffusion barriers within the sampled space [Saa,Swi]. Therefore, the objective of this work was the determination and quantification of the influence of gas diffusion on the appearance of MR-images. Additionally, strategies had to be tested to optimize resolution and contrast for different applications.
In the chapter III an introduction of the basics in NMR and MRI can be found, concluding in the concepts that are related to the influence of diffusion on the resolution of MR-images. A summary of the used experimental devices and setups follows in chapter IV.

Chapter V explains how diffusion coefficients can be spatially resolved, how the timing of the sequence determines the contrast, and particularly how cavities contribute different due to their size.

Due to the biological restrictions of pressure and temperature in clinical imaging studies, the Brownian motion of particles can only be controlled by varying the concentration of the gas mixture resulting in different diffusion coefficients. This new concept of controlling the MRI contrast and resolution is discussed in chapter VI. Firstly a revision of the existent theory of diffusion is presented, especially for gas mixtures. This is completed by measurements of the diffusion coefficient of hyperpolarized gases in different concentrations in binary mixtures.

Finally chapter VII demonstrates the dependence of the MRI signal on the concentrations in binary gas mixtures. Additionally the contrast was altered by studying the sequence timing in images. These studies were performed on suitable phantoms and preserved rodent lungs [Blü2].
III Principles of NMR.

III.1 Introduction to NMR

Nuclear Magnetic Resonance (NMR) is a phenomenon that occurs when the nuclei of certain atoms are brought into a static magnetic field.

All nuclei with an odd number of protons or neutrons possess an intrinsic angular momentum or spin characterized by a spin quantum number, \( I \). Since the nucleus has both, spin and charge distribution, it will have an associated nuclear magnetic moment, \( \mu \), which is collinear and proportional to the spin angular momentum \( I \),

\[
\mu = \gamma I \tag{3.1}
\]

with a proportionality constant, \( \gamma \), the gyromagnetic ratio. As a consequence, the nuclei have a potential energy when brought into a magnetic field of flux density \( B_0 \). From quantum mechanics it is known that angular momentum and the associated energies are quantized and can only assume discrete values. Hence in the presence of such an external magnetic field \( B_0 \), the degeneracy of the eigenstates of the nuclear spins vanishes, resulting in energy levels with

\[
E = \mu B_0 = -m\gamma h B_0 \tag{3.2}
\]

which are proportional to the magnetic quantum number \( m = -I, -I+1, \ldots, I \). As a result a nucleus with quantum number \( I \) may assume \( 2I+1 \) discrete energy levels. An observation known as Zeeman splitting.
Since this work exclusively deals with nuclei ($^1$H, $^3$He and $^{129}$Xe) having $I = \frac{1}{2}$ only two such energy levels or directions of the spins exists (“up” and “down”) as shown in Fig. 3.1.

Fig. 3.1 Distribution of spin population in energy levels due to the action of a magnetic field. The shown orientation of the spin depends on the magnetic moment. The shown is valid for $^1$H; $\mu > 0$, while for $^{129}$Xe and $^3$He; $\mu < 0$.

In this case the energetic distance between the two levels of Eq. (3.2) are given by

$$\Delta E = E_{1/2} - E_{-1/2} = \frac{\gamma}{2}B_0$$

which corresponds to an excitation frequency

$$\omega_0 = \frac{\Delta E}{\hbar} = \gamma B_0$$

where $\omega_0$ is also known as the Larmor frequency.

As indicated in Fig. 3.1, the population of the two energy levels is very similar, because the energy difference is small compared to the thermal energy of the system at ambient temperature. The ratio of the populations in thermal equilibrium at temperature $T$ is then given by a Boltzmann distribution

$$\frac{N_-}{N_+} = \exp\left(-\frac{\Delta E}{k_B T}\right) = \exp\left(-\frac{\hbar \omega_0}{k_B T}\right) = \exp\left(-\frac{\hbar \gamma B_0}{k_B T}\right)$$
where \( k_B \) is Boltzmann’s constant and \( N_+ \) and \( N_- \) are the number of spins in the \( m_I = +\frac{1}{2} \) and the \( m_I = -\frac{1}{2} \) states respectively. A related quantity is the polarization, \( P \), which describes the excess population of the two energy levels

\[
P = \frac{N_+ - N_-}{N_+ + N_-}
\]

and with Eq. (3.5)

\[
P = \tanh \left( \frac{\gamma h B_0}{2 k_B T} \right).
\]

This expression is simplified by the fact that the thermal energy is much bigger than the magnetic dipole energy, thus \( T >> \frac{h \omega_0}{k_B} \). This is the so-called “high temperature” approximation, in which Eq. (3.7) becomes

\[
P \approx \frac{\gamma h B_0}{2 k_B T}.
\]

For example, \(^1\text{H}\) nuclei at room temperature and a magnet field of 4.7 T have a polarization of about \( 1.6 \times 10^{-5} \).

Finally the observable NMR-signal has an intensity which is proportional to the sum of all magnetic moments. This macroscopic magnetization, \( M_0 \), is then given by

\[
M_0 = \sum_i N_i \mu_i = \frac{1}{2} N_S \gamma h P
\]

where \( N_S = N_+ + N_- \) is the total number of spins.

In order to observe such a signal, the thermal equilibrium must be perturbed by applying an additional magnetic field exactly at the resonance condition described by Eq. (3.4). This perturbation field will therefore be perpendicular to \( B_0 \) and oscillating with a frequency \( \omega_0 \) (typically a radiofrequency). In a classical picture this applies a torque, \( \tau = \mu \times B \), to the magnetic dipoles or in a quantum magnetic description generates transitions
between the two energy levels. Classically the torque corresponds to a displacement of the magnetization vector described by the following equation of motion

$$\frac{dM}{dt} = \gamma (M \times B),$$  \hspace{1cm} (3.10)

where $B$ consists of both, the static applied field $B_0 = (0, 0, B_0)$ defining the $z$-direction, and the magnetic vector of the radiofrequency field $B_1$. The latter can be thought of as a field rotating in the $xy$ plane at angular frequency $\omega_0$. Thus the components of $B$ are

$$B_x = B_1 \cos (\omega_0 t), \quad B_y = -B_1 \sin (\omega_0 t), \quad B_z = B_0. \quad (3.11)$$

Equations (3.10) and (3.11) may then be combined to give three equations for the time dependence of the components of $M$, also known as the Bloch equations:

$$\frac{dM_x}{dt} = \gamma \left[ M_y B_0 + M_z B_1 \sin (\omega_0 t) \right]$$

$$\frac{dM_y}{dt} = \gamma \left[ M_z B_1 \cos (\omega_0 t) - M_x B_0 \right]$$ (3.12)

$$\frac{dM_z}{dt} = -\gamma \left[ M_x B_1 \sin (\omega_0 t) + M_y B_1 \cos (\omega_0 t) \right].$$

Equations (3.12) are not yet complete, since they do not account for relaxation times.
III.2 The rotating co-ordinate frame

In a classical representation, the magnetization is viewed as a vector aligned with the external magnetic field. The perturbation/excitation field \( B_1 \) causes then a complex motion of this vector by moving it away from the \( z \)-axis in spiral with frequency \( \omega_0 \) as explained by Eq. (3.12). To simplify the description of NMR-experiments, the concept of the rotating co-ordinate frame (RCF: \( x', y', z' = z \)) is introduced, which rotates at an angular velocity of \( \omega \) around the \( z \)-axis, as illustrated by Fig. 3.2. Hence, the notation of the magnetization vector during an NMR-experiment greatly simplifies.

Fig. 3.2 Representation of magnetization vector \( M_0 \) tipped by an angle \( \alpha \): a) in a static reference frame, where \( M_0 \) precesses around the \( z \)-axis and b) in the rotating co-ordinate frame, where the magnetization vector appears static because the entire co-ordinate frame rotates with angular frequency \( \omega \) around the \( z \)-direction.

Equation (3.10) in the RCF (rotating with angular frequency \( \omega \)) is then derived from the static frame of reference by

\[
\left( \frac{dM}{dt} \right)_{RCF} = \left( \frac{dM}{dt} \right)_{static} - \omega \times M
\]  

(3.13)

rearranging terms in Eq. (3.13), the following is obtained
\[
\left( \frac{d\mathbf{M}}{dt} \right)_{\text{RCF}} = \gamma \mathbf{M} \times \mathbf{B} + \frac{\gamma \mathbf{M} \times \omega}{\gamma} = \gamma \mathbf{M} \times [\mathbf{B} + \omega / \gamma] = \gamma \mathbf{M} \times \mathbf{B}_{\text{eff}} \tag{3.14}
\]

The term \(\omega / \gamma\) has the dimensions of a magnetic field and can be considered a “fictitious” field, \(\mathbf{B}_{\text{eff}}\), that arises from the effect of the rotation, with

\[
\mathbf{B}_{\text{eff}} = \mathbf{B} + \omega / \gamma \tag{3.15}
\]

Equation (3.14) demonstrates that the ordinary equations of motion applicable in the laboratory frame are valid in the rotating frame as well, provided \(\mathbf{B}_{\text{eff}}\) as defined in Eqs. (3.12) is used in place of \(\mathbf{B}\). Hence the complete expression is

\[
\mathbf{B}_{\text{eff}} = \mathbf{B}_0 + \omega / \gamma + \mathbf{B}_1 = \frac{\omega_0 - \omega}{\gamma} \mathbf{e}_z + \mathbf{B}_1 . \tag{3.16}
\]

### III.3 Relaxation times

#### III.3.1 Spin-Lattice Relaxation

The application of a \(\pi/2\) pulse perturbs the spins from their thermal equilibrium state causing the net magnetization to lie on the \(xy\)-plane, while the longitudinal \(M_z\) becomes zero. For a spin-1/2 nucleus, the spin populations in the two energy levels become equal. After the application of the pulse, the spins tend to return back to their equilibrium state by exchanging energy with their surrounding neighborhood, the so-called lattice. This is done through a relaxation mechanism which is called ‘spin-lattice relaxation’ and it is described by the spin-
lattice relaxation time $T_1$. Spin-lattice relaxation describes the restoration of $M_z$ back to its initial value $M_0$ after the application of the $\pi/2$ pulse. The rate of change of $M_z$ is described by the equation

$$\frac{dM_z}{dt} = -\frac{(M_z - M_0)}{T_1}$$

or

$$M_z(t) = [M_z(0) - M_0] \exp\left(-\frac{t}{T_1}\right) + M_0.$$  \hspace{1cm} (3.17)

### III.3.2 Spin-Spin Relaxation

Following the $\pi/2$ pulse, the tipped spins in the transverse $x'y'$-plane have phase coherence but soon they move out of phase due to field inhomogeneities, internuclear dipole-dipole interactions, chemical shift, and other types of inter-nuclear interactions. This loss of phase coherence is called ‘spin-spin relaxation’ and it is described by the spin-spin relaxation time $T_2$. The rate of change of the magnetization in the $x'y'$-plane is described by the equation:

$$\frac{dM_{x'y'}}{dt} = -\frac{M_{x'y'}}{T_2}$$

or

$$M_{x'y'}(t) = M_0 \exp\left(-\frac{t}{T_2}\right).$$  \hspace{1cm} (3.18)

In solids, internuclear dipole-dipole interactions are profound and they cause very strong relaxation with a small $T_2$, while in liquids these interactions can be averaged out and as a result $T_2 \leq T_1$. But usually, $T_2 < T_1$. 

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III.3.3 Free Induction Decay Signal

In pulsed NMR-experiments an intense r.f. pulse with amplitude $B_1$ is applied. The direction of notation of the magnetization in the rotating co-ordinate frame is described by the phase of the pulse, which defines the direction of $B_1$ in the $xy$-plane. Then the magnetization will rotate about $B_1$ with an angular velocity $\omega_1 = \gamma B_1$. A pulse of duration $t_p$ will therefore tip the magnetization by an angle

$$\alpha = \gamma B_1 t_p.$$  \hspace{1cm} (3.19)

The pulses are then classified by this tip angle and the rf-phase (e.g. $\pi$, pulse, which rotates $M$ around $x'$ by 180°). The oscillation of the macroscopic magnetization induces an alternating current of the order of a few $\mu$A in the receiver coil. This sinusoidal oscillating current at $\omega_0$ decays exponentially with time, see Fig. 3.3.

![Fig. 3.3 Free Induction Decay (FID) showing the exponential decay with $T_2^*$. The oscillation is due to a small offset from the Larmor frequency](image)
In a homogeneous $B_0$ field, the decay of the signal, is due to the spin-spin interactions, which in NMR applications is generally denoted by $T_2$. On the other hand, for an inhomogeneous $B_0$ field, the rotating spins in the transverse plane experience different fields and rotate at slightly different angular frequencies. This leads to an additional loss of phase coherence which causes the signal to decay more quickly than the time constant $T_2$. This signal decay, which is generally met, is called the ‘Free Induction Decay’ (FID) and it is characterized by the time constant $T_2^*$:

$$M_{x'y'}(t) = M_0 \exp\left(-\frac{t}{T_2^*}\right),$$

(3.20)

the relation between the $T_2$ and $T_2^*$ time constants is given by the equation:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} + \gamma \Delta B_0$$

(3.21)

where $T_2'$ are local changes in the magnetic susceptibility and $\gamma \Delta B_0$ inhomogeneities in the external field inhomogeneities.

III.4 Magnetic Resonance Imaging (MRI).

III.4.1 Spatially dependent NMR signals, $k$-space

Spatial information can be introduced in NMR very straight-forward, by making the observed frequency spatially dependent. The easiest way to realize this is to perform the experiment in spatially varying magnetic field, $B(r)$.
\( \omega (r) = \gamma B(r) \) \hspace{1cm} (3.22)

which is superposed to the static magnetic field \( B_0 \). Usually this additional field has a linear dependence on space or a constant gradient. Therefore, these fields are called “gradients”. For instance a magnetic field gradient in the \( x \)-direction is given by \( G_x = \frac{\partial B}{\partial x} \) and will cause the following dependence of the NMR-frequency on space

\[
\omega(x) = \gamma B(x) = \gamma \left( B_0 + x \frac{\partial B}{\partial x} \right) = \gamma (B_0 + x G_x) = \omega_0 + \gamma G_x x , \hspace{1cm} (3.23)
\]

Without any field variation the NMR-signal can be expressed as a spatial integral with a local weighting factor, \( \rho(r) \), the spin density:

\[
S(t) = \int_{-\infty}^{\infty} \rho(r) \exp(-i\gamma \omega_0 t) \, dr \hspace{1cm} (3.24)
\]

this represents a spatial encoded frequency that will be weighted by the local spin density, \( \rho(r) \). Hence, in the presence of a gradient this expression simply has to be substituted by Eq. (3.23)

\[
S(t) = \int_{-\infty}^{\infty} \rho(r) \exp[-i\gamma (\omega_0 + G_x x) t] \, dr \hspace{1cm} (3.25)
\]

Mansfield [Man] introduced the concept of a reciprocal space vector, \( k \), defined by

\[
k \equiv \frac{1}{2\pi} \int_{t_1}^{t_2} G(t) \, dt \hspace{1cm} (3.26)
\]

for a gradient lasting from \( t_1 \) to \( t_2 \). The \( k \)-vector has a magnitude expressed in units of reciprocal space, and from Eq. (3.26) it becomes clear that the \( k \)-space may be traversed by changing either the duration of the gradient or the gradient amplitude.

The frequency-encoded spatial distribution (image) can be uncovered by a Fourier transform of the time signal in Eq. (3.25),
\[ \rho(x) = \frac{1}{2\pi} \int_{-\infty}^{\infty} S(k) \exp\left[i2\pi k_x x\right] dk \]  
(3.27)

which for a one dimensional case corresponds to a 1D projection of the spin density, as illustrated in Fig. 3.4.

Fig. 3.4 Process of one-dimensional imaging demonstrated on two tubes filled with water: When a gradient \( G_x \) is applied across the tubes, the precession frequency of the nuclear spins becomes spatially dependent. This is recorded by the signal acquired in the time domain as shown before and after the FT, which unravels the density profile of the sample along the gradient direction [Cal].

This concept can be easily be extended to two or more dimensions by introducing further gradients, e.g. for a complete 3D-image

\[ \rho(x, y, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} S(k) \exp\left[i2\pi \left(k_x x + k_y y + k_z z\right)\right] dk . \]  
(3.28)

Hence, the size and resolution of the image is defined by the way \( k \)-space is scanned (see Fig. 3.5). The \( k \)-vector, on the other hand, can be scaled by changing either strength or duration of the gradient pulses in an imaging sequence.
As a frequency is only a temporal change of phase

\[ \omega = \frac{d\phi}{dt}, \]  

Eq. (3.23) can be integrated in the RCF to

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

which is the phase evolution at position \( r \) during the application of an arbitrary gradient shape, \( G(t) \), during time \( t \), as shown in Fig. 3.6. This also explains the loss of phase coherence in the presence of field inhomogeneities, in this case a gradient, as discussed in Eq. (3.21).
For a static sample (i.e. \( r(t) = r \)) this equation simplifies to

\[
\phi(r, t) = \gamma r \int_0^t G(t') dt' = 2\pi kr
\]

(3.31)

The product of \( kr \) can therefore be identified as a phase.

### III.4.3 Echoes

The application of gradients rapidly dephases the NMR-signal (see Fig.3.7), which makes the concept of rephasing echo sequences very favorable for the complete acquisition of the NMR-signal. For NMR-imaging sequences two strategies of refocusing such dephased signals are of importance, one is using r.f.-pulses (the so-called Hahn- or spin-echo) and the other gradients (hence called gradient-echo).

The latter is easily understood, because Eq. (3.30) already shows that any dephasing due to the application of a gradient pulse can be undone by inverting the sign of the gradient. This Gradient Echo (GE) acts as follows: an r.f.-pulse excites the spins and brings a noticeable component of the magnetization into the \( x' y' \)-plane. Subsequently, a gradient \( G \) induces a rapid dephasing of the spins during a time \( \tau \), resulting in a phase spread.
\[ \Delta \phi_{\text{dephase}}^{GE} = \gamma r G \tau , \]  

(3.32)

where a static sample \((r(t) = r)\) and rectangular gradient shape \((G(t) = G)\) are assumed. Rephasing is achieved by inverting the gradient amplitude to \(-G\), so that after a time \(\tau\) all phase spread is refocused

\[ \Delta \phi_{\text{rephase}}^{GE} = -\gamma r G \tau . \]

(3.33)

This is identical to the spins reaching their initial position in the \(RCF\) independent on their spatial position, the definition of an echo (see Fig. 3.7)

\[ \Delta \phi_{\text{dephase}}^{GE} + \Delta \phi_{\text{rephase}}^{GE} = 0 . \]

(3.34)

![Diagram](image.png)

Fig. 3.7 a) Graphic representation of gradient echo sequence: The top line shows the r.f. excitation (green) and the resulting NMR-signals, of which the latter is the gradient echo. The central row depicts the gradient amplitude which is reversed during the second pulse to invert the phase spread, shown in b). Here the gradient is also represented over the sample as a function of space. In the \(RCF\) (bottom) the individual phases at different locations (indicated by color) and different times in the sequence are shown.
The rephasing and dephasing of this echo is recorded in the presence of the gradient, which therefore must have a duration of $2\tau$. This corresponds to the acquisition of a full trajectory through $k$-space, see Eq. (3.31).

Alternatively, an echo can also be generated by inverting every phase of the spin system. This can be done by the application of a $\pi$-pulse in the centre of the sequence, which inverts the phase distribution symmetrical to its direction in the $RCF$, as illustrated in Fig. 3.8.

Fig. 3.8 Schematic representation of a spin-echo sequence. a). A gradient can be present continuously without affecting properties of the sequence. The spins dephase in one direction, after the $\pi$ r.f. pulse in the $x'$-direction is applied, they continue dephasing in the same direction, but the spins are now in the opposite site. b): the sample (blue) is affected by different magnetic fields intensities depending on the position along the $x$-axis that produces the dephase and rephase.

Such spin-echoes allow for complete rephasing independent of the field inhomogeneities (the gradient is switched on during the entire sequence). Therefore, changes in local susceptibilities and inhomogeneities of the main magnetic field are also refocused. Of course, the gradient echo misses such “extra-inhomogeneities” because it can only rephase the phase-spread due to the field inhomogeneity of the gradient field itself.

Nevertheless, the gradient echo is more favorable for samples which are not in thermal equilibrium (e.g. hyperpolarized gases). This is because so far the inhomogeneity in the $B_1$ field was neglected. This is usually bigger than the imperfections in $B_0$. In reality a $\pi$-pulse will therefore only cause a perfect phase inversion for a very small region of the sample and
destroy significant amounts of hyperpolarization everywhere else. An effect less important in the case of gradient echoes, since the first and only r.f. pulse can be set to very small amplitude (typically 5°-10°).

III.4.4 A complete MRI sequence: Read and Phase gradients.

As discussed in section III.4.1 the acquisition of a distortion free image requires a homogeneous and complete sampling of a subsection of $k$-space. So far only the concept of frequency encoding has been discussed in section III.4.1. Therefore, a gradient is switched on during the sampling of the NMR-signal. In order to acquire a complete trajectory in $k$-space, the $k$-vector and the associated phase, see Eq. (3.31), must firstly become negative and evolve through a condition equals to zero (that is the echo maximum) to a corresponding positive value. This corresponds to a dephasing interval (points 1-2 in Fig. 3.9) to achieve a maximal negative $k_{\text{read}}$-value followed by a rephasing interval centred on the maximum of the echo (points 4-5 in Fig. 3.9). Because the complete signal is recorded during this interval, the associated gradient is called “read”.

Perpendicular directions of $k$-space are then accessible by adding a phase-contribution to the $k$-vector prior to sampling. This is typically done in the dephasing interval during which an additional gradient is switched on (point 3 in Fig. 3.9). This sets a second component of the $k$-vector, which then points in the second dimension of $k$-space. Because only one such step is possible per “read”-trajectory, the procedure has to be incrementally repeated in separate experiments. This gradient manifests its influence on the recorded signal solely by a spatial phase, see Eq. (3.31), therefore it is called the “phase” gradient.

This concept can easily be extended to 3D by adding a second phase gradient to the sequence, which is then stepped in an independent loop. However, this is a very time consuming process, because a complete third dimension has to be acquired. Typically only a limited region of a sample is of interest anyway, therefore a spatial restriction to a few slices through this volume are sufficient. Such NMR-tomography can be realized by the application of selective rf-excitation with shaped pulses. Details about this technique of slice selection can be found elsewhere [Cal, Boe].
Fig. 3.9 Time diagram of a 2D spin-echo imaging sequence (left) and the resulting path through $k$-space (right): The numbers indicate the position in the $k$-space reached at certain times during the sequence. Point 1 starts at $k = (0,0)$, because without gradients $k$ does not vary. The read gradient dephases the spins, hence pushing the associated component, $k_{\text{read}}$, to its positive maximum. However, at the same time an orthogonal gradient adds another phase contribution, resulting in a $k$-vector pointing to 3. An $\pi$-pulse subsequently inverts all phases of the spin system, corresponding to a complete inversion of $k$-space, which brings the $k$-vector to point 4. This is where the rephrasing starts, and at the same time the sampling of the NMR-signal is begun. Leaving the read gradient on for twice the dephasing duration, $\tau$, samples a complete trajectory in $k$-space (from point 4 to 5). In repeating this process for different intensities of the phase gradient, the entire $k$-space is sampled.

III.5 Hyperpolarized gases

Conventional NMR methods suffer from a common drawback that in many circumstances can limit their power and applicability—a notorious lack of sensitivity. This fundamental insensitivity originates from the miniscule size of nuclear magnetic moments, which results in an exceedingly small equilibrium nuclear spin polarization in even the largest magnet fields.

In certain systems, however, the sensitivity of NMR spectroscopy and MRI can be greatly enhanced via optical pumping. In that way, angular momentum is transferred from laser photons to electronic and finally via magnetic coupling (hyperfine interaction) to nuclear
spins, thereby temporarily enhancing the nuclear spin polarization in these systems by four to five orders of magnitude, as schematically shown in Fig. 3.10.

Fig. 3.10 Effect of laser-polarization of an ensemble of spin-1/2 nuclei in comparison with the Boltzmann distribution. a) Thermal equilibrium: the number of spins aligned antiparallel to the magnetic field is nearly equal to the number of spins aligned parallel, resulting in a small polarization. b) Optical pumping: with optical pumping the population distribution of the spins can be driven away from equilibrium, thereby increasing the polarization to order unity, [Goo].

Two methods are common to achieve optical pumping of nuclear spins of noble gases: alkali metal spin exchange, (used for $^{129}$Xe or $^3$He), [Bou] and metastability exchange, (used for $^3$He) [Col].

III.5.1 Alkali metal exchange

It is well known that alkali metals vapour can be optically pumped [Goo]. Therefore using saturated rubidium vapour at temperatures between 100°C and 200°C, inside a pump cell made from glass, does not suffer damage because of chemical reactions. Rubidium vapour can for instance be optically pumped with a circularly polarized laser light with a wave length of $\lambda$=795 nm. Together with the alkali metal vapour there are other gases ($^{129}$Xe or $^3$He, $^4$He and N$_2$) present; of elevated pressures, where $^3$He or $^{129}$Xe are the NMR isotopes to polarize. Nitrogen is needed to make non-radiative transitions to the ground state, and without N$_2$ the unpolarized fluorescence light will be absorbed again by the alkali atoms, thus reducing drastically the achievable an electronic polarization.
The process has two steps; firstly the valence electrons of rubidium are polarized by the laser, reaching polarizations close to 1, see Fig. 3.11 (a). The orientation of the electronic spins ($J$) is then transferred to the nucleus spin ($I$) of $^{129}$Xe or $^3$He during the characteristic formation of a Van der Waals molecule that links both atoms; see Fig. 3.11 (b), via hyperfine coupling $H_{\text{int}} \propto I \cdot J$; to achieve this, the cell is placed in a magnetic field of low intensity ($\sim 10^{-3}$ T), used as guiding field for the spins.

Nitrogen is added to the gas mixture to quench the fluorescence of the electronically excited alkali metal atoms, which would otherwise work to depolarize the electron spins. The typically achieved polarization values are around 10-30% for $^{129}$Xe. $^4$He is added to raise the pressure in the cell to broaden the absorption line of rubidium by collisions.

The alkali metal exchange method is also suited for hyperpolarizing $^3$He, but it is less effective than for $^{129}$Xe. This is due to the very small cross section since $^3$He is a small atom for making a Van der Waals molecule. Polarization of the order of 40% or more [Lea] are achieved for $^3$He with this method. In the following subsection a more effective method is described.

![Fig. 3.11 Alkali-metal optical-pumping/spin-exchange processes. (a) Optical pumping of the electronic spins of the alkali atoms (neglecting the hyperfine couplings between the electronic and nuclear spins of the alkali metal atom). (b) Polarization of the xenon nuclei via collision and spin exchange. [Goo](fig:3.11)]

**III 5.2 Metastability exchange**

Before the $^3$He gas can be optically pumped, a small portion of the gas must first be excited from the ground electronic state ($1^3S_0$) into the metastable state ($2^3S_1$), see Fig. 3.12 (a); this is achieved by applying a weak r.f. discharge to the optical pumping cell. Metastable
atoms can then be optically pumped by absorbing circularly polarized laser light at ($\lambda$=1083 nm), which drives population from the state ($2^3 S_1$) (F =1/2) level or the state ($2^3 S_1$) (F =3/2) level to the $^3 P_0$ (F =1/2) level. The polarization of the $^3$He atom is then transferred to the nuclear state of the ground state, as is shown in Fig. 3.12 (b), via so called metastability exchange collisions. In these processes the metastability is exchanged while keeping the total angular moment conserved. This means that:

$$ ^3\text{He}(m = - \frac{1}{2}) + ^3\text{He}^*(m_F) \leftrightarrow ^3\text{He}(m = + \frac{1}{2}) + ^3\text{He}^*(m_F = -1) . $$

This is a purely electrostatic process being much more effective than the spin-exchange via hyperfine coupling. Since due to optical pumping the metastable $^3$He*-atoms with $m_F>0$ are more populated, the above transfer reaction goes predominantly from left to right terms, populating the nuclei of the ground state atoms in the $m=1/2$ state.

Fig. 3.12 Metastability exchange: (a) relevant energy levels involved in the creation and subsequent nuclear spin polarization of metastable $^3$He gas. (b) He*-He collisions permitting energy-conserving metastability exchange. [Goo].
III.6 Principles of Diffusion

Diffusion is usually defined as the transport of matter (gas, liquid or solid mixtures) by relative movement of the particles in concentration, temperature or pressure gradients. The classical description of diffusion is given by Fick’s laws, (diffusion at constant temperature and pressure).

\[ j(r,t) = -D \nabla c(r,t). \]  \hfill (3.35)

This equation states that a gradient of concentrations, \( \nabla c(r,t) \), is proportional to the induced flux of matter, \( j(r,t) \), where \( r \) is the position of the particle at the time \( t \), as defined in Fig. 3.13. The factor of proportionality is the diffusion coefficient, or more generally the diffusion tensor. It is a tensor because matter can diffuse differently depending on the direction.

Combining the continuity equation

\[ \frac{\partial c(r,t)}{\partial t} = -\nabla j(r,t) \]  \hfill (3.36)

with Eq. (3.35), Fick’s second law is obtained to describe the temporal behaviour of the concentration:

\[ \frac{\partial c(r,t)}{\partial t} = \nabla D \nabla c(r,t). \]  \hfill (3.37)

However this model of diffusion does not give a good explanation of the movement of a particle when the concentration plays no role, i.e. when the particle is moving in the absence of a concentration gradient, the so called self-diffusion. Self-diffusion is the random translational motion of molecules driven by internal kinetic energy, it is also closely related to molecular size, as it can be seen from the Stokes-Einstein equation:

\[ D = \frac{k_B T}{6 \pi \eta r} \]  \hfill (3.38)
where $T$ is the temperature of the system, $fr$ is the friction coefficient and $D$ is the scalar diffusion coefficient, i.e. the diffusion tensor when it is completely isotropic. The friction coefficient $fr$ is not easy to calculate because molecular shapes are complicated and may include contributions from factors such as hydration. Therefore, a statistical description of self-diffusion is usually more successful. For this purpose a probability function $P(r|r',t)$, which describes the probability of the movement of a particle from $r$ to $r'$ in a time $t$, is introduced. This probability function also follows Fick’s second law:

$$\frac{\partial P(r|r',t)}{\partial t} = \nabla D \nabla P(r|r',t).$$

(3.39)

For isotropic diffusion a solution of Eq. (3.39) is a Gaussian, as depicted in Fig. 3.13.

$$P(r|r',t) = (4\pi Dt)^{-3/2} \exp\left(-\frac{(r'-r)^2}{4Dt}\right)$$

(3.40)

![Fig. 3.13 Representation of self-diffusion: translation of a particle in space and time (trajectory in brown) and its probability function for moving from $r$ to $r'$ in a time $t$. The probability is a Gaussian described by Eq. (3.40).](image-url)

Another important parameter for the description of diffusion is the mean path that the particle travels during a certain time. This parameter is also known as the mean square displacement and is given by the Einstein-Smoluchowski equation:

$$\langle (r' - r)^2 \rangle = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} (r' - r)^2 \rho(r) P(r|r',t) drdr' = 2nDt$$

(3.41)

where $n$ is the number of dimensions in which the particle is allowed to move.
III.6.1 Free and restricted diffusion

The considerations made above are only valid for particles which are allowed to move everywhere, resulting in a Gaussian probability. However, reality is different and usually diffusion is spatially restricted. In such a case the probability function will be different and harder to calculate. Therefore, $\xi$, a ratio between the measured (experimental or apparent), $D_{app}$ (also ADC), and the diffusion coefficient for the free diffusion (unrestricted), $D$, is defined, [Pri]. This dimensionless variable $\xi$ will indicate the level of restriction due to obstacles.

$$\xi \equiv \frac{2nD_{app}t}{\langle (r'-r) \rangle^2_{free\,diff}} \leq 1$$

(3.42)

where $\langle (r'-r) \rangle^2_{free\,diff}$ is the mean square displacement of the particle when it diffuses freely.

There will be two different regimes of $\xi$ depending on the time used to measure the diffusion. Measurements for a short time do not allow the particles to collide extensively with the walls that limit the movement. On the other hand in long time limit measurements of the mean square displacement of the particle have to be the cavity size. A visual description is given by Fig. 3.14

If the shape of the cavity deviates from a sphere, then the observed diffusion coefficient also depends on the direction of the measurement. In the case of a cylinder parallel to the z-axis, as shown in Fig. 3.15, the diffusion in the x or y direction is restricted by the diameter while it is free along the z-direction.
Fig. 3.14 Comparison of a spherically restricted and a free particle measured at different times, the empty circle represents the particle when its position is encoded in the beginning of the measurement and the full one at the end. The length of the arrows represents the mean square displacement of the particle in one direction. There are two different regimes considered: for a short time limit, \( \xi \approx 1 \), only a negligible fraction of particles begins to suffer the restriction; long time limit, \( \xi < 1 \) all particles suffer the restriction and \( \xi \) does not depend on the measurement time but on the restriction length.

Fig. 3.15 Particle diffusing inside a cylinder parallel to the z-axis. The empty circle represents a particle when its position is initially encoded and the full one when the measurement stops. The red arrows shows the mean square displacement along to each axis.

Thus the diffusion coefficient becomes a tensor. In real samples this is the most common case and the most general description. Because of the sign independence of the diffusing particle mean path \( \langle (r' - r)^2 \rangle \). The tensor is symmetric and can be written as:

\[
D = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{xy} & D_{yy} & D_{yz} \\
D_{xz} & D_{yz} & D_{zz}
\end{pmatrix}
\]

(3.43)
III.7 Measurement of diffusion by NMR.

Because diffusion is defined by the distance a particle travels randomly in a certain time, it is clear that spatially varying magnetic fields, i.e. field gradients, can be used to observe its influence on the NMR signal. Therefore, two gradients of identical intensity and duration are added to a spin echo sequence, as shown in Fig. 3.16 (a). In case of static particles, the dephasing of the spins during the first gradient is perfectly rephased and results in an not attenuated echo, see Fig. 3.16 (b). However if the particles diffuse, they change their position, during the experiment and hence their phase spread is longer refocused perfectly, resulting in an attenuation of the echo, see Fig. 3.16 (b).

![Diagram of NMR signal with static and diffusing particles]

Fig. 3.16 Difference of dephase and rephase between a diffusing particle and a static particle. Since the static particle is in the same position into the gradient, the quantity that the spin is dephased is the same as rephased. However, as the diffusing particle moves, its spin is dephased a certain quantity and rephasing another different.

This process can be expressed by writing Eq. (3.25) in a general form including Eq. (3.40):

\[
S(t, G) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \rho(r)P(r|r', t) \exp(i\gamma \int_{0}^{t} G \cdot r \, dt) \, dr \, dr'
\]  

(3.44)
where the density is weighted by the probability function. To solve this equation the application of gradient and r.f. pulses has to be known. For the sequence of the Fig. 3.16 (a) this gives the following solution:

\[
E(G, \delta, \Delta) = \frac{S(G, \delta, \Delta)}{S(0, \delta, \Delta)} = \exp\{-\gamma^2 G^2 D \delta^2 (\Delta - \delta / 3)\}, \tag{3.45}
\]

also known as Stejskal-Tanner equation [Ste]. \(E(G, \delta, \Delta)\) defines a normalized echo attenuation, which depends on the gradient duration, \(\delta\), and interval \(\Delta\) as defined in Fig. 3.16 (a).

In the absence of gradient, the echo intensity \(S(0, \delta, \Delta)\) will be maximal. By increasing the gradient intensity, the echo signal \(S(G, \delta, \Delta)\) will decrease due to the fact that spread of phases is increasing, which in case of diffusing phase carriers causes imperfect signal refocusing.

In order to avoid infinite voltage generation at the infinitely step rising and falling gradient slopes, in a real sequence the ideal gradient shape of a step function is smoothed by applying short ramps during a time \(\varepsilon\) (as defined in Fig. 3.17) in the beginning and the end. The solution of Eq. (3.44) for such trapezoidal gradients results in the following expression for the echo attenuation

\[
E(G, \delta, \Delta) = \exp\{-\gamma^2 G^2 D[\delta^2(\Delta - \delta / 3) + \varepsilon^3 / 30 - \delta \varepsilon^2 / 6]\}. \tag{3.46}
\]

Fig. 3.17 Timing diagram in the diffusion sequence for trapezoidal gradients, in a spin echo sequence, i), and in a gradient echo sequence, ii).
Varying the strength of $G$ in a diffusion sequence will produce a Gaussian dependence of the echo amplitude on the gradient strength. The diffusion coefficient can be obtained by fitting such curve (see Fig. 3.18) or with a linear regression of $\ln E$ versus $G^2$.

![Figure 3.18 Measurement of the self diffusion coefficient of $^{129}\text{Xe}$. The experimental points are the red stars and the fitted curve by a Matlab program is the black line.](image)

In the case of anisotropic diffusion, Eqs. (3.45) and (3.46) have to be modified by the tensorial description of the diffusion coefficient $D$ (with ideal gradients, i.e. $\varepsilon \to 0$).

$$E(G, \delta, \Delta) = \exp\{-\gamma^2 G \mathbf{D} \mathbf{G} \delta^2 (\Delta - \delta / 3)\}$$

(3.47)

where the product of gradients and diffusion tensor resulting in:

$$\mathbf{G D G} = \begin{pmatrix} G_x & G_y & G_z \\ \end{pmatrix} \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \begin{pmatrix} G_x \\ G_y \\ G_z \end{pmatrix} = \sum_{\alpha=x,y,z} \sum_{\beta=x,y,z} D_{\alpha\beta} G_\alpha G_\beta$$

(3.48)
Because of the symmetric nature of the tensor only 6 different diffusion coefficients have to be determined; for example the gradient directions xx, yy, zz, xy, xz, yz in the following equation derived from Eq. (3.47)

\[
\ln E(G) = -\gamma^2 \delta^2 (\Delta - \delta/3) \sum_{\alpha=\beta} \sum_{\alpha=\beta} D_{\alpha\beta} G_\alpha G_\beta
\]  

(3.49)

III.7.1 Measurement in restricted geometries

In case of restricted diffusion (see section III.6.1) eq. (3.39) can be no longer solved exclusively in the time domain (i.e. the NMR sequence acting on freely diffusing particles), because \( P(r|r',t) \) then obviously has spatial “cut-offs” which have to be taken into account. This represents a severe complication and can only be solved analytically for simple geometries, which are only summarised here (for details see [Cal]). The analytical solutions for a rectangular (i.e. walls in a distance \( a \)), a cylindrical and spherical pore of radius \( a \) are listed below:

**Rectangular:** [Cal]

\[
E(q) = \frac{2 - 2 \cos(2\pi qa)}{(2\pi qa)^2} + 4(2\pi qa)^2 \sum_{i=1}^{\infty} \exp \left( -\frac{i^2 \pi^2 D\Delta}{a^2} \right) \left[ \frac{1 - (-1)^i \cos(2\pi qa)}{(2\pi qa)^2 - (i\pi)^2} \right]
\]  

(3.50)

with \( q = \frac{\gamma \delta G}{2\pi} \).

**Cylindrical:** [Cal]

\[
E(q) = \exp \left( -2\gamma^2 G^2 \sum_{i=1}^{\infty} f_i \right)
\]

with \( f_i = \frac{2D\delta\alpha_i^2 - 2 + 2 \exp \left[ -D\alpha_i^2 \delta \right] + 2 \exp \left[ -D\alpha_i^2 \Delta \right]}{D^2 \alpha_i^6 \left( a^2 \alpha_i^2 - 1 \right)} \)

\[
- \exp \left[ -D\alpha_i^2 (A - \delta) \right] - \exp \left[ -D\alpha_i^2 (A + \delta) \right]
\]

(3.51)
where the $\alpha_i$ are the roots of the following Bessel-function equation [Cal].

$$\alpha_i a J_0(\alpha_i a) = J_1(\alpha_i a)$$

\(3.52\)

\textbf{Spherical:} [Cal]

$$E(q) = \exp\left(-2 \gamma^2 G^2 \sum_{i=1}^{\infty} g(\beta_i)\right)$$

with

$$g(\alpha_i) = \frac{1}{\beta_i^2 \left( \beta_i^2 a^2 - 2 \right)} \left[ \frac{2\delta}{\beta_i^2 D} - \frac{2 + \exp(-\beta_i^2 D(\Delta - \delta)) - 2\exp(-\beta_i^2 D\delta)}{\beta_i^4 D^2} \right.$$

$$\left. - \exp(\beta_i^2 D\Delta) + \exp(-\beta_i^2 D(\Delta + \delta)) \right]$$

\(3.53\)

where the $\beta_i$ are the roots of the following Bessel-function equation

$$\beta_i a J'_1(\beta_i a) = \frac{1}{2} J_1(\beta_i a)$$

\(3.54\)

For all three equations the timings ($\delta$ and $\Delta$) are defined as before and $D$ as the unrestricted diffusion coefficient.

\[\begin{align*}
\text{a)} & \quad \langle x_a \rangle \\
\text{b)} & \quad \langle x_b \rangle
\end{align*}\]

Fig. 3.19 Schematic explanation of the effect of diffusive “edge enhancement”: A particle starts to diffuse and its position is spatially encoded (empty circle) until it is acquired (full circle). The travelled distance, $\langle x \rangle$, is marked by arrows. a) The particle diffuses freely travelling a maximum distance $\langle x_a \rangle$. b) The particle hits a wall and is reflected, which results in a shortening of the path $\langle x_b \rangle$. 
Especially in the case of the extremely rapid diffusion in gases additional effects become observable. One is the so-called “edge enhancement”, where the image intensity close to boundaries appears unnaturally enlarged. This is because the particles close to such boundaries collide with the walls and are reflected (see Fig. 3.19 (b)). Their average displacement is therefore smaller than the displacement in the middle of the sample. In other words, the spins near the edges lose their memory slower than those in the middle of the sample, and thus the diffusive signal from spins close to inner boundaries is less attenuated. This effect is illustrated in Fig. 3.20. So far this effect can not be equated but only simulated. [Swi2].

Fig. 3.20 NMR-Image of 3He in a freezing unit, which consists of two collinear cylinders (see sketch on the right). Diameters of the sketch on the right are in mm. Here only the helium close to the walls gives a detectable signal, which illustrates nicely the effect of diffusive “edge enhancement”.

At last the effect of “motional averaging” should be explained in a qualitative fashion. This is observed in the so-called “strong diffusion regime”, where the particles move so fast that the effect of the spatial encoding of the gradients is averaged. In the case of free diffusion this would cause a complete loss of signal from these particles, however if the material is captured within a pore, all the positions are averaged, resulting in a mean position. In other words, all of the spins have essentially lost their spatial memory and only a single Lorentzian line is observed in the centre of the pore [Swi2].
III.8 Signal to noise ratio (SNR).

The signal detected in the absence of a sample is the so-called noise; it can be produced by random or systematic factors. The ratio between this noise and the “true” signal is the signal-to-noise ratio (SNR). It is an important parameter of the effectiveness of any NMR experiment. Applying Lenz’s law for a sample inside a coil, after an $\alpha$ r.f. pulse the signal amplitude will be

$$S(t) = -\sin(\alpha) \frac{\partial}{\partial t} \int_{V_s} B_1 \cdot M_0 d\mathbf{r}.$$  
(3.55)

where $B_1$ denotes the induced magnetic field produced by a coil carrying unit current at the location of $M_0$.

An elegant way to determine the induced e.m.f. of a coil is the principle of reciprocity proposed by Hoult and Richards, [Hou], which results in the following equation employing Eq. (3.9):

$$S(t) = (1/2)\sin(\alpha)K_0 B_{1,x} V_s N S_\gamma h P \cos \omega_0 t$$  
(3.56)

where $V_s$ is the sample volume where $B_1$ is assumed to be spatially constant per unit current and $K$ is a factor to correct the possible inhomogeneities of the magnetic field. The noise e.m.f. against which the signal must compete is calculated as follows. The thermal noise power per unit frequency bandwidth, $\Delta f$, is determined by the coil resistance, $R$, and the coil temperature, $T_C$. The time domain r.m.s. noise e.m.f. is then, [Cal]:

$$\sigma_i = \sqrt{4k_B T_C \Delta f R}$$  
(3.57)

$\Delta f$ depends on the chosen band pass filter, which should be set exactly equal to the desired bandwidth of the spectrum or image.
Houl and Richards considered two coil geometries drawn in Fig. 3.21. For a sample enclosed by an ideal solenoid, $K \approx 1$. For the coil in Fig. 3.21 (left), with $N_t$ turns in a standard coil configuration, i.e. $2a \approx L$:

$$B_{i,xy} = \mu_0 N_t / \sqrt{4a^2 + L^2} = \mu_0 N_t / \sqrt{2L}$$  \hspace{1cm} (3.58)

where $\mu_0$ is the magnetic permeability of vacuum, $L$ and $a$ are the length and the radius of the coil as defined in Fig. 3.21.

For the coil configurations of Fig. 3.21, the coil resistance $R$ is proportional to the square root of the frequency; therefore the thermal noise will be proportional to the frequency as follows:

$$\sigma \propto \omega_0^{1/4}$$  \hspace{1cm} (3.59)

As shown in Eq. (3.56) the signal depends linearly on the polarization. Hence, for samples that are thermally polarized a linear dependence on the frequency is found for the polarization in the high temperature limit, and as the induced e.m.f in the coil is linear dependent on the frequency, dependence $S \propto \omega_0^2$ is found. Thus the SNR in the case of the thermal polarization is, [Cal]:

Fig. 3.21 Solenoidal and saddle r.f. coil winding considered by Hoult and Richards. Capacitor C ensures proper resonance frequency.
Typically the SNR is improved by co-adding multiple scans, which are identical except for the stochastic nature of the noise. It can easily be shown by the “stochastic theorem” that the SNR\(_m\) of \(m\) co-added scans improves only by the square root of \(m\) (compared to the SNR\(_1\) of a single scan):

\[
\frac{SNR_m}{SNR_1} = \frac{m}{\sqrt{m}} = \sqrt{m}.
\]  

(3.61)

From the last equation, one could be tempted to simply average the signal very often to improve the SNR. However, this cannot be done arbitrarily fast, because the nuclear spin system must be allowed to return to thermal equilibrium between the experiments. As explained in section III.3.1 this process is determined by spin-lattice relaxation and to recover a substantial amount of the magnetization in thermal equilibrium several times \(T_1\) have to be waited (typically 5 \(T_1\)). However, a compromise between excited (determined by the tip angle) and recovered magnetization (determined by the recycle delay, \(T_R\)) can be made to optimize the SNR. Of course, in such a rapidly repeated sequence, the spins recover only to a fraction and are said to be “partially saturated”. The optimum tipping for such an experiment is given by the Ernst angle \(\theta_E\):

\[
\cos \theta_E = e^{-T_R/T_1}
\]  

(3.62)

In the case of hyperpolarized gases, the analysis is very different. On the first place, as the polarization is increased artificially, it does not depend on the frequency or magnetic field since the spins are not in thermal equilibrium. The signal acquired will depend on the e.m.f induced, so it will be linear with the frequency, resulting in a SNR \(\propto \sin(\alpha) \omega_0^{3/4}\).

However averaging the NMR signals from a hyperpolarized gas can result in drawback; the non renewable nature of the polarization implies an irreversible lost signal after each r.f. pulse. If \(n\) pulses of an identical \(\alpha\) tip angle are used, the signal will decay as:
\[ S = S \sum_{i=1}^{\infty} \cos^{-1}(\alpha) \sin(\alpha) \]  

resulting in a SNR as follows for a small \( \alpha \) (for \( n \) experiments)

\[ \text{SNR} \propto \frac{1 - (1 - \alpha)^n}{\sqrt{n}} \]  

The big advantage with the non thermal polarization is that no waiting period between pulses must be introduced resulting in very short acquisition times

III.9 Spatial resolution.

Spatial resolution is conceptually easiest explained by discussing the point-spread function, \( \text{PSF}(r) \), which convolves the pure spatial information, \( \rho(r) \). The width of this point-spread function in relation to the width of an image pixel then directly gives a measure of the spatial resolution. An NMR-image, \( I(r) \), is then described by the following convolution

\[ I(r) = \text{PSF}(r) \otimes \rho(r) + \text{noise}. \]  

The width of the point-spread function can be directly obtained by switching the ‘spatial term’ off, which means to measure at gradient strength zero \( (G=0)\) and then Fourier-transform the result.

The frequency encoded dimension is then simply the normal NMR-spectrum, and the maximum dispersion of chemical shifts or line width determines the total width of the point-spread function, \( \Delta \omega \), hence the blurring of the image along this dimension. The minimum resolved distance, \( \Delta r \), is consequently defined by the width of the point-spread-function and the (spatial) frequency spread by the read gradient, \( \gamma G \).

Frequency: \[ \Delta r = \frac{\Delta \omega}{\gamma G} \]  

43
From this equation it is obvious, that if the line width increases, the resolution decreases accordingly, unless the gradient strength is enlarged. This explains the difficulties of NMR imaging of solids, where line widths can be 5 or more orders of magnitude broader than in liquids, because the dipole-dipole interactions are no longer averaged out as a consequence of reduced mobility.

The case is quite different when the spatial information is obtained via phase-encoding with constant evolution time. If the gradient is switched off, nothing is varied, hence resulting in a constant which Fourier-transforms into a delta-function. That means that the point-spread function has no width, and the minimum resolvable distance $\Delta r$ is no longer determined by any intrinsic NMR-parameter, but exclusively by instrumental variables, namely the maximum gradient amplitude $G_{\text{max}}$ and the evolution time $\tau$

$$\text{Phase: } \Delta r = \frac{1}{\gamma G_{\text{max}} \tau}. \quad (3.67)$$

Typically a combination of both, frequency and phase encoding techniques, are used as shown in Fig. 3.9. Figure 3.22 demonstrates the discrepancy in spatial resolution by the frequency and phase encoding on a phantom made from three chemically different components.

This latter equation could be misunderstood that infinitely high spatial resolution can be obtained by simply increasing $\tau$. This is a naïve idea, because the signal will decay...
completely when $\tau$ is made much longer than $T_2$. However, from this Gedankenexperiment it becomes clear that the spatial resolution in MRI is only determined by the sensitivity.

Of course, co-adding multiple experiments can boost the signal and hence the resolution, as seen in Eq. (3.61). Therefore, it is difficult to quantify the possible spatial resolution, but for liquid samples a voxel volume of $10^4$-$10^5 \mu m^3$ is typically achieved with micro-imaging equipment (see section IV.2).

Similar considerations hold for the influence of self-diffusion on the resolution. The random walk of the observed molecules causes a spatial offset, which can blur the image in the frequency encoded dimension. This happens according to the Einstein-Smoluchowski equation, rewriting Eq. (3.41) for 1D case:

$$\Delta r = \sqrt{2D \Delta t}$$

(3.68)

where $D$ is the self-diffusion coefficient and $\Delta t$ a sampling interval with which the signal is recorded. Furthermore, self-diffusion also has a strong influence on the amplitude of the point-spread function, which is given by,

$$PSF = \exp\left(-\frac{2}{3}D \frac{m \tau^3}{G^2}\right)$$

(3.69)

where $m = 2$ for the frequency encoded dimension and $m = 1$ for the phase encoded dimension where $\tau$ is defined in Fig. 3.9. The influence of self-diffusion is usually smaller than chemical shifts, dipolar couplings and other interactions as long as liquids are considered. For water as an example (with $D = 2.3 \cdot 10^{-9} m^2/s$ at 25°C) a typical experimental setup gives $\Delta r \approx 0.3 \mu m$ and a $PSF \approx 1-10^{-6}$ which is negligible.

III.9.1 Gases

Although, about 3 orders of magnitude are lost due to the lower density of gases when compared to liquids or solids, hyperpolarization exceed the signals from thermally polarized water at high fields (ca. 7 – 10 T). Therefore, hyperpolarized $^3$He and $^{129}$Xe were originally expected to overcome the sensitivity limited resolution in MRI of gases.
However, self-diffusion also increases by 4-5 orders of magnitude ($^3$He: $D = 1.8 \cdot 10^{-4}$ m$^2$/s [Boc] and $^{129}$Xe: $D = 5.71 \cdot 10^{-6}$ [Hir] at 25°C and 1 bar). In difference to liquids the main cause of resolution limits may be expected from rapid Brownian motion of the gas atoms. The same experimental values in the example above (using Eq. (3.69) give for $^3$He $\Delta r \approx 90$ μm and a PSF $\approx 0.5$ for the frequency encoded dimension, which are both substantial.

However, this calculation assumes free, unrestricted diffusion. In a realistic sample, one will find walls, which restricts the diffusivity of the gas atoms close to them. Pores will cause restricted diffusion of the gas inside their entire volume. In such situations the effective diffusion coefficient can also be estimated by the Einstein-Smoluchowski equation when the pore size, $r$, is smaller than a critical distance, $r_c$

$$r_c = \sqrt{2D_0\tau} \quad (3.70)$$

where $D_0$ is the coefficient for free diffusion, so that the effective diffusion coefficient can be approximated as

$$D = \begin{cases} \frac{r^2}{2\tau} & \text{for } r < r_c \\ D_0 & \text{for } r > r_c \end{cases} \quad (3.71)$$

The spatial restriction by pore walls therefore reduces the effective diffusion coefficient and increases the amplitude of the diffusion point-spread function in Eq. (3.66). From these facts it is expected, that MRI of hyperpolarized gases in porous media lead to better resolved images. Consequently it is of interest to investigate how the “coherent” resolution, $\Delta r$, of the image in Eq. (3.66) is related to the size of a pore, $r$, and whether there is an optimum of resolution, respectively sensitivity. For such a relation one has to combine Eq. (3.67), Eq. (3.69) and Eq. (3.71) giving

$$PSF(r) = \exp\left(-\frac{r^2}{6\Delta r^2}\right) \quad (3.72)$$

A consequence of this equation is that if the resolution of the image is set much better than the size of the pore, the signal is decaying exponentially. For instance if only 3 pixels per pore ($3\Delta r = r$) should be resolved, the PSF drops to 22% of its maximal amplitude, and for $5\Delta r = r$ it is already down to about 1%. This effect is experimentally demonstrated in Fig. 3.23, where for the better resolved images, the effect of edge enhancement by unilateral restrictions
can be clearly recognized. The relation between resolution and pore size is best studied at the central pore (2.5 mm diameter). Following the increasing resolution from image 3e to 3p the signal loss becomes visible for instance following the signal inside the 2.5 capillary in the centre of the phantom.

Fig. 3.23 a) – p) 16 images of a resolution-phantom made from PTFE (sketch on the right, measures in mm) inside a larger tube and filled with hyperpolarized ³He. The resolution / gradient strengths were increased from left to right and top to bottom 64 × 64 points were acquired with a evolution time of $\tau = 310$ µs and a sampling interval of $\Delta t = 10$ µs. The strengths of the frequency and phase encoding gradients were chosen to be equal and increased from image a) to p) according to the following list of values in mT/m: a) 8.9, b) 13.4, c) 17.8, d) 22.3, e) 26.7, f) 33.4, g) 35.6, h) 40.0, i) 44.5, j) 49.0, k) 55.6, l) 66.8, m) 77.9, n) 89.0, o) 100.1, p) 111.3. Right schematic representation of the phantom with its dimensions in mm.
IV Experimental setup.

IV.1 The Polarizers

In this work, two hyperpolarized gases are used: $^3$He and $^{129}$Xe: Their hyperpolarization is achieved by different methods explained in the point III.4. The instrumentation for both cases is explained in the following.

IV.1.1 Hyperpolarization of $^3$He.

In Fig. 4.1 a schematic drawing of the polarizer and compressor is presented. The process begins in a titanium getter, where the $^3$He gas is purified. Then it flows throughout five glass cells, where it is excited in the metastable state by an rf-plasma. Therefore, foil-electrodes are attached to the sides of each glass cell. A circularly polarized laser beam with a wave length $\lambda=1083$ nm is guided through the cells by the aid of mirrors and excites the metastable state of $^3$He. Two fibre-lasers with 15 W each are combined to obtain sufficient power. The flow rate of the gas is adjusted to achieve a polarization in the order of 60-80%. However, the fact that plasma has to be ignited sets a lower limit to the usable pressures, which must be in the range of $10^3$ bars. As a consequence the polarized $^3$He has to be compressed to useful pressures. This is achieved by a hydraulic titanium compressor with an interior volume of 15 L, which presses the gas in a storage deposit of 4L at a pressure of about 300 mbar. In a second step of compression, the gas is brought from the storage deposit to a glass transport cell. Of course the entire equipment must be placed inside a low magnet field.
of 8 G. With this instrumentation production rates of 3 bar·L/hour of hyperpolarized $^3$He of $P \approx 60$-$65\%$ can be achieved [Den].

The glass transport cell is made from an alkaline-earth-alumina-silicate glass with a small fraction, lower than 20 ppm, of paramagnetic Fe$^{3+}$ impurities. These glass cells have a volume of ca. 1 L and a relaxation time, $T_1$, between 20 to 200 hours. The final pressure inside the transport cell is ca. 2-3 bar.

![Fig. 4.1 Schematic representation of the $^3$He polarizer. Due to dimensions, only one instead of 5 optical pumping cells has been drawn. See text for details.](image)

The polarization of the gas will only survive when the cell always stays inside an homogeneous magnetic field. As a consequence, special containers have to be designed for the transportation of these cells. They contain permanent magnets for field generation and shielded from external fields by a double layer of $\mu$-metal [Gro]. The relaxation time of the gas inside such boxes is higher than 100 hours. With such a box the gas can easily transported from the central $^3$He production facility in the Institut für Physik to the Max Planck-Institut für Polymerforschung (MPI-P). Once in the MPI-P, the glass cell is stored inside a home made electromagnet of 25 G shown in Fig. 4.2.
Fig. 4.2 Home made cylindrical electromagnet to store the hyperpolarized $^3$He in MRI-lab of the MPI-P. Left: photo of the electromagnet with the dimensions. The coil produces 25 G with a current of 2 A. Right: 2D axisymmetric FEM calculation of the flux lines inside this coil the grey scale intensities denotes the magnetic flux density, which is optimized for homogeneity and a maximal access to the center. Therefore the equally spaced coils had to have 229 windings at the ends while 158 were sufficient for the three in the center.

IV.1.2 Hyperpolarization of $^{129}$Xe

$^{129}$Xe is polarized in a home-built polarizer, of which a sketch is shown in Fig. 4.3. A high-pressure gas-bottle of xenon and buffer gases (94 % $^4$He and 5 % N$_2$ and 1 % xenon) is connected to the apparatus. The $^4$He is needed to increase the pressure to broaden the absorption lines by collision. The working pressure is adjusted to 7 bars and the flow of this gas mixture throughout the device is controlled by a needle valve that opens to ambient pressure.

The gas flow is directed through a flow meter that measures the flux in mL/minute and was usually adjusted to 300mL/minute. Behind the flow meter the gas is mixed with rubidium vapour and allowed to enter the polarizing chamber. The rubidium vapour is produced by heating a small reservoir by a temperature controlled heat gun (with the temperature usually adjusted to 200-220°C). The polarization chamber is made from 5 mm thick glass and has plane-parallel sides where the laser light enters to excite the rubidium (see section III.5). The laser has two laser-diodes (Coherent Inc) producing each 30W of light with a wavelength of $\lambda$= 794.7 nm. They were combined in a fibre and after a circular polarizer focused on the chamber. The entire setup has to be placed in a relatively strong magnetic field of 9.32 G generated by a Helmholtz-coil.
The polarized xenon is then separated from the buffer gases by directing the gas flow through a cold finger, which is submerged in liquid nitrogen. However, the condensed xenon has to be stored in a relatively strong field, to avoid relaxation of $^{129}\text{Xe}$ via $^{131}\text{Xe}$. Therefore, a special permanent magnet was designed (see Fig. 4.4), which produced a relatively homogeneous field of 0.3 T [Blü3].
The amounts (pressure) of hyperpolarized $^{129}$Xe were controlled by the duration of the freezing time and the gas flux. Typical values were polarization times lasting between 5-20 minutes at a 300 mL/min. The resulting pressures of xenon (after evacuating the buffer gases) at room temperature are listed in Tab. 4.1.

Tab. 4.1 Pressures of hyperpolarized xenon produced in a bottle of 0.3 L by different polarization times. The gas flux was adjusted to 300 mL/min and the buffer gases removed.

<table>
<thead>
<tr>
<th>Time [minutes]</th>
<th>7.5</th>
<th>12</th>
<th>16</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure [bar]</td>
<td>1.10±0.05</td>
<td>1.60±0.05</td>
<td>2.05±0.05</td>
<td>2.35±0.05</td>
</tr>
</tbody>
</table>

IV.2 NMR console and magnet equipment

All measurements were made in a horizontal magnet of 4.72 T with a 20 cm bore. Shielded gradients (Bruker, Rheinstetten) with strengths up to 300 mT/m were driven by DC-amplifiers (Copley Controls Corp.). A double resonant birdcage coil (Bruker) with an inner diameter of 26.5 mm was used to excite $^{129}$Xe and $^3$He at Larmor-frequencies of 55.59 MHz and 153.096 MHz, respectively. For $^1$H-experiments another birdcage coil (Bruker) was used with an inner diameter of 20 mm at a frequency at 200.973 MHz. The gradients and the r.f. pulse were controlled from a Maran DRX console (Resonant Instruments) which runs under a Matlab (Mathworks Inc.) home made environment.

In order to know the time available for measuring hyperpolarized $^{129}$Xe, $T_1$ relaxations times were measured in different places of the magnet (see Fig. 4.5). By this way possible locations for placing a reservoir bottle with hyperpolarized $^{129}$Xe during the experiments were found.
Two different gradient coils were used: the “Mini”-gradient and the “Micro”-gradient (Bruker). The “micro”-gradient achieves a gradient strength of ca. 1 T/m and was used for measuring protons, while the “mini”-gradient only reached a maximum gradient strength of ca. 0.3 T/m but at a bigger diameter. The latter was used for measuring xenon and helium.

For controlling the gradients strengths from the scale of the Maran console, different images of samples with a known size, were made following the sequence illustrated in Fig. 3.9. Comparing the size of the sample with the field of view (FOV) achieved in the image, the gradients can be determined following

\[ G_{\text{Read}} = \frac{SW}{\gamma FOV} \quad (4.1) \]

for the read direction, where \( G_{\text{Read}} \) is the gradient strength and \( SW \) is the spectral width, and

\[ G_{\text{Phase}} = \frac{SI \cdot 2}{2 \tau FOV} \quad (4.2) \]

for the phase direction, where \( G_{\text{Phase}} \) is the gradient strength, \( SI \) is the number of points acquired and \( 2\tau \) is the acquisition time as defined in Fig. 3.9. Then a relation between the Maran scale and \( G_{\text{phase}} \) and \( G_{\text{Read}} \) can be used to calibrate the gradient strength, as shown in Fig. 4.6. The calibration values are summarized in Tab. 4.2.
Tab. 4.2 Relation between the Maran scale (Ms) and the real gradient strength. Fitted parameters from the results shown in Fig. 4.6.

<table>
<thead>
<tr>
<th>Gradient direction</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minigradient [T/m]</td>
<td>$(1.32 \pm 0.02) \times 10^{-5} \cdot Ms$</td>
<td>$(1.14 \pm 0.03) \times 10^{-5} \cdot Ms$</td>
<td>$(1.52 \pm 0.04) \times 10^{-5} \cdot Ms$</td>
</tr>
<tr>
<td></td>
<td>$-0.0037 \pm 0.0015$</td>
<td>$-0.003 \pm 0.002$</td>
<td>$-0.004 \pm 0.003$</td>
</tr>
<tr>
<td>Microgradient [T/m]</td>
<td>$(4.3 \pm 0.3) \times 10^{-5} \cdot Ms$</td>
<td>$(4.59 \pm 0.14) \times 10^{-5} \cdot Ms$</td>
<td>$(7.9 \pm 0.2) \times 10^{-5} \cdot Ms$</td>
</tr>
<tr>
<td></td>
<td>$+0.003 \pm 0.02$</td>
<td>-</td>
<td>$-0.0267 \pm 0.009$</td>
</tr>
</tbody>
</table>

Fig. 4.6 Measurement of the gradient strength as function of scale used by the Maran console in the two sets of gradients; “minigradients” (right) and “microgradients” (left). Data are empty points and the fitting are the red line, the fitted parameters are summarized in Tab. 4.2.
IV.3 Gas handling system.

A set of pneumatic pistons and magnetic valves were combined to even operate in the strong magnetic field of the superconducting NMR-magnet. Therefore, commercially available piston valves (Festo) had to be modified and tested. Firstly all magnetic parts were replaced in the piston valves by non-magnetic ones, so that they could be mounted close to the NMR coil. The air flow which closes and opens the piston (see Fig. 4.6) was controlled by a second set of magnetic valves outside the strong field of the superconducting magnet. Location of the pistons in an experiment can be seen in Fig. 6.5.

These magnetic valves are controlled by switching 24 V which can be controlled manually or automated via the spectrometer. In this way valve operations can be included in the NMR pulse-programs, which made the measurements very fast, sable and reliable.
V Spatially resolved diffusion coefficient

V.1 Distribution of diffusion coefficients in a sample.

So far only experiments, which determine the diffusion coefficient for the entire sample, have been discussed. This approach becomes problematic when there is more than one substance with different diffusion coefficient present. This is illustrated on a phantom made from two tubes; one containing a solution of water doped with CuSO$_4$ and the other ethanol.

To demonstrate this, the integral diffusion coefficient of both liquids, placed next to each other in separate containers, as shown in Fig. 5.3, and each liquid individually were measured. All measurements were performed at 294 K using the PGSE sequence shown in Fig. 3.17 (a) (pulse sequence program LAPGSE is listed in appendix ). The sequence timing is the same for the three experiments with $\delta = 8$ ms and $\Delta = 28$ ms.

![Graph](image-url)

**Fig. 5.1** Bulk diffusion measurements of water (red circles), ethanol (black squares) and both containers together (green triangles). The amplitudes of all three data sets were normalized since only the width is analyzed. The measurement was done using the sequence described in Fig 3.17 (a).
The three different data sets were fitted separately to Eq. (3.45). From Fig. 5.1, it can already be seen that it will be hard to distinguish two Gaussians in the curve of the mixture (green triangles). The fitted values are presented in Tab. 5.1.

<table>
<thead>
<tr>
<th></th>
<th>Water</th>
<th>Ethanol</th>
<th>Water &amp; Ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{\text{measured}}$ $[10^{-9}$ m²/s$]$</td>
<td>2.30 ± 0.01</td>
<td>1.01 ± 0.02</td>
<td>2.10 ± 0.03</td>
</tr>
<tr>
<td>$D_{\text{literature}}$ $[10^{-9}$ m²/s$]$</td>
<td>2.29</td>
<td>1.08</td>
<td></td>
</tr>
</tbody>
</table>

V.2 Spatially resolved diffusion coefficient.

If a sample consists of areas with different diffusion coefficients, due to different substances or spatial restrictions, they can only be separated when their signal is spatially encoded. Therefore, a method, which correlates the location with the diffusion coefficients, must be implemented. This method is usually known as diffusion imaging.

V.2.1 Pulse sequence

In order to perform spatially resolved images, the 2D spin echo imaging sequence of Fig. 3.9 is modified by adding a third dimension, in which a diffusion gradient is stepped through different values. This can be understood as a combination of the sequences of Figs. 3.9 and 3.17 (a) as depicted in Fig. 5.2. Hence, for each strength of the diffusion gradient a separate 2D image is acquired (see the pulse sequence program ImdifWE in appendix ). The third dimension contains then information similar to that presented in Fig. 5.1.
Fig. 5.2 2D diffusion imaging for thermally polarized samples. The read and phase gradients act as in a usual spin echo image sequence, the third gradient is used to add diffusion gradients of duration $\delta$ and intensity $G_d$. While the second read gradient is applied the signal is acquired, during the acquisition time $Acq$. $Gr$ and $G_p$ are strength of the read and the maximum of the phase gradient, respectively. $G_c$ is the strength of the crusher gradient, applied during $T_c$ to dephase remaining magnetization. The arrows crossing $G_p$ and $G_d$ denote that the gradient strength varies from $-G_p$ to $+G_p$ and from $-G_d$ to $G_d$ respectively.

The analysis of the third dimension at the position $(x,y)$ in the 2D image results in a diffusion coefficient map $D(x,y)$. If the procedure is repeated for all positions in the image, it results in a 2D image which now displays diffusion coefficients rather than spin densities.

V.2.2 Demonstration on a liquid sample

The pulse sequence explained in the previous section, Fig. 5.2, is applied to the samples used in V.1, which are positioned as shown in Fig. 5.3. The following experimental values: $G_d = 0.0876$ T/m, $Gr = 0.1168$ T/m, $G_c = 0.292$ T/m, $G_p = 0.1192$ T/m, $T_c = 0.5$ ms, $\delta = 8$ ms and $Acq = 0.64$ ms were used.
Fig. 5.3 NMR proton (spin density) image illustrating the arrangement of two samples placed inside the NMR coil to measure their different diffusion coefficient. The left tube contains 0.156 cm³ of water and the right one 0.179 cm³ of ethanol.

Fig. 5.4 2D map of the local diffusion coefficients for the two tubes shown in Fig. 5.3. The different colours indicate the diffusion coefficients with values indicated by a colour bar at the right in m²/s. 20 images with different Gd were acquired. The field of view of each image was 2×2 cm² acquired in 64×64 pixels. Only pixels with a SNR>20 were analyzed to determine their diffusion coefficients.
Special care had to be taken in the data analysis because the fitting procedure had to be automated. To avoid instable fitting conditions during data processing, the data had to be masked by a threshold, set well above the noise floor (see the Matlab’s program RimdifWE in appendix). Subsequently the third dimension was fitted to a Gaussian for every unmasked point and the resulting diffusion coefficient mapped was shown into a new image presented in Fig. 5.4.

As it can be seen in Fig. 5.4, the spatially resolved diffusion coefficients (see colours scale) are a bit smaller than the literature and bulk values from Tab. 5.1, but are sufficiently precise for this demonstration.

V.2.3 Restricted diffusion for gases.

The procedure shown in the previous section is applied to a phantom made up by capillaries of different diameters and filled with hyperpolarized $^3$He. In this case, the different diffusion coefficients observed are due to the different spatial restriction in each capillary. In a first step two diffusion maps will be analyzed, one where the diffusion gradient is set parallel to the long axis of the capillaries and a second one where the diffusion gradient is set transversal. The influence of the restricted diffusion of the gas on the sensitivity of an image is also analyzed as a function of the timing of the experiment.

V.2.3.1 Description of the phantom

In order to test the interrelationship of diffusion coefficients and spatial resolution, a phantom is needed where various spatial restrictions are accessible for a gas. A phantom consisting of different capillaries of diameters ranging from 0.5 mm to 3.2 mm was prepared by gluing them together and immersing them in epoxy, a sketch is shown in Fig. 5.5. The sample thus prepared was cut at both ends to give access to the gas. The phantom was placed in a bottle of similar diameter, which can be connected to the gas handling system. In this way the sample can be flushed with hyperpolarized $^3$He, or with a mixture of gases, while remaining in a stable position, so that reproducible measurements can be carried out. The epoxy cylinder is of 4 cm length, and hence, longer than the dimension of the r.f. coils. It does
not fit tightly in the glass tube. Therefore an outer ring of gas in the gap can be observed in all the images. 2D-ADC maps and 2D images are made by applying a hard $\alpha = 5^\circ$ r.f. pulse. A selective pulse was avoided at this stage for the sake of understanding the undergoing processes.

In a next step, posterior to this work this procedure will be repeated with a selective excitation. It is worth mentioning that the residual volume of the sample acts as a reservoir which enables the repetition of experiments without the need of refilling with helium.

![Fig. 5.5 Schematic representation of phantom built to demonstrate restricted diffusion in gases. The inner diameters of the different glass tubes are shown in mm. These glass capillaries (grey) are moulded into another cylinder by epoxy resin. The interior of the tubes is empty (without resin) to be taken up by helium. The grid is a reference for the pixels (32×32) that compose the image. In top right of the figure a reference frame is sketched as the phantom was placed in the magnet, being the z-axis the direction of the magnetic field and also the direction of the glass tubes, the x-axis the horizontal and the y-axis the vertical direction.](image-url)
V.2.3.2 Diffusion measurements

ADC measurements of gases and liquids, often encounter the problem that the voids are smaller than the resolution of the image. This is typically the case in ADC maps of lungs. In order to show how this situation influences the determination on the localized diffusion coefficient two measurements of the bulk diffusion coefficient in directions parallel, $D_{//}$, and perpendicular, $D_{\bot}$, to the capillaries were made. The results are shown in Tab. 5.2. It can be observed that $D_{//}$ corresponds to the free diffusion coefficient, while $D_{\bot}$ is smaller due to diffusion restrictions. Both measurements were done at 1 bar and at 294 K.

Tab. 5.2. Bulk diffusion coefficient of hyperpolarized $^3$He in the sample of Fig. 5.5. The average of the restricted diffusion coefficient transversal to the capillaries, $D_{\bot}$, does not give spatial information about the different restricted diffusion coefficients. The diffusion in the direction of the long axis of the capillaries, $D_{//}$, gives the free diffusion coefficient.

<table>
<thead>
<tr>
<th>$D_{\bot}$ [m²/s]</th>
<th>$D_{//}$ [m²/s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(1.065 \pm 0.017) \cdot 10^{-4}$</td>
<td>$(1.798 \pm 0.007) \cdot 10^{-4}$</td>
</tr>
</tbody>
</table>

V.2.3.3 Diffusion maps.

In order to resolve the ADCs in each capillary of the phantom, spatially resolved measurements (similar to that in section V.2.2) have to be done. However, the pulse sequence shown in Fig. 5.2 has to be adapted to the special case of hyperpolarized gases, changing the spin echo by a gradient echo as depicted in Fig. 5.6. Six different values for Gd were used, increasing from 0 to 60 mT/m in equally spaced steps. Imaging gradients were set to $Gr=Gp=0.056$ T/m and the acquisition time to $Acq = 640$ µs.

The diffusion gradient is oriented in the same two directions as in V.2.3.1, obtaining two diffusion maps. In Fig. 5.7 the diffusion gradient direction is parallel to the glass tubes, measuring free diffusion, and in Fig. 5.8 the diffusion gradient direction is perpendicular to them, corresponding to the horizontal axis, measuring different restricted diffusion coefficients. Both measurements were done at 1 bar and at temperature of 294 K.
Fig. 5.6. Sequence used to measure the diffusion map of the sample in with hyperpolarized $^3$He. The principle layout is the same as in Fig. 5.2. The spin echo sequence in the read direction is replaced by a gradient echo to avoid the use of a $\pi$ pulse. The excitation pulse is $\alpha$ is ca. 5°.

A threshold of 2 times the noise value used in the fitting routine in order to mask the noise of the images, which would give incorrect values for D. As the epoxy cylinder is in contact with the glass tube at one point, the amount of gas in that region is quite small and is masked out by this procedure, this effect is observed in the upper section of both figures. For the capillary with diameter $\phi = 3.2$ mm the effect of edge enhancement and motional narrowing discussed in the previous chapter is observed simultaneously. A detailed study of this effect on the determination of ADC maps will be carried out in the future; in the present work experimental evidence and calculations of restricted diffusion on imaging are presented.

Fig. 5.7 shows that when the direction of the diffusion gradient is set parallel to the long axis of the capillaries, $D_{\parallel} (x,y)$, free diffusion for all the capillaries is observed, as was expected from the bulk measurements. This is true even for the gas that occupies the gap between the epoxy cylinder and the glass container.
Fig. 5.7 Diffusion coefficient map of the sample shown in Fig. 5.5 in the direction of the diffusion gradient parallel to the glass tubes (z-axis). The value of the color scale (right) shows the diffusion coefficient in $10^{-4}$ m$^2$/s. Hyperpolarized $^3$He seeped in the gap.

Fig. 5.8 Diffusion coefficient map of the sample shown in Fig. 5.5 in the direction perpendicular to the glass tubes. Values of the color scale (right) shows the diffusion coefficient in $10^{-4}$ m$^2$/s. The restriction is clearly observed in the smaller capillaries and on the gas on the outer image ring.
Fig. 5.8 shows $D_\perp(x,y)$. For the two bigger capillaries ($\varnothing = 3.2$ mm and $\varnothing = 2.4$ mm) the diffusion coefficient close to the edges is around $8 \times 10^{-5}$ m$^2$/s, while in the center of the biggest capillary values close to the free diffusion value are observed. This is reasonable considering that the mean free path for free helium with the timing used ($\Delta = 500$ µs) is of the order of 0.42 mm. For the rest of the capillaries the restriction results in values for $D_\perp$ lower than $8 \times 10^{-5}$ m$^2$/s. The effect of the restriction is also visible on the outer gap, close to the bottom of the diffusion map a much higher value is obtained than on the sides, where the gas diffusion is more restricted.

V.2.3.4 Influence of restricted diffusion and sequence timing in gas imaging

As introduced in Eq. (3.68), the mean path of a diffusing particle is $\langle x \rangle = \sqrt{2D\Delta}$. Thus the sensitivity on an image will depend on the timing of the imaging sequence as the diffusion in the gas will be restricted depending on the variation of $\Delta$. In the following a qualitative description of this effect is presented, since the aim in the present work is to observe the influence of gas mixtures on the mean free path as will be shown in the following chapters. A quantitative description is beyond the scope of this work.

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Fig. 5.9 Pulse sequence used for measuring $\Delta$ weighted images. The times $\Delta$ and $\delta$ have the same meaning as in a diffusion sequence.

Fig. 5.9 shows a sketch of the pulse sequence used to perform 2D images weighted by the diffusion time $\Delta$. The read gradient is set in the horizontal axis while the phase gradient is
on the vertical axis. A set of images is presented in Fig. 5.10, where $\Delta$ was varied between 320 $\mu$s and 2320 $\mu$s. For this values mean free paths in the order of 0.34 mm to 0.91 mm are covered.

Fig. 5.10 Set of images of the phantom in Fig. 5.5 acquired with the sequence of Fig. 5.9. The value of $\delta$ is 320 $\mu$s for all images and their FOV is 24.6 mm in the read (horizontal) and phase (vertical) direction. Each image is rescaled to its intensity maximum. The NMR images from a) to g) were acquired with values of $\Delta$ ranging from 320 ($\Delta=\delta$) to 2320 $\mu$s respectively. In h), a photo of the phantom is shown; the inner walls of the glass tubes were touched up. All images were measured at 1 bar and 294 K.

Fig. 5.11 SNR versus $\Delta$. Left: From the seven images shown in Fig. 5.10, the SNR in the centre of each glass tube was measured and plotted versus the timing. Each data set was normalized to its maximum. The graphics are labeled by the inner diameter of the glass tubes shown on the top in mm. Right: calculation of the SNR versus $\Delta$ for diffusion in cylinders. Colors are referred to the capillary size.
For the smaller capillaries ($\varnothing = 0.5 \text{ mm}$ and $\varnothing = 0.75 \text{ mm}$) restricted diffusion can be observed for all the values of $\Delta$, while for the bigger diameters initially only edge enhancement is observed and as the timing increases a distortion due to motional narrowing appears on the read direction.

The normalized signal intensity on the center of each capillary as a function of the diffusion time is shown in Fig. 5.11(left). A slow decay is observed for the smaller diameters, while for the two bigger ones a transition from the two regimes is observed for values of $\Delta$ ranging from 570 $\mu$s to 820 $\mu$s. Fig. 5.11(right) shows a calculation of the decay of the signal intensity due to restricted diffusion in cylinder using Eq. (3.51). Although mechanism like edge enhancement and motional narrowing are not considered, the observed deviations are not understood and need clarification by simulation in the future.

V.3 Discussion.

Measurements on samples with a spatial distribution of diffusion coefficients are presented. In order to develop and test the software for data analysis a setup consisting on two sample tubes, one filled with a solution of water doped with CuSO$_4$, and another with ethanol were used, as shown on Fig. 5.3. In a first step it was shown how the measurement of the bulk diffusion coefficient can give an inaccurate value, Fig. 5.2. The pulse sequence for imaging proton diffusion maps was developed together with the processing algorithm. The obtained results are summarized in Fig. 5.4. This algorithm, together with a modified pulse sequence, optimized for imaging of hyperpolarized gases, were applied for the study of the influence of a distribution of confinements (Fig. 5.5) on the diffusion measurement of $^3$He. Diffusion maps along two different directions of a phantom made of capillaries are presented in Fig.s 5.7 and 5.8. They clearly demonstrate the effect of restricted diffusion on ADC maps.

In a second step it is shown how the timing of the imaging sequence (through a variation of the diffusion time, $\Delta$) influences the sensitivity of the image, depending on the dimension of the restriction, Fig. 5.10 and Fig. 5.11.

Even though there are a great number of examples related to this topic, this is the necessary first step for the study of the influence of gas mixtures on the image sensitivity,
which is the central topic of the present work. Before showing the obtained results, an analysis of state of the art measurement of diffusion coefficients in binary mixtures will be presented.
VI Mixture of gases

VI.1 Existing theory for ideal gases

The simplest theory for the description of diffusion of gases is the so-called kinetic theory of gases, which assumes three basic points:

1. The gas consists of particles of equal mass in ceaseless random motion.
2. The size of the particle is negligible, in the sense that their diameters are much smaller than the average distance traveled between collisions.
3. The particles do not interact, except when they are in contact, doing perfect elastic collisions.

The random motion of the particles leads to the fact that each particle has a different speed, which in practice is impossible to determine individually, thus the speed is described as an average of the system:

\[
\bar{v} = \sqrt{\frac{2RT}{\pi M}}. \tag{6.1}
\]

where \( T \) is the temperature of the gas, \( M \) the molar weight of the particle and \( R \) the gas constant. In a gas, the speed of individual particles spans a wide range and the collisions continually redistribute the speeds among the particles. The fraction of particles that have speeds in the range between \( v \) and \( v + dv \) is written as \( f(v)dv \) where

\[
f([v]) = 4\pi \left( \frac{M}{2\pi RT} \right)^{3/2} v^2 e^{-\frac{M}{2RT}v^2}, \tag{6.2}
\]
is the well known the Maxwell-Boltzmann distribution. Examples of the speed distribution for xenon and helium are shown in Fig. 6.1.

Another concept that has to be introduced is the collision frequency. For this simple theory a collision occurs whenever the center of two particles is within a distance $d$ of each other, where the collision parameter $d$ is of the order of the particle’s diameter. The number of collisions made by one particle in a volume $V$ with $N$ particles divided by the time interval during which the collisions are counted is

$$ w = \sigma v_r c, \quad (6.3) $$

[Atk], where $c = N/V$ is the concentration and

$$ v_r^2 = 2\bar{v}^2 = 16 \frac{RT}{\pi M} \quad (6.4) $$

the relative mean speed. $\sigma$ is the collision cross section of the particles and has the dimension of area, [Atk].

Once the collision frequency is known, the mean free path $\lambda$, is another useful concept to describe the kinetics of a gas. If a particle collides with a frequency $w$, then the time

---

2 Notice that this definition differs from other books [Hir, Tab, Cus] where $\sigma$ is the diameter of the particle with the dimension of length, a parameter named $\kappa$ in this text.
between collisions will be $1/w$, and the distance traveled during this time is the so called mean free path

$$\lambda = \frac{v}{w} = \frac{k_B T}{\sqrt{2} \sigma P}$$

(6.5)

where the factor $\sqrt{2}$ comes from the definition of $v_\epsilon$ and the concentration $c$ is substituted by $P/(k_B T)$ with $P$ the pressure.

With these tools on the hand, the diffusion coefficient can be developed analyzing the movement of particles diffusing throughout imaginary planes as presented in Fig. 6.2.

Consider the plane XX normal to the x-axis. Two planes, P and Q, are positioned to the left and right of the XX-plane respectively and parallel to it at distance $v_x \Delta t$, as in Fig. 6.2. A particle moving from the XX-plane in the positive direction of the x-axis, will reach the Q-plane in a time $\Delta t$ if it has a velocity $v_x$. Therefore, all particles in a volume $Av_x \Delta t$, where $A$ is a surface parallel to the planes, and moving with positive $v_x$ will cross Q in an interval $\Delta t$.

The total number of collisions in this interval is therefore the volume $Av_x \Delta t$ multiplied by the concentration of particles $c$. However, to take the presence of a range of velocities in the sample into account, the result has to be summed for all positive values of $v_x$ weighted by the probability distribution of velocities; then the number of collisions is
\[ N_C = cA\Delta t \int_0^\infty v_x f(v_x) dx = \frac{1}{4} A\Delta t c \bar{v} \]  \hspace{1cm} (6.6)

where

\[ f(v_x) = \left( \frac{M}{2\pi R T} \right)^{\frac{1}{2}} e^{-\frac{M}{2RT}v_x^2} \]  \hspace{1cm} (6.7)

is the probability distribution of velocities in the x-direction. Consider now that the distance between planes \( v_x \Delta t = \lambda \), such that \( \lambda \) is the mean path described in Eq. (6.5). The concentration of particles at a distance \( +\lambda \) (in the positive x-axis direction) is evaluated by a Taylor expansion of first order of \( c \)

\[ c(\lambda) \approx c(0) + \lambda \left( \frac{dc}{dx} \right)_0 \]  \hspace{1cm} (6.8)

The average number of impacts over the surface \( A \) of the plane \( Q \) is \( N_C \), which gives for the flux from XX to \( Q \)

\[ J(XX - Q) = \frac{N_C}{A\Delta t} = \frac{1}{4} c(\lambda) \bar{v} . \]  \hspace{1cm} (6.9)

The same reasoning applied for the P-plane leads to the flow from XX to \( P \)

\[ J(XX - P) = \frac{N_C}{A\Delta t} = -\frac{1}{4} c(-\lambda) \bar{v} \]  \hspace{1cm} (6.10)

taking into account that in this case the concentration is

\[ c(-\lambda) \approx c(0) - \lambda \left( \frac{dc}{dx} \right)_0 \]  \hspace{1cm} (6.11)

the net flux in XX is then the sum of both
This crude calculation does not take the fact into account that there can also be collisions before the particle arrives to the planes P or Q, which gives an additional factor 2/3, [Atk].

The diffusion coefficient can be calculated comparing the net flow presented in (6.12) with the Fick’s second law Eq. (3.37), yielding in

\[
D = \frac{1}{3} \lambda \nu = \frac{1}{3} \frac{k_B T}{\sqrt{2 \sigma D}}. \tag{6.13}
\]

This value for the diffusion coefficient of an ideal gas is using only the three assumptions in the beginning of this chapter.

For real gases, the most common method for theoretical estimation of gaseous diffusion is that developed independently by Chapman [Cha2] and by Enskog [Ens]. Various books [Cus, Tab] deal with the subject, of which the one of Hirschfelder et al [Hir] is the most complete and the most often referred.

A more accurate expression of Eq. (6.13) can be found taking more complicated collisions into account. This is done by considering corrective parameters as the collision integral \( \Omega^{(1,1^*)} \), resulting in the following expression for the diffusion coefficient, [Hir],

\[
[D] = 0.002628 \frac{\sqrt{T^3/M}}{P \kappa^2 \Omega^{(1,1^*)}} \tag{6.14}
\]

where the collision integral depends on the reduced temperature \( T^* = kT/\varepsilon \) and \( \varepsilon \) is a parameter of the potential function of the interaction that depends on the gas component, the same way as \( \kappa \), which is a collision diameter. The subscript 1 denotes that Eq. (6.14) is the first approximation of the Chapman-Enskog theory. The different theoretical and empirical values of self diffusion of xenon and helium are shown in Tab. 6.1, where the extreme improvement by the Chapman-Enskog theory becomes clearly visible in particular for the real gas xenon.
Tab. 6.1 Comparison of different values of diffusion coefficient of xenon and helium. The first and the second columns are calculated values following the Eq. (6.13) and Eq. (6.14) respectively. The third are own measurements made by a gradient echo sequence and the fourth are literature values: All diffusion coefficients are related to 1 bar and a temperature of 294 K.

<table>
<thead>
<tr>
<th></th>
<th>( D ) [m²/s] (6.13)</th>
<th>( D_1 ) [m²/s] (6.14)</th>
<th>Meas. [m²/s]</th>
<th>Lit. [m²/s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^3)He</td>
<td>3.081·10⁻⁴</td>
<td>1.76·10⁻⁴</td>
<td>(1.84 ± 0.03)·10⁻⁴</td>
<td>1.8·10⁻⁴ [Boc],[Che]</td>
</tr>
<tr>
<td>(^{129})Xe</td>
<td>1.295·10⁻⁵</td>
<td>5.71·10⁻⁶</td>
<td>(6.0 ± 0.5)·10⁻⁶</td>
<td>5.71·10⁻⁶ [Hir]</td>
</tr>
</tbody>
</table>

The goal of the experiments of this chapter, is not measuring the diffusion coefficient for a single gas component but for a binary mixture. Hirschfelder et al, [Hir], presented the first Chapman-Enskog approximation for a binary mixture of a species-1 and species-2 as follows

\[
[D_{12}] = 2.628 \cdot 10^{-7} \sqrt{\frac{(M_1 + M_2)}{2M_1M_2}} \frac{T^3}{P \kappa_{12}^2 \Omega_{12}^{(1,1)*}}
\]

given in m²/s for the total pressure \( P \) in bar, the dimensionless collision integral \( \Omega_{12}^{(1,1)*} \), the temperature \( T \) in Kelvin and

\[
\kappa_{12} = (\kappa_1 + \kappa_2)/2
\]

in Angstroms (1Å = 10⁻¹⁰ m) where the subscript \( i=1, 2 \) or \( 12 \) denote species-1, species-2 or both mixed, respectively.

The value of Eq. (6.15) for a mixture of helium and xenon at 1 bar and temperature 294 K is \([D_{12}] = 8.78 \cdot 10^{-6} \text{ m}^2/\text{s}\) (note that the concentration cannot be taken into account).

VI.2 Concentration dependence of the diffusion coefficient in a binary mixtures

The dependence of the diffusion coefficient on the molar ratio is found in a second approximation of the Chapman-Enskog equation (approximations done by Kihara [Kih] lead to a similar result).
\[
[D_{12}]_k = [D_{12}] f_D^{(k)}
\]  

(6.17)

is the \( k \)th-approximation of the diffusion coefficient. For \( k = 2 \), \( f_D^{(2)} \) is a function of the molecular weights, viscosities, temperature and molar fractions of the two components and is expressed as, [Hir]:

\[
f_D^{(2)} = \frac{1}{1 - \frac{(6C_{12}^* - 5)^2}{60(x + y)}}
\]  

(6.18)

where \( C_{12}^* \) is a function of the temperature and \( x, y \) and \( w \) are function of the molar weights, temperature and molar fractions as follows:

\[
x = \frac{X_1^2}{[\lambda_1]} + \frac{2X_1X_2}{[\lambda_{12}]} + \frac{X_2^2}{[\lambda_2]}, \quad (6.19)
\]

\[
y = \frac{X_1^2}{[\lambda_1]} U^{(1)} + \frac{2X_1X_2}{[\lambda_{12}]} U^{(2)} + \frac{X_2^2}{[\lambda_2]} U^{(3)}, \quad (6.20)
\]

and

\[
w = \frac{X_1^2}{[\lambda_1]} \left( \frac{M_1}{M_2} \right) + \frac{2X_1X_2}{[\lambda_{12}]} \left( 1 + \frac{15}{8A_{12}^*} \frac{(M_1 - M_2)^2}{M_1M_2} \right) + \frac{X_2^2}{[\lambda_2]} \left( \frac{M_2}{M_1} \right).
\]  

(6.21)

All three parameters depends on the thermal conductivity \( \lambda_i \) (the subscript \( i = 1, 2 \) or 12 denotes species-1, species-2 or both mixed, respectively). The constant \( A_{12}^* \) in Eq. (6.21) depends on the temperature, and \( U^{(1)}, U^{(2)} \) and \( U^{(3)} \) depend on the temperature and on the molar weights \( M_i \). As seen, \( x, y \) and \( w \) are a second grade polynomials of the molar fractions \( X_i \).

The presented theory determines the diffusion coefficient of a binary gas mixture as a bulk property, ignoring the fact that there are two very different gases in this mixture, which
move and hence diffuse individually. However, NMR experiments observe only one isotope, which means that when the diffusion is measured by NMR, only the motion of this very isotope is measured. Of course the lighter isotope (He) will move faster than the average, a fact not included in the presented theory. There is no theoretical work on this particular issue, however a semi-empirical equation is proposed by Wilke [Wil], which was found to describe the observed effects very accurately. This equation describes the diffusion coefficient of one species in a mixture with \( L \) others [Bud],

\[
D_i = \frac{1 - X_i}{\sum_{j \neq i} \frac{X_j}{D_{ij}}},
\]

(6.22)

where \( X_i \) is the molar fraction of the species \( i \) and \( D_{ij} \) is the binary diffusion coefficient of the mixture of the species \( i \) and \( j \).

For the case of a mixture of two species of different gases, a further development of Eq. (6.22) leads to the following empirical approximation of the observed diffusion coefficient \( D(X) \) of one species of the gas mixture, as a function of its molar fraction, \( X \), [Mai]:

\[
\frac{1}{D(X)} = \frac{X}{D(1)} + \frac{1 - X}{D(0)}
\]

(6.23)

where the subscript \( D(1) \) denotes the diffusion coefficient of the studied species when the molar fraction is 1 (i.e. the self diffusion coefficient of the detected isotope) and \( D(0) \) denotes the diffusion coefficient in an infinite dilution of the detected spins by the buffer gas.

VI.3 Results

The free diffusion coefficients as a function of the concentration in two gas mixtures are measured, \(^3\text{He}-\text{xenon} \) and \(^3\text{He}-\text{SF}_6\). For the first mixture, both species were detected individually (\(^{129}\text{Xe} \) and \(^3\text{He} \)). In the second one, only the free diffusion coefficient of \(^3\text{He} \) was detected.
VI.3.1 Mixture of hyperpolarized $^{129}$Xe with hyperpolarized $^3$He.

Mixtures of hyperpolarized $^3$He and $^{129}$Xe were produced in different concentrations. Therefore, bottles with different amounts of hyperpolarized $^{129}$Xe were frozen out using a glass tube designed like a gas washer, which was submerged into liquid N$_2$. Subsequently the buffer gases ($^4$He and N$_2$) were removed by evacuation and the vacuum was filled with hyperpolarized $^3$He. The determination of the molar concentration proved to be the most significant source of error. Even though the initial helium pressure is known, as xenon must be in a frozen state before the mixing, the sample tube in which it is contained cools the gas and so results in greater helium pressure than the one that had been measured. The first attempt was to produce defined mixtures, and determine the concentration after the measurement of the individual diffusion coefficients. This was done by measuring the total pressure in the sample tube and, after freezing the xenon and evacuating the helium, determines the pressure of xenon. This method proved to be very time consuming, as the pressure is very sensible to temperature changes, long time has to be waited to establish thermal equilibrium in the sample tube. Nevertheless the mayor drawback aroused form the inaccuracy of the pressure gauges available at the moment. Therefore, a different approach was tried out, which consisted on weighting the sample bottle instead of measuring the pressure. The obtained results are described below.

The diffusion coefficient of each component of the mixture was determined by means of the Stejkal and Tanner equation (Eq. (3.45)) following the sequence illustrated in Fig. 3.17-b, with a r.f. pulse of $\alpha = 5^\circ$. The parameters used for the measurement of the diffusion coefficient of $^3$He and $^{129}$Xe are presented in Tab. 6.2. The measured diffusion coefficients were rescaled to 1 bar and fitted to Eq. (6.23) by Origin5.

$$\frac{1}{D_{He}(X_{He})} = \frac{X_{He}}{D_{He}(1)} + \frac{1-X_{He}}{D_{He}(0)}.$$  \hspace{1cm} (6.24)

where $D_{He}(1)$ is the self diffusion coefficient for pure helium $X_{He} = 1$. $D_{He}(0)$ represents the case of infinite dilution of the detected helium in xenon, hence $X_{He} \to 0$. The same can be
done for xenon, obtaining the value of the self diffusion coefficient of pure xenon$^3$ $D_{\text{Xe}}(0)$ when $X_{\text{He}} \rightarrow 0$ and the diffusion coefficient $D_{\text{Xe}}(1)$ for an infinite dilution in helium when $X_{\text{He}} \rightarrow 1$ as shown in Fig. 6.4 and Tab. 6.2.

$$\frac{1}{D_{\text{Xe}}(X_{\text{He}})} = \frac{X_{\text{He}}}{D_{\text{Xe}}(l)} + \frac{1 - X_{\text{He}}}{D_{\text{Xe}}(0)}$$

(6.25)

Fig. 6.4 Simultaneous measurement of the diffusion coefficients of He and Xe versus the molar fraction of helium. Points are experimental data (black for He and red for Xe) and the lines are their correspondent fits to Eq. (6.24) in the case of helium and Eq. (6.25) in the case of xenon.

Tab. 6.2 Characteristics diffusion coefficients of the binary mixture Xe-He and sequence timing. The first and second column data were obtained from fitting the data for Eq. (6.24) and Eq. (6.25) in the case of helium and xenon respectively. All measurements were rescaled to 1 bar and done at 294 K.

<table>
<thead>
<tr>
<th></th>
<th>$D_{\text{He}}(1)$ [$\text{m}^2/\text{s}$]</th>
<th>$D_{\text{Xe}}(l)$ [$\text{m}^2/\text{s}$]</th>
<th>$D_{\text{He}}(0)$ [$\text{m}^2/\text{s}$]</th>
<th>$D_{\text{Xe}}(0)$ [$\text{m}^2/\text{s}$]</th>
<th>$\Delta$ [µs]</th>
<th>$\delta$ [µs]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^3\text{He}$</td>
<td>$(1.50 \pm 0.10) \cdot 10^{-4}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{129}\text{Xe}$</td>
<td></td>
<td>$(2.00 \pm 0.13) \cdot 10^{-5}$</td>
<td></td>
<td>$(5.6 \pm 0.4) \cdot 10^{-7}$</td>
<td></td>
<td>3010</td>
</tr>
</tbody>
</table>

$^3$ Notice that the molar fraction is still referenced to helium.
VI.3.2 Mixture of SF₆ with hyperpolarized $^3$He

For mixing different amount of helium and SF₆ a different procedure was tried out by using valves as sketched in Fig. 6.5. The experiment is started with a certain pressure of pure helium in the sample tube. Ambient pressure is achieved by opening valve A to a soft bag that was previously evacuated of cage volume, see Fig. 6.5. Then the helium is diluted by pressing SF₆ from a high pressure reservoir (gas bottle) by opening valve C. After evacuating the helium in the soft bag by opening valve B, the ambient pressure is established again via valve A, measuring the diffusion coefficient at ambient pressure. This process of pressing SF₆ in the mixture can be repeated multiple times to reduce the amount of helium at constant pressure, hence varying the molar fraction.

![Fig. 6.5 Experimental dispositive for measuring the diffusion coefficient of helium mixed with SF₆.](image)

VI.3.2.1 Calculation of the molar fraction for diffusion of $^3$He in SF₆

The molar fraction established by the procedure described above can the be calculated as follows. Starting with $k$ number of helium moles present in the volume $V$ of the sample tube at 1 bar and ambient temperature. All measurements of the diffusion coefficient are done under the same conditions of pressure, temperature and volume, so that $k = PV/RT = \text{constant.}$
When $m_1$ moles of SF$_6$ are pressed in the volume $V$, the helium is diluted by a factor $f_1$, which is the same as the helium molar fraction of the first mixture

$$f_1 = X_1 = \frac{k}{k + m_1}. \quad (6.26)$$

The excess pressure is released to 1 bar by opening to the prior evacuated soft bag. The gas concentration will remain the same, so the number of helium moles remaining in the sample, $k_1$, is

$$X_1 = \frac{k_1}{k} \rightarrow k_1 = kX_1 = \frac{k^2}{k + m_1}. \quad (6.27)$$

With the same reasoning the molar fraction of SF$_6$ does not change and the number of SF$_6$ moles remaining in the sample, $m'_1$, is

$$X_{SF_6} = \frac{m'_1}{k} = \frac{m_1}{k + m_1} \rightarrow m'_1 = \frac{km_1}{k + m_1}. \quad (6.28)$$

Repeating the procedure, that is, pressing $m_2$ moles of SF$_6$ in the sample, the new helium molar fraction will be

$$X_2 = \frac{k_1}{k_1 + m'_1 + m_2}, \quad (6.29)$$

and inserting Eq. (6.27) and Eq. (6.29) gives:

$$X_2 = \frac{k^2}{k + m_1} = \frac{km_1}{k^2 + km_1 + m_2(k + m_1)} = \frac{k}{k + m_1 + m_2\left(\frac{k + m_1}{k}\right)} \quad (6.30)$$

which can be understood as
The quantity \( f_2 = \frac{k}{k + m_2} \) can be expressed as the dilution of the gas mixture corresponding to \( X_1 \) by the addition of \( m_2 \) moles of SF\(_6\). The helium molar fraction for the second experiment will then be

\[
X_2 = X_1 f_2. \tag{6.32}
\]

For the \( n^{th} \) experiment this can be generalized as

\[
X_n = X_1 \prod_{i=2}^{n} f_i. \tag{6.33}
\]

The determination of the molar fractions will be carried out through the inspection of the signal intensity of the first signal acquired in each measurement of the diffusion coefficient. Initially, for pure \(^3\)He at 1 bar, the magnetization is \( M_0 \). After the diffusion measurement, which consists of 10 gradient amplitudes measured with two repetitions each the signal will decay as according to the application of \( N = 20 \) rf pulses

\[
M'_1 = a_N M_0, \tag{6.34}
\]

where \( a_N = \cos^{N-1} \alpha \), and \( \alpha = 3 \) degrees. Relaxation due to collisions with container walls will be ignored as the total duration of the experiment is less than 10 minutes, being the typical relaxation times longer than 10 hours. After SF\(_6\) is pressed into the sample and the exceeding pressure is released to 1 bar, the magnetization will become

\[
M_1 = a_N M_0 f_1 = a_N M_0 X_1. \tag{6.35}
\]

Again, after the diffusion coefficient is measured the magnetization decays to

\[
M'_2 = a_N M_1 \tag{6.36}
\]
which, taken to 1 bar is

\[ M_2 = a_N M_1 f_2 = a_N^2 M_0 X_1 f_2 = a_N^2 M_0 X_2 , \]  

(6.37)

this expression can be generalized for the \( n^{th} \) experiment as:

\[ M_n = a_N^n M_0 X_n . \]  

(6.38)

The acquired signal will be \( S_n = M_n \sin(\alpha) \), and the following expression is used to obtain the helium molar fractions

\[ X_n = \frac{S_n}{a^n S_0} = \frac{S_n}{(\cos^{-1} \alpha)^n S_0} . \]  

(6.39)

VI.3.2.2 Results

The sequence for measuring the diffusion coefficient of \(^3\)He, in mixture with SF\(_6\) is shown in Fig. 3.17 (b). Figure 6.6 is in excellent agreement with Wilke’s semi empirical equation (Eq. (6.23)). This represents an outstanding improvement of the quality in the determination of the diffusion coefficient vs. molar fraction when compared to Fig. 6.4.
Using the same analytical approach as in section VI.3.1 the diffusion coefficient of \(^3\text{He}\) in a mixture with SF\(_6\) are obtained as listed in Tab. 6.3 fitting to

\[
\Delta = \delta + 2b \quad [\mu\text{s}] \\
\delta \quad [\mu\text{s}]
\]

<table>
<thead>
<tr>
<th>(D_{\text{He}}(0) ,[\text{m}^2/\text{s}])</th>
<th>(D_{\text{He}}(1) ,[\text{m}^2/\text{s}])</th>
<th>(\Delta)</th>
<th>(\delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>((5.00 \pm 0.02) \cdot 10^{-5})</td>
<td>((1.900 \pm 0.008) \cdot 10^{-4})</td>
<td>400</td>
<td>200</td>
</tr>
</tbody>
</table>

VI.4 Discussion

In this chapter the diffusion coefficient of mixtures has been studied. The theoretical curve of the diffusion coefficient of a gas composed by a mixture of helium and xenon as a function of the helium molar fraction was calculated, which according to literature agrees well with bulk measurements in a diffusion cell.

Since NMR experiments detect only one isotope, this study is focused on the diffusing components in the mixtures individually. However, the kinetic theory of gases, or its improvement done by Chapman-Enskog [Cha2,Ens] or Kihara [Kih], does not give a good theoretical explanation of the observed dependence of the diffusion coefficient of one component in a binary mixture. Therefore, the semi empirical equation of Wilke [Wil], Eq. (6.22), has to be considered. Different mixtures of helium with SF\(_6\) and xenon were measured as a function of the helium molar fractions, Figs. 6.4 and 6.6, corroborating this semi empirical law. Two experimental methods were presented to control the concentration. Because the first technique was very time consuming and inaccurate, a second method was developed as described in section VI.3.2.

This protocol proved to be very precise as demonstrated by the determination of the concentration of \(^3\text{He}\) in SF\(_6\). In a close future a continuous flow of hyperpolarized \(^{129}\text{Xe}\) will be implemented, and these measurements will be repeated. Nevertheless, the results of Fig. 6.4 and Tab. 6.2 are presented since this is the first experimental evidence to show the different diffusion coefficient for individual isotopes in a mixture measured simultaneously by NMR.
VII Influence of gas mixtures on the sensitivity of MRI

In this chapter, the influence of gas mixtures on the sensitivity of MRI experiments is presented. In the first section it is shown, how the SNR can be optimized by varying only the molar fraction of $^3$He in a binary mixture with SF$_6$. With these results, different conditions will be evaluated for 2D images of the capillaries of the phantom presented in V.2.3.1. Finally, the influence of a $^3$He-$^{129}$Xe binary mixture and a $^3$He-SF$_6$ binary mixture will be studied on preserved mouse and rat lungs, with different encoding times.

VII.1 Sensitivity as a function of the molar fraction in gas mixtures.

Equation (3.47) describes the NMR signal attenuation for a diffusing particle in the presence of a field gradient.

If the procedure for mixing $^3$He with SF$_6$, as outlined in section VI.3.2, is repeated, and the attenuation is measured for each concentration, two competing processes influence the NMR signal. On one hand the signal scales directly with the helium concentration. The amount of helium in the sample tube will decrease with decreasing concentration, giving rise to weaker signal intensity. On the other hand, it was shown in the previous chapter that the diffusion coefficient of $^3$He is reduced by almost one order of magnitude in a binary mixture with SF$_6$. Hence, a less attenuated NMR signal might be observed in an MRI experiment. For a fixed choice of gradient intensity and encoding time this concepts can be written in the following manner by combining Eq. (6.23) with Eq. (3.45) and directly scale with the concentration, $X_{He}$, of the signal carrier.
Following the procedure for mixing different quantities of $^3\text{He}$ and SF$_6$ and the determination of the molar fraction as explained in section VI.3.2, a set of different measurements of the SNR versus the molar fraction were done. The signal was acquired by the sequence shown in Fig. 3.7. Typical MRI values were chosen, such as a gradient strength of $G = 216$ mT/m and an encoding time $\delta = 1280 \mu$s. The results are summarized in Fig. 7.1, where the red line shows Eq. (7.1). A big factor in sensitivity improvement can be obtained when using an optimum gas mixture instead of pure gas.

$$E(X_{^3\text{He}}) = X_{^3\text{He}} \exp \left\{ \frac{-\gamma^2 \delta^2 G^2 (\Delta - \delta/3)}{1 - X_{^3\text{He}} \frac{X_{^3\text{He}}}{D(0)} + \frac{X_{^3\text{He}}}{D(1)}} \right\}$$

Fig. 7.1 NMR signal attenuation versus molar fraction of helium in SF$_6$. The theoretical estimation (red curve) follows Eq. (7.1). Measurements were done at 1 bar and at 294 K.

**VII.2 Influence of the timing on MRI using gas mixtures**

In this section the influence of the composition of a binary gas mixture of $^3\text{He}$-SF$_6$ and the timing of the used sequence timing is studied on the phantom from section V.2.3.1. A calculation of Eq. (7.1) results in the curve shown in Fig. 7.2. For a chosen molar fraction of
$X_{\text{He}} = 0.46$, images were measured for $\Delta$ varying from $\Delta = 320 \mu s$ to $2320 \mu s$ as shown in Fig. 7.3.

![Graph](image)

Fig. 7.2 NMR signal attenuation versus molar fraction of helium in SF$_6$ following Eq. (7.1) for $G = 0.056$ T/m and $\delta = 320 \mu s$.

![Images](image)

Fig. 7.3 Sequence of images for different $\Delta$. a) to g) The diffusion time $\Delta$ was increased from 320 to 2320 $\mu s$. h) shows a photo of the sample as reference. In all images the pressure of the mixture was 1 bar and the temperature 294 K.

Two mayor differences with respect to the case of pure $^3$He (Fig. 5.10) can be observed. Firstly, the intensity of the larger capillaries is higher than in the smaller ones, this is due to the fact that the diffusion coefficient is reduced due to the presence of SF$_6$. Secondly, the
signal attenuation with increasing $\Delta$ is greatly reduced. Figure 7.4 shows the normalized intensity for the centre of each capillary together with a calculation of the expected signal in a cylinder according to Eq. (3.51). When these results are compared to Fig. 5.11, the same discrepancies between measurement and theoretical prediction are found. Possibly for the same reason discussed there. In this respect the theoretical curves of Figs. 5.11 and 7.4 show a qualitative correct prediction.

![Graph showing signal attenuation and calculation](image)

Fig. 7.4 Attenuation of the NMR signal versus $\Delta$ in the centre of each capillary. Left: From the seven images shown in Fig. 7.4, the SNR in the centre of each glass tube was measured and plotted versus $\Delta$. All measurements were normalized to its maximum. Right: calculation of the SNR versus $\Delta$ for diffusion in cylinders. Colours are referred to the capillary size. It should be noted that the mean free path has a range from 0.34 mm to 0.91 mm for the timings used.

VII.3 Mixtures in preserved lungs

Finally the ideas discussed in the previous section will be applied to gas MRI of mouse and rat lungs. Two different set of experiments were performed, both for concentration corresponding to $X_{\text{He}} = 0.5$. Firstly a rat lung with a $^3$He-SF$_6$ binary mixture is imaged, and secondly, images of a mouse lung with a $^3$He-$^{129}$Xe mixture are presented. In this second case the results from the images of the mixture and that of both pure gases are compared. Both experiments were done with different timings to show how the larger airspace corresponding to the trachea can be enhanced relative to that of the alveoli.
VII.3.1 Mixture of SF$_6$ with He in a rat lung

A preserved rat lung was filled with pure hyperpolarized $^3$He (see Fig. 7.5-a) and with helium in a mixture with SF$_6$ at $X_{He}=0.56$ (see Fig. 7.5-b). In both cases, images of the lung were acquired with the same parameter settings. A FLASH 3D gradient echo sequence was used and only the central slice of the 3D data set is presented. In the images of the gas mixture (Fig. 7.5-b) an increase of the signal can be observed with respect to the pure gas in Fig. 7.5-a. This was further analysed by dividing Fig. 7.5-b by Fig. 7.5-a pixel by pixel. Figure 7.5-d shows the histogram of this ratio, from which it becomes clear, that the SNR of the image with the mixture is approximately two times bigger than in the image with pure helium. This gain of 2 is mainly found in the region of the alveoli, while an increase of around 6 can be obtained in the larger airways.

![Image a) b) c) d)](image)

Fig. 7.5 Images of rat preserved lungs filled with a) pure hyperpolarized $^3$He at 2 bars and b) with a mixture of helium with SF$_6$ at 4 bars and $X_{He}=0.56$. The images were composed by 64×64 pixels and applying a gradient $G=0.049$ T/m in the read and phase direction of $G'=0.049$ T/m (FOV 3×4×3 cm). The timing was $\Delta-\delta=640$ µs. The SNR of the image of the mixture was divided by the SNR of the image of pure helium pixel by pixel, achieving an SNR gain map, c), of which a histogram of the enhancement of the SNR versus the number of pixels is presented.
VII.3.2 Mixture of He with Xe in a mouse lungs

In this section, images of a mouse lung are presented. The lung was first filled with hyperpolarized $^3$He, then evacuated and filled again with hyperpolarized $^{129}$Xe. Images of each filling were done. After that, a mixture of $^3$He and $^{129}$Xe of helium molar fraction of 0.5 is introduced in the lung, and images of each isotope were performed directly one after the other. All images were acquired with the same pulse sequence (see Fig. 5.9) timing and FOV. The images of helium, pure and in the mixture, are presented and studied in Fig. 7.6.

Fig. 7.6 Images of mouse preserved lungs filled with hyperpolarized $^3$He at 2 bars, a), and with a mixture of helium with xenon at 4 bars, b). The images were composed by 64×64 pixels and with a FOV 2×3 cm². The timing was $\Delta=\delta=320$ µs. The SNR of the image of the mixture was divided by the SNR of the image of pure helium pixel by pixel, achieving an SNR gain map, c). In d), a histogram of the enhancement of the SNR versus the number of pixels is presented.

In Fig. 7.6-c it can be observed that for the alveoli a gain of 1.5 is obtained while in the trachea the SNR increases by a factor 7 up to 10. The effect is more pronounced because of the shorter acquisition time compared to the images of a rat lung presented in the previous section.

In the case of the $^{129}$Xe images an inverse effect is expected as the diffusion coefficient of xenon will be bigger for the mixture than in the pure state. Although the SNR is
much lower for xenon, due to the low gyromagnetic ratio and natural abundance ($[^{129}\text{Xe}] = 26\%$), a corresponding SNR loss can be observed in the mixture. So that, instead of a gain, a loss factor was defined by dividing Fig. 7.7-a by Fig 7.7-b, as shown in Fig. 7.7-c. Figure 7.7-d shows the histogram of the obtained loss values.

![Fig. 7.7 Images of mouse preserved lungs filled with a) pure hyperpolarized $^{129}\text{Xe}$ at 2 bars and b) with a mixture of helium with xenon at 4 bars, b). The images were composed by 64×64 pixels and with a FOV 2×3 cm$^2$. The timing was $\Delta=\delta= 320\ \mu\text{s}$. The SNR of the image of the pure xenon was divided by the SNR of the image of the mixture pixel by pixel, achieving an SNR map due to mixing, c). In d), a histogram of the SNR versus the number of pixels due to mixing is presented.](image)

**VII.4 Discussion**

In this chapter it was demonstrated how the sensitivity of MRI can be enhanced by lowering the diffusion coefficient of $^3\text{He}$ by mixing it with heavier buffer gases, such as SF$_6$ and $^{129}\text{Xe}$. These results were tested on a phantom made from different capillaries, and it was found that a dramatic enhancement is obtained for larger size confinements compared to the results for pure gas obtained in chapter V. It was also observed that the influence of the timing
pulse sequence is greatly reduced. The consequence of such procedures was further illustrated on realistic samples by the SNR improvement of gas MRI on two different lung samples. A factor 2 in the alveoli and more than a factor 5 in the trachea can be obtained in that way.
VIII Conclusions

The objective of this work was the investigation of the influence of self-diffusion on the quality and appearance of gas MR-images. As conceptually discussed in the theoretical section (III.8 and III.9) the influence of diffusive processes during the image acquisition can be understood by a point-spread function, whose amplitude is determined by the competition of a coherent and incoherent term. The coherent term arises from the spatial displacement of the signal by the application of gradients, which determines the image resolution, while the incoherent diffusive spread of particles destroys the underlying phase coherence resulting in a signal loss. However, this is only valid as long as free and unrestricted diffusion is considered. In real samples (e.g. lungs) the free path a particle moves can also be determined by the size of its container, when it is observed long enough. This latter case of restricted diffusion will therefore cause smaller “apparent” diffusion coefficients for small voids.

Combining these basic ideas it can be understood that the sensitivity and hence the resolution can essentially be influenced by the timing of the experiment and the diffusion coefficient only.

The time during which the signal is encoded, determines the mean diffusive path and hence selects those structural elements which show restricted diffusion (see section III.6). On the other hand the diffusive properties of the gas and thus the speed of the underlying Brownian motion can only be controlled by the diffusion coefficient. Since pressure and temperature are predetermined by the envisaged application in clinical lung studies, the only parameter left to vary is the concentration of the gas in a mixture.

By the revision of the existing theory for the diffusion of gases, it was found, that no quantitative model exists for the special needs of NMR. This is mainly due to the fact that NMR is able to observe the individual isotopes in gas mixtures. However, a semi-empirical approach was developed which describes the measured data with great accuracy (see section VI.3). Therefore, considerable effort and extreme care had to be taken in the design of the gas handling system and the procedures of gas mixing (see sections IV.3 and VI.3). Therefore a reliable and reproducible gas mixture had to be produced to validate the theoretical model.
With these results it was possible to show that the signal-to-noise ratio in MRI has a distinct maximum at lower concentrations of helium in a heavier buffer gas. This results in the –on first sight- paradox observation that less gas gives more signal in MR-images (see section VII.1), as verified on a dedicated resolution-phantom.

It is easy to foresee that these original results can have a considerable impact on clinical lung studies. Particularly the used gas mixtures have to be re-investigated for the purpose of improving the resolution and image quality in such studies. It is possible to create such gas mixtures that only the alveoli become visible or the entire air spaces. Furthermore, diffusion measurements of gases in lungs with the aim to study the underlying microstructure will also profit from these results.

Future work has to concentrate on the development of a complete theory for the gas diffusion by taking the motion of individual components into account. Additionally, the developed ideas have to be validated in clinical applications.
IX References


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Danksagung

An dieser Stelle möchte ich mich bei all den Personen bedanken, die zum Gelingen dieser Arbeit beigetragen haben:

Besonders bedanken möchte ich mich bei….

…. Herrn Prof. Dr. W. Heil und Herrn Prof. Dr. H. W. Spiess für die Möglichkeit, diese Arbeit unter hervorragenden Bedingungen in ihren Arbeitsgruppe anfertigen zu dürfen und ihren wertvollen Anregungen.

…. Herrn Dr. Peter Blümler ( Don Pedro ) für seine Einführung in die NMR Bildgebung, endlose Geduld und seine Lebensphilosophie. Aber vor allem für seinen Begleitschutz durch die Hölle des Zusammenschreibens.

…. Dr. Don Rodolfo Hector Acosta ( Dr. Don Alfonso Acosta ) por intentar hacerme entender la NMR de los dedos a las fórmulas, las incontables correcciones, cómo hacer dulce de leche y los trucos para ser una estrella del fútbol. Cuando sea hombre tomaré mate, prometido.

…. Meinen Kollegen und Freund Han-Bong ( Hans ) für seine Hilfe bei der Bearbeitung der Abbildungen, endlosen, nicht immer fruchtbaren Diskussionen und das Überreden doch noch eine Danksagung zu schreiben.

…. Dem Laserzerstörer Paul Zänker und meinem Bürokollegen Jochen Schmidt für ihre Freundschaft und Tipps in allen Lebenssituationen.

….. sowie allen anderen Mitarbeitern des AK Spiess für die freundliche Arbeitsatmosphäre und ihrer stetigen Hilfsbereitschaft.
Appendix

Program LAPGSE:

PROGRAM LAPGSE;
{Cartesian sampling of K space with Spin Echo - Hard Pulses}
{Lluis 28/03/2003}
{$I COMPILE.INC }
USES
Grad,
{$I UNITSDIG.INC }
{*******************************************************************************}
PROCEDURE BinProc;
BEGIN
DataBin(BinCounter MOD GradCount(IG5));  {Index goes from 0 to IG5 and restarts at 0}
END;
{*******************************************************************************}
PROCEDURE GradOffs;
BEGIN
If (FP1 > 0.1) or (FP1 < -0.1) then FP1:=0;
If (FP2 > 0.1) or (FP2 < -0.1) then FP2:=0;
If (FP3 > 0.1) or (FP3 < -0.1) then FP3:=0;
GXOffset:=FP1;
GYOffset:=FP2;
GZOffset:=FP3;
END;
{*******************************************************************************}
Procedure GrTable(Gradval:Integer);

VAR
n: Integer;

Begin
If Mode<>MODE_RUN Then Exit;
For n:=0 to Gradval-1 do
Begin
SetTableGradient(TG1,n+1,round( G5*(2*n-Gradval)/Gradval));
SetTableGradient(TG2,n+1,round(-G5*(2*n-Gradval)/Gradval));
End;
End;
PROCEDURE Sequence;

BEGIN
{MultiAcquire(SI,GradCount(IG2),1,0,BinProc); {Set Up Data Buffer}
MultiAcquire(SI,GradCount(IG5),1,1,StdMulti);

GradOffs;
Duration(D1,0);

StartSequence;  {Loop for NS}
   StartSequence;  {Loop for Grads}
      Duration(D1,TXEnable);  {Enable RF}
      ZeroTime;  {Time Origin}
      Duration(P90,RF(PH1));  {Hard 90 Degree Pulse Phase PH1}
      Duration(D1,TXDisable);
      Gradient(D5,IGPhase(IG5));  {Gradient On}
      Gradient(D1,GPhase(0));  {Gradient Off}
      Duration(D2,0);  {Delay for whole echo acquisition}

      Duration(D1,TxEnable);  {Enable RF}
      Duration(P180,RF(PH3));  {Hard 180 Degree Pulse Phase PH3}
      Duration(D1,TXDisable);
      Gradient(D5,IGPhase(IG5));  {Gradients On}
      Gradient(D1,GPhase(0));

      Duration(D2-(Si*dw+dead2)/2,0);

      Acquire(PH2);  {Acquire Phase PH2}

      Gradient(D4,GPhase(G4));
      Gradient(D1,GPhase(0));

      RepeatSequence(NS);  {End Loop for Scans}
      Duration(10,Next(PH1)+Next(PH2)+Next(PH3));  {Increment Phase lists}
      NextGrad(IG5);
      RepeatSequence(GradCount(IG5));  {End Loop for Grads}

      RstGrad(IG5);

END;

BEGIN
Run(Sequence);
END.

Program LASEDT.PAS

PROGRAM LASEDT;

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{Cartesian sampling of K space with Spin Echo - Hard Pulses}  
{to become a diffusion tensor in a plane}  
{Lluís  28/07/2003}  

{$I COMPILE.INC$}

{*****************************************************}
PROCEDURE BinProc;
BEGIN
DataBin(BinCounter MOD GradCount(IG2));
END;
{*****************************************************}
USES
Grad,
{$I UNITSDIG.INC$}

PROCEDURE GradOffs;
BEGIN
If (FP1 > 0.1) or (FP1 < -0.1) then FP1:=0;
If (FP2 > 0.1) or (FP2 < -0.1) then FP2:=0;
If (FP3 > 0.1) or (FP3 < -0.1) then FP3:=0;
GXOffset:=FP1;
GYOffset:=FP2;
GZOffset:=FP3;
END;

{*****************************************************}
PROCEDURE Sequence;
BEGIN
MultiAcquire(SI,GradCount(IG2),1,1,StdMulti); (Set Up Data Buffer)
GradOffs;
Duration(d7,0);
StartSequence; {Loop for NS}
StartSequence; {Loop for Grads}
Duration(D1,TXEnable); {Enable RF}
ZeroTime; {Time Origin}
Duration(P90,RF(PH1)); {Hard 90 Degree Pulse Phase PH1}
Duration(D1,TXDisable);
Gradient(D5,GSlice(G5)); {Diffusion gradient up}
Gradient(D2,GSlice(0));

Gradient((SI*DW-Dead2)/2,GRead(G1)+IGphase(IG2)); {Read and Phase Gradients On}
Gradient(D2,GRead(0)+GPhase(0));
Duration(D1, TXEnable);
Duration(2*P90, RF(PH3));  {Hard 180 pulse}
Duration(D1, TXDisable);

Gradient(D5, GSlice(G5));
Gradient(D2, GSlice(0));

Gradient(D1, GRead(G1));  {Read change }  
Acquire(PH2);

Gradient(D1, GRead(0));
Duration(1000, 0);
Gradient(D4, GRead(G4));  {Crusher gradient }
Gradient(D1, GRead(0));

RepeatSequence(NS);  {End Loop for Scans}
Duration(10, Next(PH1)+Next(PH2)+Next(PH3));  {Increment Phase lists}
NextGrad(IG2);
RepeatSequence(GradCount(IG2));  {End Loop for PhaseGrads}
RstGrad(IG2);

END;
BEGIN
Run(Sequence);
END.

Program ImdifWE.m

% image of the diffusion of two tubes with water and micrograd

outfile='C:\luis\arbeit\H20_Ethanol\1106\WEdif_';
RI=actxserver('rinmr.nmr');
Grad5=20000;
num=20;
G5=Grad5/num;
for i=2:2:num
    g5(i)=G5*i;
    g5(i+1)=-G5*i;
end
    g5(1)=0;
for i=1:num+1
    invoke(RI,'execute','~AMODE');
    invoke(RI,'execute','LOAD LASEDT');
    invoke(RI,'execute','SF 200.973');
    invoke(RI,'execute','O1 -850');
    invoke(RI,'execute','RD 1S');
    invoke(RI,'execute','NS 4');
    invoke(RI,'execute','DS 2');
    invoke(RI,'execute','P90 12');
    invoke(RI,'execute','P180 24');
invoke(RI,'execute','RFA0 100');
invoke(RI,'execute','Dead1 5');
invoke(RI,'execute','D1 10');
invoke(RI,'execute','RG 2');
%invoke(RI,'execute','PH1 0213');
%invoke(RI,'execute','PH2 0213');

invoke(RI,'execute','DW 40');
invoke(RI,'execute','SI 64');

invoke(RI,'execute','IG2 64');

invoke(RI,'execute','G1 500');
invoke(RI,'execute','D5 3000');
str=['G5 ',num2str(g5(i),'%3.3g')];
invoke(RI,'execute',str);

invoke(RI,'execute','GRead 32767');
invoke(RI,'execute','GPhase 500');
invoke(RI,'execute','GSlice 32767');
invoke(RI,'execute','G4 15000');
invoke(RI,'execute','D4 500');

invoke(RI,'execute','GReadX 1');
invoke(RI,'execute','GReadY 0');
invoke(RI,'execute','GReadZ 0');

invoke(RI,'execute','GPhaseX 0');
invoke(RI,'execute','GPhaseY 0');
invoke(RI,'execute','GPhaseZ 1');

invoke(RI,'execute','GSliceX 0');
invoke(RI,'execute','GSliceY 1');
invoke(RI,'execute','GSliceZ 0');

invoke(RI,'GO');
str=['WRI ',outfile,num2str(g5(i)/1000,'%3.3g')];
invoke(RI,'execute',str);
%pause(10)
end

**Program RimdifWE.m**

infile='C:\Dokumente und Einstellungen\agulles\Eigene Dateien\diffusion\luis Pcnmr11\arbeit\H20_Ethanol\1106\WEdif_';
Grad5=20000;
num=20;
G5=Grad5/num;
g5(1)=0;
for i=2:2:num
end

% reading the data where there's NO diffusion gradient
str=[infile,num2str(g5(1)/1000,'%3.3g'),'.Rimage'];
data=riread(str);
D1=data.acq.Dim(1);
D2=data.acq.Dim(2);
daten=zeros(D1,D2,num+1); % matrix to store all images
ftdat = abs(fftshift(fft2(data.data,D1,D2)));

ScaleX=4.3e-5;
ScaleY=4.6e-5;
ScaleZ=7.9e-5; % (micrograd without filter)

GSX=data.acq.GSliceXYZ(1);
GSY=data.acq.GSliceXYZ(2);
GSZ=data.acq.GSliceXYZ(3);
freq=data.acq.SF;

for s=1:num+1
  x(s)=((-1)^s*(sqrt((g5(s)*ScaleX*GSX)^2+(g5(s)*ScaleY*GSY)^2+(g5(s)*ScaleZ*GSZ)^2)));
end

L=sum(abs(ftdat(1,:)))/D2;
B=sum(abs(ftdat(:,1)))/D1;
R=sum(abs(ftdat(D1,:)))/D2;
T=sum(abs(ftdat(:,D2)))/D1;
V0=((T+B+R+L)/4);

for j=1:D1
  for k=1:D2
    da=(ftdat(j,k))/V0;
    if da>20 % only choose the values 20 times bigger than the mean value of each arist
      daten(j,k,1)=ftdat(j,k); % create a 3D-matrix to fit
    end
  end
end

% reading of the data
for i=2:num+1
  str=[infile,num2str(g5(i)/1000,'%3.3g'),'.Rimage'];
data=riread(str);
ftdat = abs(fftshift(fft2(data.data,D1,D2)));
  for j=1:D1
    for k=1:D2

if daten(j,k,1)~=0 %choose the pixel that has a good
S/N
daten(j,k,i)=ftdat(j,k); %create a 3D-matrix to fit
end
end
end
end
Imag=zeros(D1,D2); %Matrix of the image of the diferents DC in each pixel
freq=data.acq.SF;
gamma=2*pi*freq/4.72;
delta=data.acq.D(5);
Delta=data.acq.D(5)+data.acq.D(2)+2*data.acq.D(1)+(data.acq.SI
*data.acq.DW-data.acq.Dead2)/2;
factor=((gamma*delta)^2*(Delta-delta/3));
for j=1:D1
    for k=1:D2
        if daten(j,k,1)~=0
            for i=1:num+1 y(i)=daten(j,k,i); end
            [ip]=gaussfit(x,y);
            Imag(j,k)=ip(2)/factor;
        end
    end
end
figure;
surf(abs(Imag));

Program Gaussfit.m

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%
%%                 FUNCTION GAUSSFIT
%%
%% fits a Gaussian with variable parameter number to data.
%% The general Gauss-model is :
%%
%% f(x)= amplitude*exp(-(x-origin).^2*width)+offset
%%
%% call:  par = gaussfit(x,y);
%% [par,delta]=gaussfit(x,y);
%% [par,delta]=gaussfit(x,y,n);
%% [par,delta]=gaussfit(x,y,n,out);

par = fitted parameter [amplitude, width, origin, offset]
delta = error estimate (optional) in abs. values
n = control on fit parameters (optional, default=4)
    n = 2 : only width and amplitude are fitted
    n = 3 : width, ampl. and origin are fitted
    n = 4 : all fitted
    n = 5 : width, ampl. and offset fitted
function [ip,delta]=gaussfit(x,y,p,out)
    % estimating starting values
    ip=zeros(1,4);
    if p<2
        p=2;
    end
    if p==4
        ip(4)=min(y);
    end
    ip(3)=find(y==max(y));
    ip(1)=y(ip(3))-ip(4);
    ip(3)=x(ip(3));
    [ip(1),ip(2)]=lgf1(x-ip(3),y-ip(4)); %linear regression
    switch p
    case 2
        [ip, res, J]=nlinfit(x,y,@gauss2,ip(1:2));
        ci = nlparci(ip, res, J);
        ip=[ip(1),ip(2),0,0];
        ci=zeros(4,2);
        ci(1:2,:)=ci(1:2,:);
    case 3
        [ip, res, J]=nlinfit(x,y,@gauss3,ip(1:3));
        ci = nlparci(ip, res, J);
        ip=[ip(1),ip(2),ip(3),0];
        ci=zeros(4,2);
        ci(1:3,:)=ci(1:3,:);
    case 4
        [ip, res, J]=nlinfit(x,y,@gauss4,ip);
        ci = nlparci(ip, res, J);
ip=ip';
case 5
    [ip,res,J]=nlinfit(x,y,@gauss5,[ip(1),ip(2),ip(4)]);
    cii = nlparci(ip,res,J);
    ip=[ip(1),ip(2),0,ip(3)];
    ci=zeros(4,2);
    ci(1:2,:)=cii(1:2,:);   
    ci(4,:)=cii(3,:);
end
delta=abs(ci(:,2)-ci(:,1))/2; %estimate error
delta=delta';
if out~=0 %make a plot of values, fit and confidence intervals
    plot(x,y,'bo');hold on;
    xi=linspace(min(x),max(x),length(x)*10);
    yi=ip(1)*exp(-(xi-ip(3)).^2*ip(2))+ip(4);
    plot(xi,yi,'r-');
    yi=ci(1,1)*exp(-(xi-ci(3,1)).^2*ci(2,1))+ci(4,1);
    plot(xi,yi,'g--');
    yi=ci(1,2)*exp(-(xi-ci(3,2)).^2*ci(2,2))+ci(4,2);
    plot(xi,yi,'g--');hold off
end

function estim=gauss2(beta,x)
estim=beta(1)*exp(-x.^2*beta(2));

function estim=gauss3(beta,x)
estim=beta(1)*exp(-(x-beta(3)).^2*beta(2));

function estim=gauss4(beta,x)
estim=beta(1)*exp(-(x-beta(3)).^2*beta(2))+beta(4);

function estim=gauss5(beta,x)
estim=beta(1)*exp(-x.^2*beta(2))+beta(3);

%linear regression of gaussian  (amp and width)
function [a,b]=lgf1(xi,yi)
x=xi;

N=length(x);
y=zeros(1,N);
for t=1:N
    if yi(t) >0
        y(t)=log(yi(t));
    end
end
Sy=sum(y);
Sxx=sum(x.^2);
Sxxxy=sum(x.^2.*y);
Sx4=sum(x.^4);
a=(Sy*Sx4-Sxxxy*Sxx)/(N*Sx4-Sxx^2);
b=(a*Sxx-Sxxxy)/Sx4;
a=exp(a);