Feasibility Study of Phase Measurements of the Arterial Input Function in Dynamic Contrast Enhanced MRI

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Abstract

Acquired data from dynamic contrast enhanced MRI measurements can be used to non-invasively assess tumour vascular characteristics through pharmacokinetic modelling. The modelling requires an arterial input function which is the concentration of contrast agent in the blood reaching the volume of interest as a function of time. The aim of this work is testing and optimizing a turboFLASH sequence to appraise its suitability for measuring the arterial input function by measuring phase.

Contrast concentration measurements in a phantom were done with both phase and relaxivity techniques. The results were compared to simulations of the experiment conditions to compare the conformance. The results using the phase technique were promising, and the method was carried on to in-vivo testing. The in-vivo data displayed a large signal loss which motivated a new phantom experiment to examine the cause of this signal reduction. Dynamic measurements were made in a phantom with pulsatile flow to mimic a blood vessel with a somewhat modified turboFLASH sequence. The conclusions drawn from analyzing the data were used to further improve the sequence and this modified turboFLASH sequence was tested in an in-vivo experiment. The obtained concentration curve showed significant improvement and was deemed to be a good representation of the true blood concentration.

The conclusion is that phase measurements can be recommended over relaxivity based measurements. This recommendation holds for using a slice selective saturation recovery turboFLASH sequence and measuring the arterial input function in the neck. Other areas of application need more thorough testing.
Acknowledgment

Throughout this work, I have benefited from help and suggestions from a lot of people, and I would like to express my sincere gratitude to all of them.

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### Nomenclature

Abbreviations, acronyms and symbols used in the text in alphabetical order.

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<tr>
<th>Abbreviation</th>
<th>Explanation</th>
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<td>1D</td>
<td>One dimensional</td>
<td></td>
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<td>3D</td>
<td>Three dimensional</td>
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<tr>
<td>AIF</td>
<td>Arterial input function</td>
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<tr>
<td>BBB</td>
<td>Blood Brain Barrier</td>
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<td>BMS</td>
<td>Bulk magnetic susceptibility</td>
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<tr>
<td>CNR</td>
<td>Contrast-to-Noise Ratio</td>
<td></td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>$C_t$</td>
<td>Contrast concentration in tissue</td>
<td>mM</td>
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<tr>
<td>$C_p(t)$</td>
<td>Concentration of contrast in plasma as a function of time, see also AIF</td>
<td>mM</td>
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<tr>
<td>DCE-MRI</td>
<td>Dynamic Contrast-Enhanced MRI</td>
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<tr>
<td>DSC-MRI</td>
<td>Dynamic Susceptibility Contrast MRI</td>
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<tr>
<td>FLASH</td>
<td>Fast Low-Angle Shot - Gradient echo sequence with spoiling of the transverse magnetisation and low flip angles</td>
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<tr>
<td>FOV</td>
<td>Field of view</td>
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<td>GRAPPA</td>
<td>Generalized auto calibrating Partially Parallel Acquisition</td>
<td></td>
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<tr>
<td>$\frac{\gamma}{2\pi}$</td>
<td>Gyromagnetic ratio</td>
<td>MHz×Tesla$^{-1}$</td>
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<tr>
<td>In-vivo</td>
<td>Experiment on a living organism</td>
<td></td>
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<tr>
<td>$K_{trans}$</td>
<td>Volume transfer constant between $v_p$ and $v_e$</td>
<td>min$^{-1}$</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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</tr>
<tr>
<td>MR/MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PSF</td>
<td>Point spread function</td>
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<tr>
<td>SPECT</td>
<td>Single-Photon Emission Computed Tomography</td>
<td></td>
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<tr>
<td>rCBV</td>
<td>Relative cerebral blood volume</td>
<td></td>
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<tr>
<td>rf</td>
<td>Radio frequency</td>
<td></td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
<td></td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-Noise Ratio</td>
<td></td>
</tr>
<tr>
<td>$T$</td>
<td>Temperature (K)</td>
<td></td>
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<tr>
<td>$T_1$</td>
<td>Spin-lattice relaxation time (\text{ms})</td>
<td></td>
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<tr>
<td>$T_2$</td>
<td>Spin-spin relaxation time (\text{ms})</td>
<td></td>
</tr>
<tr>
<td>$T_2^*$</td>
<td>Spin-spin relaxation time including effects from other field inhomogeneities (\text{ms})</td>
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<td>$TE$</td>
<td>Echo time (\text{ms})</td>
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<tr>
<td>$TI$</td>
<td>Inversion time (\text{ms})</td>
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</tr>
<tr>
<td>$TR$</td>
<td>Repetition time (\text{ms})</td>
<td></td>
</tr>
<tr>
<td>TurboFLASH</td>
<td>An ultrafast gradient echo pulse sequence</td>
<td></td>
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<tr>
<td>$v_e$</td>
<td>Extra vascular extra cellular fraction</td>
<td></td>
</tr>
<tr>
<td>$v_p$</td>
<td>Intra vascular, extra cellular (blood plasma) fraction</td>
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**Introduction**

It is estimated that every third Swedish citizen once in their lifetime will suffer from some sort of cancer disease. The number of people falling ill with cancer is increasing each year, but at the same time the trend for mortality is decreasing because of better treatment and diagnosing, [Socialstyrelsen and Cancerfonden 2009].

An interesting field under study, which could improve both treatment and diagnosing, is functional imaging of tumour and normal tissue. Functional imaging involves looking at metabolic, biochemical and other physiological aspects of the tissue. By measuring the values of these factors and being able to see how they change during treatment, it is not only possible to individualize the treatment plan for better tumor control, but also to monitor the treatment response of the tumor, [Dau 2008].

Functional imaging can be performed with a number of different imaging methods, such as positron emission tomography (PET), computed tomography (CT), ultrasound or single-photon emission computed tomography (SPECT), and of course magnetic resonance imaging (MRI) methods. MRI has a number of advantages which makes it attractive for use in the oncological clinic. The signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) are high for MR images and MRI is regularly used in routine oncological imaging which makes it easy to incorporate functional studies with routine examinations, [Padhani 2002]. MRI is also non-invasive and does not involve radiation exposure which is of utmost importance where several examinations are required to follow lesions over time, [Barrett et al. 2006].

For functional imaging of lesions in the brain, dynamic contrast-enhanced MRI (DCE-MRI) using a contrast media such as a Gd-chelate gives very good results because of the brain’s structure. In the healthy brain, in all but a few regions, the contrast agents can not pass into the tissue because of the blood brain barrier (BBB), [Tofts 2004]. But as a tumour grows it will stimulate growth of new blood vessels, a process called angiogenesis. These tumour vessels differ from normal vessels as they are structurally irregular and leaky. Generally the more aggressive the tumour, the less functional is the vasculature, [Jackson, Buckley and Parker 2003], making it possible for the contrast to pass from the vessel out into the tissue. This accumulation will affect the MR signal and give an enhanced signal for T1-weighted images. Susceptibility effects from the contrast agent will also cause a local shift in the magnetic field, and this will cause a phase shift in the image which can also be measured. Both signal enhancement and phase shift can be used to measure the contrast concentration.
Using either technique, measuring the contrast concentration before injection, during build-up after injection, and later during diffusion back into the vasculature will make it possible to calculate parameters, such as

- Blood flow/perfusion
- The product of vessel wall permeability and vessel surface area
- Plasma volume fraction ($v_p$)
- Extra cellular extra vascular volume fraction ($v_e$)

These parameters describe the contrast movement across the vasculature endothelium and can be used to characterize the microvasculature, which in turn provides information about tumour micro vessel structure and function, [Padhani 2002 and Yankeeelov, Cron, Addison et al. 2007]

To correctly estimate these parameters however, the contrast concentration in the blood arriving to the region of interest must be known. The concentration of contrast agent in plasma $C_p$ at a chosen point as a function of time is called the Arterial Input Function (AIF). Unfortunately, the measurement of the AIF is not all that straightforward. For current techniques, it needs to be measured at the same time as the data for the parameters above, which might pose problems in finding a sequence fulfilling the requirements for both time resolution and precision. Also to avoid partial volume effects and to get a proper SNR, the measurements need to be done in a quite large blood vessel which is most likely hard to find close to the investigated tissue. Early attempts used a population-averaged AIF, which, while easy to use, neglected variations between patients. This introduces an error as the shape of the AIF curve depend on injection timing and dose, heart output rate, distribution of the contrast agent in the body and kidney function, [Jackson, Buckley and Parker 2003]. Generally for brain tumour measurements, the AIF is measured in one of the large blood vessels supplying the whole brain. This is likely to give more accurate results than using a population average but there still is a problem of the dispersion from the point of measurement to the region of interest. There is also the matter of getting a proper time resolution for both AIF and dynamic data when they are measured at the same time.

Studies indicate that the use of phase measurements to determine AIF would give better results, both regarding SNR and linearity over a larger interval of contrast concentrations than relaxivity measurements, [Akbudak 1996]. The present work is a first study of the use of phase measurements for the specific purpose of measuring the AIF for brain lesion studies. The specific goal is to study a turboFLASH sequence and examine its aptitude for this task and what sources of error and uncertainties that need to be understood. This in turn is a pre-study to a research project where the possibility of administering the contrast agent in two smaller injections will be investigated. The purpose of two injections is that one of them can be used for measuring the AIF only, and the sequence can thus be optimized for this purpose.
Theory
Basics of MRI

This section will give a brief description of the basics of MRI and the equations that rule the signal. Interested readers are referred to text books such as [Haacke, Brown, Thompson and Venkatesan 1999] and [Levitt 2008] for more information.

The \(^1\)H isotope of hydrogen has one unpaired proton and is therefore a spin-\(1/2\) nucleus. Placed in a magnetic field, the proton has two quantum energy eigenstates due to the spin, sometimes referred to as “up” and “down”. This means that the value of the spin in any given direction can only take on two values \(m_s = \pm 1/2\) and the proton will also have a magnetic moment. In the presence of an external magnetic field the spin will seek a lower energy state, and thus try to align with the magnetic field. The energy of the states in an external magnetic field of \(B_0 = B_z\hat{z}\) can be found through

\[
E = -\gamma m_s \hbar B_z
\]

where \(\gamma\) is a constant called the gyromagnetic ratio. In water the hydrogen proton has a gyromagnetic ratio of \(\gamma = 2.68 \times 10^8 \text{rad/s} \times \text{Tesla}^{-1}\) or more conveniently \(\gamma/2\pi = 42.56 \text{MHz/Tesla}\). \(\hbar\) is the reduced Planck’s constant, also known as the Dirac constant, with the value \(\hbar = h/2\pi = 1.055 \times 10^{-34} \text{Js} = 6.58 \times 10^{-16} \text{eVs}\) where the unit is energy, in either Joule or electron volts, per (radian per second).

The energy difference between the anti parallel and parallel states will then be

\[
\Delta E = E_{\text{spin down}} - E_{\text{spin up}} = -\gamma \left( \frac{1}{2} \right) \hbar B_z - \left( -\gamma \left( \frac{1}{2} \right) \hbar B_z \right) = \hbar \gamma B_z = \hbar \omega_0
\]

This means that the energy absorbed or emitted during a transition between the states is a radiofrequency (rf) photon in a normal commercial MRI scanner. The frequency \(\omega_0\) is called the Larmor frequency and is central to MRI as will be apparent later in this section.

From equation (2) it is seen that the anti parallel state has slightly higher energy than the parallel state. The energy difference is small compared with the thermal energy at room temperature, resulting in only a small excess of parallel state spins. The excess number can be found from the Boltzmann law as

\[
N_\uparrow - N_\downarrow \approx N_{\text{tot}} \frac{\hbar \omega_0}{2kT}
\]

where \(N_\uparrow, N_\downarrow\) denotes the number of spins in the parallel and anti-parallel states respectively, \(k\) is the Boltzmann constant.
\[ k = 1.38 \times 10^{-23} \text{ } J \text{ } K^{-1} = 8.62 \text{ } eV \text{ } K^{-1} \text{, and } T \text{ is the temperature in Kelvin. In room temperature and in a magnetic field of 1.5 T, this means that the excess of spins in the lower energy state is only about 5 per million.} \]

As the magnetic moment of a proton has the magnitude \( \gamma \hbar / 2 \), McRobbie et al. 2007, the equilibrium value of the magnetization per volume can be found from equation (3) as

\[
M_0 = \frac{\rho_0 \gamma^2 \hbar^2}{4kT} B_0
\]

where \( \rho_0 \) is the number of spins per unit volume. Fortunately, the density of spins is so high that \( M_0 \) is a measurable quantity despite the low spin excess.

Through quantum mechanical calculations, it can be found that the superposition of the parallel and anti parallel states causes the magnetization vector of a macroscopic collection of spins to precess about the magnetic field axis with a precessional angular frequency given by

\[
\omega_0 = \gamma B_0
\]

The basic equation of motion for the magnetization vector of a collection of spins in a magnetic field is

\[
\frac{d\vec{M}}{dt} = \gamma \vec{M} \times \vec{B}
\]

The magnetization vector \( \vec{M} \) can be tipped away from the \( z \)-axis by administering an rf-pulse at the Larmor frequency. As the Larmor frequency is dependent on magnetic field strength, the effect on the magnetization vector in the sample can be restricted to a slice. This is achieved by applying a magnetic gradient along an axis parallel to the normal to the slice. The frequency of the rf-pulse is then chosen to match the Larmor frequency in the slice of interest. The components of the magnetic field during this rf-pulse will be

\[
\begin{align*}
B_x &= B_1 \cos(\omega_0 t) \\
B_y &= B_1 \sin(\omega_0 t) \\
B_z &= B_0
\end{align*}
\]

where \( B_1 \) is the magnitude of the rf-pulse and \( B_0 \) is the static magnetic field. The differential equations can be solved using the initial condition \( \vec{M}(0) = M_0 \hat{z} \)

\[
\begin{align*}
M_x &= M_0 \sin(\gamma B_1 t) \sin(\omega_0 t) \\
M_y &= M_0 \sin(\gamma B_1 t) \cos(\omega_0 t) \\
M_z &= M_0 \cos(\gamma B_1 t)
\end{align*}
\]
This solution implies a precession of the magnetization vector about $B_0$ at
the Larmor frequency and around $B_1$, or away from the z-axis, with angular
frequency $\gamma B_1$. By applying the rf-pulse for a certain time $t$, the angle the
magnetization vector is tipped away from the z-axis can be calculated, and
vice versa, for a required flip angle the time needed can be found.

However, equation (6) is not complete; there are also two relaxation
mechanisms. After excitation, these will cause the magnetization over time
to return to its original value. One of the mechanisms is the spin-lattice
decay; the spins interact with their surroundings causing the magnetization
to grow back along the original direction, here $\hat{z}$. This re-growth can be
described by the parameter $T_1$ the spin-lattice relaxation time, according to

$$M_z(t) = M_0 \left(1 - e^{-t/T_1}\right) \quad (8)$$

The other relaxation mechanism is a spin-spin decay caused by dephasing of
the transverse magnetization, that is, the magnetization in the $xy$-plane. This
is in turn governed by the parameter $T_2$, the spin-spin relaxation time, as

$$M_\perp(t) = M_\perp(0) e^{-t/T_2} \quad (9)$$

where $M_\perp(0)$ is the magnetization in the $xy$-plane at time $t = 0$.

If no measures are taken to prevent it, other field inhomogeneities will also
add to this effect, causing a faster dephasing of the transverse magnetization.
The shorter relaxation time that describes this behaviour is named $T_2^*$, and
this can be inserted into (9) instead of $T_2$.

The signal obtained at echo time $TE$ with a repetition time $TR$ for a gradient
echo sequence with 90° flip angle in a steady state becomes [Rinck 2001]

$$S = S_0 \left(1 - e^{-TR/T_1}\right) \cdot e^{-TE/T_2^*} \quad (10)$$

with $S_0$ the maximum signal proportional to the density of spins in the
sample. The echo time is the time between excitation and detection, and the
repetition time is the time between two excitations.

As the transverse magnetization of the slice returns towards its initial value,
it generates a current in a coil. This signal can through the Fourier transform
be translated into an image.

**MRI with contrast enhancement**

To be able to discern two adjacent structures in an image, the signal from
them need to differ by an amount depending on image overall brightness and
noise. This is called image contrast. From equation (10) it can be seen that
there are three parameters that influence the signal, spin density, $T_1$, and $T_2$
or $T_2^*$. Different sequences exist that by their design decide which of these
parameters will determine the contrast in the image. A closer inspection of
equation (10) show that a long TR and short TE will give minimum emphasize to the T1 and T2 weightings as

\[
\left(1 - e^{-\frac{TR}{T_1}}\right) \approx 1 \quad \text{when} \quad TR >> T1
\]

\[
e^{-\frac{TE}{T_2^{*}}} \approx 1 \quad \text{when} \quad TE << T2^*
\]

and thus a sequence with long TR and short TE will be spin density, or proton, weighted. The same reasoning gives that short TR and TE give T1-weighting, and long TR and TE, T2-weighting.

In certain examinations, the contrast achieved by the mechanisms explained above is not adequate to attain the purpose of the imaging. To enhance the contrast between the structures of interest and the surrounding tissue, a contrast agent can be given to the patient, which is a substance that influences the signal from spins in its surroundings.

There are two different mechanisms by which the contrast agent affects the signal in MRI, and depending on which is used, the method is either called susceptibility or relaxivity based contrast measurements.

Susceptibility based measurements utilise that contrast agents shorten the T2*-values, which results in a decrease in signal from areas with high levels of contrast. The susceptibility induced gradients surrounding the contrast agent will disturb the homogeneity of the magnetic environment up to several millimetres away from the contrast molecule and these gradients will shorten the T2*. Susceptibility measurements are therefore sensitive to small amounts of contrast distributed in large volumes. Collections of contrast molecules in larger vessel will give a visible effect, but only at the vessel peripheries. For this reason, the technique is often used for cerebral blood flow measurements but not commonly for tumour imaging as the contrast can quite easily pass from the dysfunctional tumour vessels out into the tissue, [Jackson, Buckley and Parker 2003].

Relaxivity based measurements uses the fact that contrast agents also cause a strongly localized relaxivity effect, which is a shortening of the T1. The sequences used are T1 weighted, and the shortening of the T1 will amount to an increase in signal. The contrast agent Gadolinium’s effect on the relaxation rates is given by

\[
\frac{1}{T_1} = \frac{1}{T_{10}} + r_1 \cdot C_{Gd}
\]  

\[
\frac{1}{T_2} = \frac{1}{T_{20}} + r_2 \cdot C_{Gd}
\]

which can be derived theoretically from the Solomon-Bloembergen equations, [Jackson, Buckley and Parker 2003]. T_{10} and T_{20} are the inherent relaxation times without influence from the contrast agent, and r_1 and r_2 are the relaxivity constants of the specified contrast agent. C_{Gd} is the
concentration of Gadolinium. For these equations to be true, an assumption is made that the bulk magnetic susceptibility (BMS) shift is not too large, that is, the shortening of the $T2$ and $T2^*$ caused by inhomogeneous magnetic field gradients is negligible, [Jackson, Buckley and Parker 2003].

The contrast concentration can be measured using a gradient echo sequence with spoiling of the transverse magnetisation (FLASH). The signal from this sequence, as derived from the Bloch equations, is described by

$$
S = g \cdot \rho \cdot \frac{\sin(\alpha) \cdot \left(1 - e^{-\frac{TR}{T1}}\right)}{1 - \cos(\alpha) \cdot e^{-\frac{TR}{T1}} \cdot e^{-\frac{TE}{T2^*}}} \quad (13)
$$

where $\rho$ is the proton density, $\alpha$ is the flip angle and $g$ is a non-important constant determined by the system characteristics. If $TE$ is short enough that $T2^*$ effects can be neglected, $\alpha$ approaches $90^\circ$ and $T1 >> TR$, then equation (13) can be reduced to a linear relationship between signal intensity and $1/T1$

$$
S \approx \frac{g \cdot \rho \cdot TR}{T1} \quad (14)
$$

To measure the contrast concentration, the pre-contrast signal, $S_0$, combined with equation (14) and using equation (11) give, [Jackson, Buckley and Parker 2003]

$$
\frac{S_{Gd} - S_0}{S_0} \approx r_1 T_{10} C_{Gd} \quad (15)
$$

where $S_{Gd}$ is the signal with contrast.

The contrast concentration data can be acquired non-dynamically, which means that the imaging is done after a certain interval of time after contrast agent injection. The appropriate choice of contrast agent will then lead to an accumulation of it in the structure of interest, making it clearly visible against the surrounding tissue. This is useful when trying to delineate a tumour for treatment planning.

The data can also be acquired dynamically which means that imaging is carried out before, during and after injection of the contrast agent. Susceptibility based dynamic measurements are called dynamic susceptibility contrast MRI (DSC-MRI), and correspondingly for relaxivity dynamic contrast enhanced MRI (DCE-MRI). The latter dynamic technique is what is used in this work.
**DCE-MRI**

The dynamic data can through pharmacokinetic modelling render parameters which have been found to reveal diagnostic and prognostic information about a tumour, [Yankeelov, Cron, Addison et al. 2007]. These parameters will be introduced in the following section along with how they are calculated.

$K_{trans}$ is the volume transfer constant, and describe the contrast’s movement between $v_p$ and $v_e$ where $v_p$ is the vascular plasma space and $v_e$ the volume of extra vascular extra cellular space per unit volume of tissue, see figure 1, [Tofts 2004].

![Diagram of contrast dynamics](image)

**Figure 1. An illustration of the compartments involved in the contrast dynamics.**

$K_{trans}$ is given by

$$K_{trans} = P \cdot S \cdot \rho$$

(16)

where $P$ is the permeability, i.e. flow over membrane per unit time, per unit area of the membrane and per unit concentration difference over the membrane ($cm \times min^{-1}$). $S$ is the surface area per unit mass of tissue ($cm^2 \times g^{-1}$) and $\rho$ is the tissue density ($g \times cm^{-3}$) which results in the unit for $K_{trans}$ as ($min^{-1}$).
The equations used to correlate these parameters with the tissue concentration of contrast through the plasma concentration, i.e. the AIF, differ in form and complexity. One popular equation reads

\[ C_t(t) = K_{\text{trans}} \cdot \int_0^T C_p(t) \cdot \exp \left( - \frac{K_{\text{trans}}}{v_e} (T - t) \right) dt + v_p \cdot C_p(t) \]  \hspace{1cm} (17)

where \( C_t(t) \) is the concentration of contrast agent in tissue, and \( C_p(t) \) in plasma as a function of time. The integral is the amount that has leaked into the tissue from blood vessels, and the last term \( v_p(t) \cdot C_p(t) \) compensates for the fact that tissue can contain blood vessels which in turn contain contrast agent, [Yankeelov, Cron, Addison et al. 2007].

Equation (17) can also be expressed as, [Tofts 2004]

\[ C_t(t) = v_p C_p + C_p(t) \ast H(t) \]  \hspace{1cm} (18)

where \( H(t) \) is the impulse response, or residue function, according to

\[ H(t) = K_{\text{trans}} \exp \left( - \frac{K_{\text{trans}}}{v_e} t \right) \]  \hspace{1cm} (19)

and \( \ast \) is the convolution operator.

As can be seen from the parameter equations above, the AIF is essential for calculations. The AIF can be measured using equation (15), but the range of contrast concentrations that can be measured is limited by signal saturation and noise. A more exact measurement over a larger range can be done with phase measurements.
Using phase for contrast concentration measurements

The phase in an MRI image is the angle of the magnetization vector in the x’y’-plane, rotating at the Larmor frequency, see figure 2. The rotating plane is a concept commonly used in MRI theory as any component moving at the Larmor frequency will seem to be stationary in this frame of reference, which facilitates calculations. From this point on, all statements assume a rotating frame of reference unless stated otherwise, and this plane is denoted as the x’y’-plane.

\[ \phi \]

Figure 2. An illustration of the phase, \( \phi \), in the rotating plane.

The susceptibility of the contrast agent changes the magnetic field locally, and this can be used to measure the contrast concentration with phase. The following derivation is a summary, and can be read in more detail in the dissertation by Erbil Akbudak, [Akbudak 1996].

Phase is shifted by susceptibility effects, motion and other factors that influence local frequency. The angular velocity of the projection of the magnetization vector into the x’y’-plane in voxel \( v \) at time \( t \) can be separated as

\[ \omega(x) = \bar{\omega}(v) + \phi(x, t) \]  

Where \( \bar{\omega}(v) \) is the average angular frequency of voxel \( v \), and \( \phi(x, t) \) is the variation about that average which is random. When the rf-pulse is applied, it will cause all the magnetisation vectors to have the same phase. The phase shift in a specified voxel measured after TE is therefore directly dependent on TE as

\[ \Delta \phi = \bar{\omega}(v) \cdot TE \]
From equation (21) it can be noted that the measurable range of phase is limited to $2\pi$ radians. If data points are acquired too sparsely, the phase can accumulate more than $2\pi$. Under these circumstances, the phase can not be determined exactly, but only as $\Delta\phi_{true} = \Delta\phi_{meas} + n \cdot 2\pi$ where $\Delta\phi_{true}$ is the true value, $\Delta\phi_{meas}$ the measured value and $n$ an integer such that $n = \pm 0, \pm 1, \pm 2, \ldots$

Phase is sensitive to motional and susceptibility effects which make it hard to measure “true phase” except in some well characterized cases. One such case is a straight vessel which can be modelled as an infinite cylinder. In an infinite cylinder, the phase shift caused by a paramagnetic susceptibility agent is

$$\Delta\phi_x = \sigma(v) \cdot TE = \gamma \Delta B_x \cdot TE$$

(22)

where $\Delta B_x$ is the change in magnetic field caused by the presence of the susceptibility agent only. In the semi-infinite cylinder, this change in magnetic field caused by the contrast agent can through calculations be found to be

$$\Delta B_x = \mu_0 \left( \Delta\chi \left( \frac{1}{3} - \frac{1}{2} \sin^2 \theta \right) \right) \left\| \vec{H}_0 \right\|$$

(23)

where the constant $\mu_0$ is the permeability of free space and has the value $\mu_0 = 4\pi \cdot 10^{-7} \text{NA}^{-2}$. $\theta$ is the angle between the $z$-axis of the slice and the main magnetic field, or more conveniently, between the axis of the cylinder and the main magnetic field, and $\Delta\chi$ is the change in magnetic susceptibility caused by the contrast agent. $\vec{H}_0$ is the magnetic field intensity without contrast agent.

To make this into a function of the change in concentration of contrast agent, the molar susceptibility, $\chi_M$, of the contrast is used. This gives

$$\Delta\chi = \chi_M \Delta C$$

(24)

From equations (22), (23) and (24) the expression for the phase shift is reached

$$\Delta\phi_x = \gamma \mu_0 \left( \Delta\chi \left( \frac{1}{3} - \frac{1}{2} \sin^2 \theta \right) \right) \left\| \vec{H}_0 \right\| \cdot TE$$

(25)

The $\chi_M$ is also temperature dependent, as

$$\chi_M = \left( \frac{\mu_{eff}}{2.84} \right)^2 \cdot T^{-1}$$

(26)
Incorporating equation (26) into equation (25) finally yield the expression for the phase shift

$$\Delta \phi_T = \gamma \mu_0 (\Delta C)_{\chi, T} \left( \frac{1}{3} - \frac{1}{2} \sin^2 \theta \right) \| \tilde{H}_0 \| T E \cdot \frac{T}{T_x} \tag{27}$$

where $T$ is the temperature during measurements, and $T_x$ is the temperature at which $\chi_M$ is defined.

The use of the infinite straight cylinder model will introduce an error as this is of course not true in the real case with a blood vessel. The magnetic field intensity offset in a finite cylinder is given by

$$\| \Delta H_{\text{macro}} \| = \left( \frac{\chi_I - \chi_x}{2} \right) \left( \frac{z + L/2}{(z + L/2)^2 + a^2} - \frac{z - L/2}{(z - L/2)^2 + a^2} - 2 \right) \| \Delta H_{0\text{II}} \| \tag{28}$$

where $z$ is a coordinate with origin in the centre of the cylinder with length $L$ and radius $a$, and $\| \Delta H_{0\text{II}} \|$ is the magnetic field without the cylinder.

Choosing a slice at the centre of the cylinder ($z = 0$) and if $L > 20a$, which is a reasonable assumption for a blood vessel, the error by assuming an infinite cylinder will be less than one percent and thus negligible, [Akbudak 1996].
Data analysis

When the time series data have been collected using phase measurements, there are still some steps that need to be taken to acquire the completed AIF.

As there is a drift in the magnetic field during measurements, the phase from a background ROI needs to be subtracted from the experimental value. This is done by multiplying the complex value in the actual ROI with the conjugate of the value for the background ROI

\[ Z_{be} = Z_{ROI} \cdot Z_{bROI}^* \]  

(29)

where \( Z_{be} \) is the background corrected value, \( Z_{ROI} \) the value from our actual ROI and \( Z_{bROI}^* \) the conjugate of the value from the background ROI.

The phase values are then calculated by pair-wise subtraction of phase which minimizes problems with wrapping

\[ \Delta \phi(i) = Z(i) \cdot Z(i - 1)^* \]  

(30)

where \( i = 1, 2, 3, \ldots, N - 1 \) and \( N \) is the number of data points in the time series.

From equations (27)-(30), the change in concentration, \( \Delta C \) can be calculated, resulting in a formula for the concentration at each point in time \( i \)

\[ C(i) = \sum_{n=1}^{i} \Delta C(n) \]  

(31)
The turboFLASH sequence

The sequence studied in this work is the turboFLASH sequence, FLASH is an acronym for fast low angle shot. It is a spoiled technique with extremely short $TR$ and very low flip angles that can acquire a whole slice in 1 or 2 s, McRobbie et al. 2007. A timing diagram for the sequence can be seen below in figure 3. The line marked rf shows the slice selective rf-pulses inducing the desired flip angle $\alpha$. Simultaneously there is a slice selective gradient depicted on the line below, the Gs line. After the excitation, the frequency and phase encoding gradients are turned on, shown in the lines Gf and Gp respectively. Finally at the bottom is the signal line which shows the echo at time $TE$ after the rf-pulse. The rf-spoiling before the slice selective gradient is included to destroy any remaining transverse magnetisation to avoid contamination of the $T1$-weighted contrast by $T2$-effects. TurboFLASH is also known as IR-FSPGR (on General Electric scanners) or sometimes T1-TurboFLASH, [McRobbie et al. 2007].

![Figure 3. A timing diagram of the turboFLASH sequence with the parameters $TR$ and $TE$ indicated](image)
An optional inversion pre-pulse, not depicted in figure 3, can also be incorporated into the sequence to increase the T1-weighting.

The point spread function

The point spread function (PSF), is a description of the imaging system’s response to a point object. In other words, it is a measure of the spreading or blurring in the image of the point object caused by the imaging system, and a convolution of the true image with the PSF renders the acquired image. In a MR image, the ideal PSF takes the shape of a sinc-curve because of the Fourier transformation of the signal, as is shown below. For simplicity, the one dimensional case is used, but the same reasoning holds for all three dimensions.

Let \( f(x) \) be the true 1D image and let its k-space, or raw data space, counterpart be \( F(k) \). These images are related through the Fourier transform as

\[
f(x) = \int_{-\infty}^{\infty} F(k) \cdot e^{i2\pi xk} \, dk
\]

(32)

The acquired raw data space is not infinite, there is a finite value for the maximum spatial frequency sampled. This can be viewed as multiplying the raw data space, \( F(k) \), with a rectangular function defined as

\[
rect\left(\frac{k}{a}\right) = \begin{cases} 
0 & \text{if } \left|\frac{k}{a}\right| > \frac{1}{2} \\
\frac{1}{2} & \text{if } \left|\frac{k}{a}\right| = \frac{1}{2} \\
1 & \text{if } \left|\frac{k}{a}\right| < \frac{1}{2}
\end{cases}
\]

(33)

The rectangular function has the value one for the interval of sampled spatial frequencies and is zero outside this interval. The desired rectangular function can be seen in figure 4 where \( k_{\text{max}} \) is the maximum spatial frequency sampled.

Figure 4. Rectangular function defining the sampled spatial frequencies where \( k_{\text{max}} \) is the maximum spatial frequency sampled.
Looking at the premises of equation (33) and the desired shape in figure 4, the constant $a$ is found to have the value $a = 2k_{\text{max}}$.

From calculations, it can be found that taking the Fourier transform of a product of two functions will yield

$$\int_{-\infty}^{\infty} F(k) \cdot e^{2\pi i k \cdot x} \cdot G(k) dk = f(x) \ast g(x)$$

(34)

where $g(x)$ is an integrable function and the Fourier transform of $G(k)$. This is called the convolution theorem. The function the true image is convoluted with, has already been defined to be the PSF, and it remains to find this $g(x)$. This entails taking the Fourier transform of the rectangular function, which is

$$\int_{-\infty}^{\infty} \text{rect} \left( \frac{k}{a} \right) \cdot e^{2\pi i k \cdot x} dk = |a| \cdot \frac{\sin(a\pi x)}{a\pi x} = |a| \cdot \text{sinc}(ax)$$

(35)

From (34) and (35) we find that the result of not sampling the entire raw data space is a convolution of the true image with a PSF which has the shape $\text{sinc}(2k_{\text{max}}x)$. To write this more conveniently, the pixel size is given by

$$\Delta x = \frac{1}{2k_{\text{max}}}$$

(36)

and using the previous conclusion that $a = 2k_{\text{max}}$, the PSF can thus be written as

$$\text{PSF} = \text{sinc} \left( \frac{x}{\Delta x} \right)$$

(37)
**Material**

The MRI-equipment used in this work was a Siemens Magnetom Espree 1.5 T. For the phantom studies, a set up with adjustable flow was utilized to get both constant and pulsatile flows. The solution was pumped from a mixed reservoir into which contrast could be added and which also contained a temperature measuring device. The set-up can be seen below in figure 5.

![Set-up for flow phantom. The arrows indicate in- and outlet.](image)

A flowchart of the inner workings of the flow phantom is shown in figure 6, with the route of the contrast solution flow and important data collection and computer control processes indicated.
Two different phantoms through which the solution was pumped were used according to the requirements of the current experiment, see figure 7 and figure 8. The first phantom in figure 7 was used for experiments where only one angle of tube to main magnetic field was needed. The phantom in figure 8 was used in an experiment where both 0° and 90° angles were required, and made it possible to measure for both these angles during the same contrast bolus passage.
Figure 8. Version 2 of the flow phantom. The tube passes through the phantom twice, re-entering the phantom at a 90° angle to the last pass. The top illustration is the phantom as viewed from above illustrating the 90° angle between the two passings. The connection arrows indicate that it is the same tube re-entering the phantom. Outside the tube in the phantom is a CuSO₄ solution diluted to a susceptibility simulating tissue.
Methods

To decide the feasibility of using the turboFLASH sequence for phase measurements of the AIF, several experiments were conducted, both in phantoms and in-vivo. For all of the experiments using phase measurements, the concentration curves were calculated from the phase values with the technique explained in equations (27) through (31).

Initially, a sequence testing for $T1$-weighted DCE-MRI was carried out to be able to estimate the relative suitability of phase measurements compared to the more conventional method. A summary of the results from this experiment can be found in appendix 1.

The next step was to make a first evaluation of phase measurements of contrast concentration with a gradient echo sequence, and this was done in a phantom experiment. Especially the linearity and range of the method was under scrutiny.

The first phantom experiment verified that phase measurements showed promise for being an appropriate method, and two in-vivo studies were made with slightly differing sequences to make a first estimation of problems arising due to the more complex in-vivo situation. The patients were all having non-dynamic examinations, and the dynamic data for this report were acquired in the interval between contrast administration and the non-dynamic measurements. The sources of errors were addressed separately in a new phantom experiment where mainly partial volume effects but also errors from uncertainties in the vessel to main magnetic field angle were tested. The findings from this experiment and associated simulations were used to improve the sequence, and the new sequence was tested in yet another in-vivo experiment. More details about the separate experiments can be found under each subheading below.

In the text, when talking about the image elements, both pixel and voxel are used. When pixel is used, it refers to the image element’s characteristics in the phase- and frequency direction plane and the slice thickness is assumed to be known from the context.

Pre-study phantom measurements

A phantom as illustrated in figure 7 was employed with an inner diameter of the tube of 6 mm. The phantom was coupled together with two bottles of saline solution to achieve proper coil-loading of the RF-coil. The imaged volume will influence the RF-coil, and thus the phantom should be approximately the same size as a human head to get the same imaging conditions as in an in-vivo situation. The flow was kept constant and this made it possible to simulate the contrast concentration in the contrast solution arriving at the phantom as a function of time. A comparison was made between the measured and simulated curves.
The contrast used was Omniscan 0.5 mmol/ml Gadodiamid diluted to 0.25 mmol/ml. The contrast was added in six steps of 1 mMol, which is 4 ml of dilute per step, with 3 minutes between each addition. Images were acquired continuously during the adding of contrast.

The sequence used was a gradient echo sequence with repetition time $T_R = 50$ ms and a three echo time train, $T_E = 20, 25, 30$ ms. The dynamic phase values were unwrapped where necessary.

**In-vivo measurements I**

The patient was a male having a non-dynamic contrast examination for a brain tumour. The sequence to be tested was a pulse gated turbo-FLASH sequence with settings as given in table 1. Two slices were acquired, one transversal in the neck and one sagittal in the brain.

The gating only allowed one slice to be acquired per heartbeat giving the dynamic series of images a time resolution of about 2 s. The patient received a manual injection of 12 ml Magnevist followed by a saline flush.

Two blood vessels had been chosen beforehand for their apparent suitability for measuring the AIF. In the neck, the arteria carotis communis and in the brain, the arteria cerebri media were chosen. The characteristics looked for was a relatively large diameter of the vessel, and that the vessel was as long and straight as possible. Before measuring with the actual turbo-FLASH sequence, a gradient echo sequence was used as an angiographic localiser. This was done to be able to estimate the angles of the chosen vessels to the main magnetic field, and to be able to place the slices at right angles to the vessels. The tested sequence was started before contrast agent injection and left running during and after administration for 5 minutes.

| Table 1. The settings of the sequence used for the measurements. |
|----------------------|-----------------|
| $TE$                 | 2.97 (ms)       |
| $TR$                 | 5.4 (ms)        |
| Voxel size           | 2 x 1 x 8 (mm$^3$) |
| (phase dir. x freq dir. x thickness) |               |
| Band width           | 320 (Hz/ Pixel) |
| FOV                  | 250 (mm)        |
| Asymmetric echo      | Off             |
| Flip angle           | 10°             |
The dynamic phase development was measured in three different ROIs, see figure 9.

![Figure 9. An illustration of the regions where the three different ROIs were chosen.](image)

From [Ellis, Logan and Dixon 1999 and Sobotta 2006] the blood vessels for the three ROIs were found to be: 1 - vertebral artery, 2 and 3 - common carotid arteries. The latter were lying very close to the internal jugular veins and could not be resolved due to the coarse resolution. There was an uncertainty in the identification of the blood vessels because of both the poor resolution but also individual variations of vessel location.

The background ROI for correction of the curves was placed in the tissue in the posterior part of the neck.

In the sagittal slice, voxels containing vessel signal only were hard to find due to the poor resolution. The same was true for finding background ROIs containing only tissue and no blood vessels. Having a peak in the background data would subtract from the peak in the concentration curve, which was already hardly visible. Therefore the analysis for the sagittal slice was done without background subtraction. Figure 10 shows where the ROI was chosen.
The vessel was found to be the transverse sinus, meaning that this was actually venal blood, [Ellis, Logan and Dixon 1999 and Sobotta 2006], but as this was the only place where a reasonable signal was achieved, it was used anyway to illustrate the interesting 90° case. The artery the slice was placed to intercept at a 90° angle could not be analysed from the data as it seemed to only contain noise.

**In-vivo measurements II**

To enhance the signal from blood and make the selection of ROIs easier, the last sequence was modified by adding a saturation recovery preparation pulse which causes flowing blood to light up relative to stationary tissue. The saturation recovery turbo-FLASH sequence had settings as given in table 2 and was pulse-gated.

<table>
<thead>
<tr>
<th><strong>Table 2. The settings of the sequence used for the measurements.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TE (ms)</strong></td>
</tr>
<tr>
<td><strong>TR (ms)</strong></td>
</tr>
<tr>
<td><strong>TI (ms)</strong></td>
</tr>
<tr>
<td>Flip angle</td>
</tr>
<tr>
<td>Voxel size</td>
</tr>
<tr>
<td>(phase dir. x freq dir. x thickness)</td>
</tr>
<tr>
<td>Phase resolution</td>
</tr>
<tr>
<td>Band width</td>
</tr>
<tr>
<td>FOV</td>
</tr>
<tr>
<td>Asymmetric echo</td>
</tr>
</tbody>
</table>
The patient was a male having a non-dynamic contrast examination for a brain tumour and received a manual injection of 14 ml Magnevist followed by a saline flush.

The ROIs chosen are illustrated in figure 11 and figure 12. The vessel in the neck is the communal carotid artery and the one in the brain slice is the transverse sinus, [Ellis, Logan and Dixon 1999 and Sobotta 2006].

Figure 11. Arrow indicating the position of the ROI in the neck slice.

Figure 12. Arrow indicating the position of the ROI in the sagittal brain slice.

**Phantom measurements of partial volume effect**

As the large problem with the in-vivo measurements seemed to be the partial volume effect, a study was made to understand how this affected the phase signal. By using different sizes of voxels and angles of the slices to the tubes, the aim was to estimate the error that can be induced in in-vivo measurements from partial volume effects and misjudgement of slice placement.

The phantom illustrated in figure 8 was placed in the head coil so that one tube was parallel, and the other 90° to the main magnetic field. De-ionized
water was pumped from a reservoir through the tube in a pulsed fashion as to mimic the output of a heart. The whole system contained 2 litres. A solution of Gd(III)Cl prepared with a concentration of 0.21 M was added in steps of 5 ml, 1.05 mmol per step, to the stirred reservoir. The concentration of this solution is however somewhat uncertain as Gd(III)Cl is hygroscopic and the number of water molecules attached to each molecule is unknown. The manufacturer provided the mean value of 5.61 water molecules per Gadolinium atom used for calculations of concentration in these experiments. Theoretically, the concentration increase per adding of contrast should be 0.53 mM, and the final concentration after seven steps was 3.7 mM.

A Turbo Flash sequence was used with settings according to table 3.

<table>
<thead>
<tr>
<th><strong>Table 3. The settings of the sequence used for the measurements.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TE</strong></td>
</tr>
<tr>
<td><strong>TR</strong></td>
</tr>
<tr>
<td>Flip angle</td>
</tr>
<tr>
<td>Voxel size (phase dir. x freq dir. x thickness)</td>
</tr>
<tr>
<td>Base resolution</td>
</tr>
<tr>
<td>Band width</td>
</tr>
<tr>
<td>FOV</td>
</tr>
<tr>
<td>Asymmetric echo</td>
</tr>
</tbody>
</table>

Six slices were acquired as illustrated in figure 13. The largest angle, 10°, was used as a reasonable approximation of maximum error in an in-vivo situation.

![Figure 13. The phantom as seen from the side with three slices drawn in. Three slices were acquired on the part of the tube parallel to the main magnetic field and three on that part at right angles to it, in all 6 slices. The slices were oriented so that one had its normal parallel to the tube and the other two with 5° and 10° angle between the normal and the tube.](image-url)
The resolution of the data was changed to see the effect on the phase measurements. The resolution depend reciprocally on the interval of spatial frequencies sampled as $\Delta x = 1/(k_{\text{max}} - k_{\text{min}})$. By taking away $n$ rows or columns of data from the edges of the raw data space, a new resolution was obtained, given by

$$\frac{(k_{\text{max}} - k_{\text{min}})}{(N-n)/N(k_{\text{max}} - k_{\text{min}})} \Delta x = \frac{N}{N-n} \Delta x$$

where $N$ was the original number of rows or columns. The data was not completely removed, only put to zero. This way of changing the resolution enabled the ROI selection to be automatic as the number of image elements remained the same.

Computer simulations were made to get a better basic understanding of how the partial volume effect changes the signal. A 3D matrix was used as a model of a slab of material (tissue) with a vessel running through. A number of data points were randomly selected from the matrix and multiplied by the 3D sinc-function defining a voxel, i.e. the point spread function, see equation (37). These products were summed to give the simulated signal. Voxel placement, voxel size and angle between normal of the slice and vessel, could all be altered to see their separate effects.

**In vivo measurements III**

A new protocol was devised with slice selective saturation recovery to see if this could repress the problem previously experienced from partial volume effects. The patient examined was a female having a non-dynamic contrast examination for a skull base dermatoid. The turbo-FLASH sequence had settings as given in table 4, pulse gating, and slice selective saturation recovery. Only one transverse slice was used situated in the neck.

The patient received 15 ml of Omniscan 0.5 mmol/ml Gadodiamid in an injection of about 10 s followed by a saline flush. During set-up of the examination, the head and neck-coil was not connected properly with the result that only one coil of possible four was used. The noise is therefore slightly higher than what would have been achieved otherwise.
Table 4. The settings of the sequence used for the measurements.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>3.95 (ms)</td>
</tr>
<tr>
<td>TR</td>
<td>6.7 (ms)</td>
</tr>
<tr>
<td>Voxel size</td>
<td>1.4 x 1.1 x 6 (mm³)</td>
</tr>
<tr>
<td>(phase dir. x freq dir. x thickness)</td>
<td></td>
</tr>
<tr>
<td>Band width</td>
<td>220 (Hz/pixel)</td>
</tr>
<tr>
<td>FOV</td>
<td>140 (mm)</td>
</tr>
<tr>
<td>Asymmetric echo</td>
<td>Off</td>
</tr>
<tr>
<td>Flip angle</td>
<td>20°</td>
</tr>
<tr>
<td>TI</td>
<td>400 (ms)</td>
</tr>
</tbody>
</table>

The ROIs were placed in vessels as illustrated in figure 14 which from [Ellis, Logan and Dixon 1999 and Sobotta 2006] were found to be the internal carotid artery and the deep cervical vein.

![Image of magnetic resonance imaging (MRI) showing two ROIs labeled 1 and 2. ROI 1 is marked as Arteria carotis interna, and ROI 2 is marked as Vena cervicalis profunda.]

Figure 14. Illustration of where the ROIs were chosen. 1 - Arteria carotis interna 2 – Vena cervicalis profunda.
Results

Pre-study phantom measurements

A plot of the dynamic phase measurements for the three different echo times can be seen in figure 15.

![Figure 15](image-url) A plot of phase vs. time for the three different echo times. The black lines are added to show the good linearity of the method.

As was expected according to (27), the phase reaches a higher value for longer echo times. A quick check was of the consistency for the different echo times by dividing the final values at \( t = 1300 \) s, by the echo time, \( TE \). According to equation (27), this should result in the same value for all three echo times, the result can be seen in table 5. It was accurate to the third decimal.

<table>
<thead>
<tr>
<th>( TE ) (ms)</th>
<th>Phase (( t ) = end) (rad)</th>
<th>Phase (( t ) = end) / ( TE ) (rad/ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2.874</td>
<td>0.144</td>
</tr>
<tr>
<td>25</td>
<td>3.571</td>
<td>0.142</td>
</tr>
<tr>
<td>30</td>
<td>4.285</td>
<td>0.143</td>
</tr>
</tbody>
</table>

Finally for comparison, phase curves were obtained theoretically by modelling the system and using (27). The result can be seen in figure 16 for the different \( TE \)-times.
Comparing figure 15 and figure 16, it can be seen that the general shape and
time-dependence is similar. To compare the phase more quantitatively, the
values for $t = 1300$s are once again used, see table 6.

**Table 6. A comparison of the results from the experiments and the model.**

<table>
<thead>
<tr>
<th>$TE$ (ms)</th>
<th>Phase measured ($t = \text{end}$)</th>
<th>Phase model ($t = 1300$)</th>
<th>Ratio measured over model value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2.88</td>
<td>2.684</td>
<td>1.07</td>
</tr>
<tr>
<td>25</td>
<td>3.626</td>
<td>3.353</td>
<td>1.08</td>
</tr>
<tr>
<td>30</td>
<td>4.336</td>
<td>4.024</td>
<td>1.08</td>
</tr>
</tbody>
</table>

The experimental values were, for all echo times, 7-8% higher than those of
the model. The similarity in deviation makes it probable that it is because of
some general error and not the precision of the method.
**In vivo measurements I**

The dynamic phase data were analyzed for the different ROIs shown in figure 9. The best signal with respect to magnitude and noise was achieved for a ROI of 2 voxels in ROI 1 of figure 9, and the resulting concentration curve can be seen below in figure 17 as a function of image number. The time resolution was approximately 2 seconds per image for both neck and brain measurements.

![Figure 17.Phase in a ROI of 2 voxels in area 1 of figure 9.](image)

For the other two ROIs the data were even noisier and the peak values lower with maximums of approximately 0.3 rad or 2 mM. The smaller peak at image ~105 in figure 17 is a motion artifact caused by the patient swallowing. This peak had approximately the same magnitude or higher in the curves from the two other ROIs and thus the same height as the actual first pass peak.

Analysing the data from the brain ROI as illustrated in figure 10 gave values as seen in figure 18. Please note from equation (27) that the 90° angle of the vessel and slice to the main magnetic field makes the phase shift negative for positive contrast difference.
Figure 18. Phase (top) and concentration (bottom) curves of the ROI indicated in figure 10.

Obviously the concentration at the peak was too low when compared to the measured values from the vessels in the neck.
In-vivo measurements II

The dynamic data from the ROI illustrated in figure 11 were analyzed and the resulting phase- and concentration curves can be viewed in figure 19. The time resolution was about 2 seconds per image.

![Figure 19. The contrast curve from the ROI indicated in figure 11 with phase shift on the left axes and contrast concentration on the right](image)

The same treatment of the sagittal brain slice gave the following results as seen in figure 20.
Figure 20. Phase (top) and concentration (bottom) curves of the ROI indicated in figure 12 with phase shift in the top graph, and contrast concentration in the lower.

In comparison with the concentration curves from the first in-vivo experiments, these are both noisier and have lower peaks.
Phantom Measurements of Partial Volume Effect

To get a notion of how the voxel size and the angle of the slices affect the obtained concentration value, the concentration curves were plotted together, see figure 21.

![Figure 21](image)

**Figure 21. Contrast concentration in mM for the different angles of slices where the tube is parallel (top) and 90° (bottom) to the main magnetic field.**

The resolution of the acquired data was changed by putting the values of rows and columns at the edge of the raw data space to zero. To illustrate how the resolution affected the outcome, the mean values of the last 70 values of the concentration curves were calculated and plotted versus the dimensionless quantity “pixel width / tube radius”, see figure 22.
Figure 22. A plot of calculated concentration values for different resolutions and the three different slices for the tube orientated parallel (top) and 90° (bottom) to the main magnetic field. The dashed line indicates the calculated final concentration of 3.7 mM.

The reason for this behaviour is most likely the sinc-curve that defines the voxel. The derivation of the PSF being a sinc-function can be found in the “The point spread function” subsection under “Theory”.

Figure 23 show how different ratios between tube and voxel size affects the signal. The signal magnitude is 1 everywhere, but inside the tube, the phase of the signal is $\pi/2$ and outside 0. In a) the voxel is quite small and most of the area under the curve is contained inside the tube. The phase of the resulting complex number in this case is $\sim 97\%$ of the true value $\pi/2$. In b), a larger positive lobe is just outside the tube and this will cause a decrease in phase signal, and the value will be $\sim 93\%$ of the true one. In c) on the other hand, a negative lobe can be seen to reach the exterior of the tube, and the phase value actually increases from an addition of negative real signal and is about 10% too high. The following are 1D examples with the further
simplification of a voxel situated in the exact centre of the tube but still give a good indication of how the sinc-curve affects the signal.

Figure 23. An illustration of how different voxel sizes affects the phase signal. The blue curve is the sinc defining the voxel in one dimension, the black dotted line is the zero level, the white circle is a tube of radius $= 2$ mm and finally the red square is a two dimensional view of the voxel with side a) 0.5 mm b) 1 mm and c) 2 mm.

The behaviour of the signal was simulated for different pixel sizes in the three-dimensional case, and the result can be seen in figure 24. As in the simulation above, the magnitude of the signal was assumed to be 1 everywhere, with a phase of $\pi/2$ inside the tube, and 0 outside. To simulate the experimental set-up more closely, the plastic tube itself was also simulated, giving 0 signal, as a shell of 1 mm thickness around the interior of the tube. The thickness of the slice was as in the experiment 6 mm.
Figure 24  Simulated signal for different pixel size over radius ratios.

The shape of the simulated curve to the experimental have several common features, for example the peak at pixel size/ radius = 1.5.

Finally, it was also of interest to see how the offset of voxel location from vessel centre would affect the signal. A similar simulation as for figure 24 was made, but the pixel size was held fixed at 1 mm for varying offsets. The result can be seen in figure 25.

Figure 25. Relative phase signal for different distances voxel to tube centre for a pixel size of 1 mm, tube radius of 2 mm, and different angles of slice to tube.
All the simulations were restricted to only one voxel, and using more should even out the effects somewhat, but these simulations still serve as an indication of possible size of errors.

The simulations also assume that the magnitude of the signal is the same inside as outside the vessel, where the only thing that differs is the phase. In saturation recovery sequences, the signal from the stationary tissue can be suppressed, while the signal from the flowing blood remains largely unaffected. In figure 26 this is illustrated for different ratios of

\[
\frac{\text{signal magnitude outside tube}}{\text{signal magnitude inside tube}}.
\]

![Figure 26](image)

Figure 26 Relative phase signal versus pixel sizes for different ratios of signal magnitude outside vessel to inside vessel.

**In vivo measurements III**

The improvement of the sequence for this experiment was adding slice selective saturation recovery to curb the partial volume effect problem. The efficiency of the saturation recovery in suppressing the signal from outside the vessel was tested by taking the ratio of signal magnitude just outside to inside the vessel for all images in the time series. The ratio was found to be at most 0.13 with a mean value of 0.08. According to figure 26, this should render a good value for a broad range of pixel sizes.

The concentration curve for the carotid artery indicated in figure 14 can be seen in figure 27 and figure 28 for two different choices of background ROI. The curves are plotted versus image number, where the time resolution was 0.74 seconds per image. The two different background measurements have
their own advantages. Choosing the background close to the vessel eliminates the erroneous positive slope of the first data points before the arrival of the contrast bolus. On the other hand, this choice decreases the peak value of the AIF, probably because of signal spilling out from the vessel into the surroundings. This causes a peak in the background data which is then subtracted from the AIF peak.

Figure 27. Concentration curve of the ROI 1 indicated in figure 14 with a background ROI surrounding the artery.

Figure 28. Concentration curve of the ROI 1 indicated in figure 14 with a background ROI selected in the fat in the back of the neck.
By changing the resolution through setting the edges of k-space to zero, the concentration curves for different voxel sizes were acquired see Figure 29. The voxel size is stated by its phase encoding direction size, the width and height ratio is kept constant and the thickness is fixed at 6 mm.

To get a broader perspective, the concentration value of the peak for different pixel size to vessel radius ratios was calculated. The radius of the vessel was estimated to 1.5 mm. The peak value decreased almost monotonously for increasing pixel size, ending at approximately 90% of its initial values for \( \frac{\text{pixel size}}{\text{vessel radius}} = 2.5 \). This actually corresponds quite well to the simulation curve in figure 26 despite the simplification of homogeneous background in the simulation case.

The background corrected concentration curve for the vein indicated in figure 14 is plotted in figure 30. The peak is seen to have a lower value than for the artery curve. The fact that the peak is located about 5 seconds later in time verifies that it is indeed a vein. A deviation from what would be expected is that the final values of the concentration are lower for the vein than for the artery. At the end of the curve, the concentration should have reached an equilibrium and be approximately equal for arteries and veins.
Figure 30. Contrast concentration curve for the deep cervical vein.
Discussion

The objective of this work was to test and optimize a turboFLASH sequence and assess its suitability for measuring the arterial input function by measuring phase. A modification of the sequence was developed that from the results in this report can be recommended for specific examination conditions.

From the first pre-study phantom measurements the results seemed to indicate that using phase measurements for contrast concentration determination is sound with a good linearity and SNR at least up to the investigated 5 mmol/l. Throughout, the measured concentration values were about 7-8% higher than the calculated values, and the similarity in deviation led to the conclusion that it was caused by some general error, and not the precision of the method. Factors that can cause a deviation include misjudgement of the volume of water, where an error would carry through to the calculated contrast concentration. An incorrect temperature measurement influences the measured concentration, as the value of magnetic susceptibility of the contrast agent is given for 290 K. Also the concentration of the contrast solution as well as the amount of contrast solution added in each step have a certain degree of uncertainty.

Further experiments in-vivo displayed a large signal loss compared to expected values of contrast concentration. A large contributing factor to this signal loss was suspected to be the partial volume effect. With the large voxels used in these first experiments, the voxels contained both vessels and tissue. This made the curves measured less accurate, both for the ROIs in the vessels and the background ROIs. The background curve might also have been further deteriorated if the vessels were placed at an angle to the main magnetic field. The susceptibility effect then spills over to surrounding tissue, introducing a dependence of contrast concentration inside the vessel to the background concentration curve. It was agreed that a finer resolution was needed. Patient movement both between localisation and measurement and during the examination was another factor that influenced the results. Movement between localisation and measurement made the vessel angle determined during localisation incorrect, and the uncertainty in angle and the error it introduces should be further examined. As for the movement during examination, it was seen that swallowing gave a visible peak in the concentration curve of the neck slice. In this particular case, it would be quite easy to smooth out this extra peak, as it can be seen from the dynamic series of magnitude images that it was coincident with the patient swallowing and because the curve at that time was expected to not change rapidly. On the other hand, swallowing or other movement during a crucial part of the AIF acquisition, like during the peak, could not be so easily corrected. Another observation as to signal quality was that the noise level in the neck slice images was quite high. This was because the slice was chosen too low in the neck and the sensitivity of the head and neck coil is better towards the centre of it. To acquire images with adequate SNR, care should be taken to choose the slice at an appropriate level. Finally, the peak value of the concentration for the brain slice was even lower than the one from the
neck slice. This might have been caused by the smaller blood vessels, resulting in a larger partial volume effect. Also, it could not be ascertained if the vessel used for measurements in the brain slice was at right angles with the slice.

In the next in-vivo experiment, a non-selective saturation recovery preparation pulse was used. The results with this sequence was significantly worse than for the sequence without the preparation pulse, both regarding signal magnitude and noise level. To investigate the reason for this behaviour might be of interest for the understanding of the subject, but was not within the scope of this work.

In the following phantom experiments, the partial volume effect and uncertainties introduced by errors in determining vessel to magnetic field angles were investigated. The concentration values measured were overall lower than the calculated values. A reason for this could be that the Gadolinium salt used for making the contrast solution is hygroscopic, and the number of water molecules attached to each Gadolinium salt molecule uncertain. A mean value provided by the manufacturer was used, but if the salt used in the experiment had absorbed more water, the contrast concentration in the solution would be lower than calculated. Also measurement uncertainties in preparing the solution would naturally carry through to the concentration of the contrast solution. The measured concentration values for different angles between vessel and main magnetic field displayed a maximum deviation of about 15%. A quite large source of error which should be minimized if possible. Manipulations of the resolution of the measurement data, combined with computer simulations illustrated how the signal was influenced by different pixel size to vessel radius ratios through the partial volume effect. This was found to have a large impact on the concentration value, but later computer simulations indicated that this could be, to a large degree, circumvented by suppressing the signal from the tissue surrounding the blood vessel.

In the final in-vivo experiment, slice selective saturation recovery was used to suppress the signal from the surrounding tissue as indicated in the previous phantom experiment. The preparation pulse was found to suppress the tissue signal to about 10% of the signal inside the vessel. The magnitude of the concentration curve peak was much improved and in the range of likely peak values. A new question arose concerning how to choose the background ROI. Choosing a background ROI surrounding the vessel, it is difficult to avoid getting a peak during passage of the bolus of contrast agent, and this will subtract from the peak value in the AIF. Choosing it in a more remote location on the other hand, prevents eliminating local deviations in magnetic field from the AIF. The choice of background ROI needs more research to find the best placing for dealing with as well general drift as local changes.

For an interesting comparison, the contrast concentration curve was also measured in the deep cervical vein. The peak could be seen to be displaced to a later time, which agrees well with theory. An unexpected characteristic
of the curve was that the measured concentration was lower at the end of the vein curve than at the end of the artery curve. It was expected that the concentration should have reached an equilibrium at this stage, and be approximately equal for artery and vein. A reason might have been that the vein was assumed to be parallel to the main magnetic field like the artery while it could have been at an angle.

Based on the findings of these experiments, phase measurements can be recommended over T1-measurements for measuring the AIF in the neck in a vessel parallel to the main magnetic field. The main reason for this recommendation is the linearity of phase measurements over the whole range of interest for AIF-measurement, but also the larger SNR distinguishes phase measurements as the better method. The overall results of the experiments in this report strongly support using slice selective saturation recovery for dealing with the partial volume effect, which otherwise deteriorates the result.

As for using turbo-FLASH, it might not be the best sequence. A sequence where the resolution can be kept adequately fine and the acquisition of one image is shorter than about 0.7 s (which is equivalent to a heart rate of 85 beats per minute) would be preferred if it could accept longer echo times without adding artefacts to the image. A faster sequence is especially of interest for use in acquiring arterial input functions in the brain, where a larger field of view is necessary to avoid aliasing. Otherwise a compromise would need to be made between time and image resolution.

For future research, it would be interesting to investigate if phase measurements could also reliably be used for AIF measurements at points closer to the ROI in the brain used for measuring AIF dependant parameters. This would decrease the problem of bolus dispersion and give a more correct AIF for modelling purposes.
References


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Appendix 1.

**Sequence testing for T1-weighted DCE-MRI**

**Material and Methods**

In this experiment, the planned sequence, srFLASH centric reordering, $TR$ 3.3 ms, $TE$ 1.2 ms, FOV 250x250x5 mm and a matrix of 256x128 pixels, hereafter called the tested sequence, was tested. The combinations of four different flows and 14 concentrations of contrast were measured to check the validity of the tested sequence.

Siemens Magnetom Espree 1.5 T was used with a flow phantom in which the contrast agent solution was flowing in tubes of an inner diameter of 4 mm. The phantom was coupled together with two bottles of saline solution to give coil-loading. A pump with adjustable flow was connected to the phantom via a long hose. The flow was varied using a variable power supply. The contrast used was Omniscan 0.5 mmol/ml Gadodiamid.

Contrast was added in steps after a first amount was added to get approximate blood equivalence of the solution. The contrast concentration after each addition was 0.1, 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 9 and 10 mM Gadodiamid above the blood equivalence concentration.

To recalculate DCE-MRI data into contrast concentration, mappings of the proton density as well as inherent $T1$ relaxation values need to be made. To find the proton densities, a proton weighted baseline was acquired with a non steady-state gradient echo, centric reordering, no preparation pulse sequence with parameters $TR$ 3.8 ms, $a$ 6°, $TE$ 1.69 ms, 20 images and a bandwidth of 651 Hz/pixel. The $T1$ map was measured with a spin echo inversion recovery sequence with five different $TI$ times adjusted to the expected $T1$ for the current contrast concentration. This sequence was also used for each contrast concentration. Despite using partial Fourier to speed up the acquisition, this is a slow technique not suitable for dynamic measurements. It was used in this experiment for its good precision as a comparison for the values of the faster techniques.

There were two faster sequences used. A srGRE sequence was used to measure the $T1$ and tested with the different flow velocities. This sequence is quite fast, and therefore a possible candidate for measuring $T1$ in patients. The tested sequence was used for all combinations of contrast concentration and flow. A summary of the sequences used can be seen in table 1.
Table 1. Parameters of the used sequences.

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<th>$TI$ (ms)</th>
<th>$TE$ (ms)</th>
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* of expected T1
Results

The calculated concentrations for the tested sequence were plotted vs. true concentrations for different flows and TI-values. Two different ROIs were used, one containing only one pixel and one with nine pixels. The same ROI was not used for the proton weighted baseline as the rest of the results, because the volume of interest moved during measurement. The results can be seen in figures 1 and 2.

![Graphs showing calculated concentrations vs. true concentrations for different flows and TI-values.](attachment:graphs.png)

Figure 1. Calculated concentration vs. true concentration from data measured in a ROI of one pixel
Figure 2. Calculated concentration vs. true concentration from data measured in a ROI of nine pixels

From the figures 1 and 2 the conclusion was drawn that flows up to about 25 cm/s is mostly within error limit from the no flow situation. As can be seen, the 50 cm/s curve deviates strongly from the 0 cm/s curve, especially for higher concentrations. In regards to $TI$, it can be seen in comparison that the higher the $TI$, the lower the concentration at which the curve starts to flatten out. On the other hand, the two longer $TI$s show better linearity at lower concentrations. The final conclusion is that concentrations of at most 3-4 mM can be measured with any certainty with the tested sequence, and then preferably with a technique gated to heartbeat so that the flow is low.