Measuring blood-brain barrier permeability in multiple sclerosis enhancing lesions

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Abstract

Dynamic contrast enhanced (DCE-) MRI data can be analyzed using a two-compartment pharmacokinetic model to measure biophysical parameters such as blood-brain barrier (BBB) permeability. This work focuses on developing a DCE-MRI based technique to accurately estimate BBB permeability in multiple sclerosis (MS) lesions. The impact of the temporal resolution of the DCE-MRI acquisition on the accuracy and precision of permeability measurements is evaluated experimentally and through simulations, and a new protocol based on a two-phase acquisition is shown to reduce the errors in permeability estimates. BBB permeability maps in MS patients are also examined for correlations with differences in regions of enhancement observed following two non-dynamic protocols: a standard and an optimized one. Results indicate that voxels only enhancing with the optimized protocol are associated with lower BBB permeability values than voxels enhancing with both protocols, which supports the hypothesis that each non-dynamic enhancement protocol has its own sensitivity threshold. This indicates that using a quantitative DCE-MRI technique, such as the one presented here, provides a more complete view of MS lesion pathology by enabling quantitative measurement of BBB permeability rather than simple binary classification as enhancing or non-enhancing.
Résumé

Les données d’IRM dynamique avec agent de contraste (DCE-MRI) peuvent être analysées à l’aide d’un modèle pharmacocinétique à deux compartiments, afin de mesurer des paramètres biophysiques tels que la perméabilité de la barrière hémato-encéphalique (BHE). Notre étude vise à développer une technique de DCE-MRI qui permette de mesurer avec exactitude la perméabilité de la BHE dans les lésions de sclérose en plaques (SEP). L’impact de la résolution temporelle de l’acquisition sur l’exactitude et la précision des mesures de perméabilité est évalué au moyen d’expériences et de simulations, et un nouveau protocole en deux temps permettant de réduire l’erreur dans les mesures est proposé. Sont analysées ensuite les corrélations entre les cartes de perméabilité et les différences de réhaussement entre deux protocoles non dynamiques: l’un standard et l’autre optimisé. Les résultats préliminaires montrent que les valeurs de perméabilité sont plus basses dans les voxels réhaussés uniquement par le protocole optimisé que dans ceux réhaussés par les deux. Ces résultats soutiennent l’hypothèse d’un seuil de sensibilité intrinsèque à chaque protocole non-dynamique avec contraste. L’utilisation d’une technique quantitative de DCE-MRI, telle que celle présentée ici, apporterait une vision plus complète de la pathologie des lésions de SEP par la mesure de la perméabilité de la BHE, comparée à la classification binaire en régions réhaussant ou non.
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<td>AIF</td>
<td>arterial input function</td>
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<tr>
<td>BAT</td>
<td>bolus arrival time</td>
</tr>
<tr>
<td>BBB</td>
<td>blood-brain barrier</td>
</tr>
<tr>
<td>CA</td>
<td>contrast agent</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>DCE-MRI</td>
<td>dynamic contrast enhanced magnetic resonance imaging</td>
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<tr>
<td>DESPOT1</td>
<td>driven equilibrium single pulse observation of $T_1$</td>
</tr>
<tr>
<td>DSC-MRI</td>
<td>dynamic susceptibility contrast magnetic resonance imaging</td>
</tr>
<tr>
<td>DW-MRI</td>
<td>diffusion-weighted magnetic resonance imaging</td>
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<tr>
<td>EES</td>
<td>extravascular extracellular space</td>
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<tr>
<td>FA</td>
<td>flip angle</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>FLASH</td>
<td>fast low angle shot</td>
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<tr>
<td>FOV</td>
<td>field of view</td>
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<tr>
<td>FSE</td>
<td>fast spin echo</td>
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<td>Gd</td>
<td>gadolinium</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>GM</td>
<td>grey matter</td>
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<tr>
<td>HSR</td>
<td>high spatial resolution</td>
</tr>
<tr>
<td>HTR</td>
<td>high temporal resolution</td>
</tr>
<tr>
<td>LSR</td>
<td>low spatial resolution</td>
</tr>
<tr>
<td>LTR</td>
<td>low temporal resolution</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MRS</td>
<td>magnetic resonance spectroscopy</td>
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<td>MS</td>
<td>multiple sclerosis</td>
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<td>MT</td>
<td>magnetization transfer</td>
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<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<td>PD</td>
<td>proton density</td>
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<tr>
<td>PPMS</td>
<td>primary progressive multiple sclerosis</td>
</tr>
<tr>
<td>PVE</td>
<td>partial volume effects</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cells</td>
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<tr>
<td>RF</td>
<td>radiofrequency</td>
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<tr>
<td>RMSE</td>
<td>root mean square error</td>
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<tr>
<td>ROI</td>
<td>region of interest</td>
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<tr>
<td>RR</td>
<td>reference region</td>
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<tr>
<td>RRMS</td>
<td>relapsing-remitting multiple sclerosis</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SNR</td>
<td>signal-to-noise ratio</td>
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<tr>
<td>SPGR</td>
<td>spoiled gradient echo</td>
</tr>
<tr>
<td>SPMS</td>
<td>secondary progressive multiple sclerosis</td>
</tr>
<tr>
<td>TE</td>
<td>echo time</td>
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<td>Abbreviation</td>
<td>Description</td>
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<td>---------------------------</td>
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<tr>
<td>TOI</td>
<td>tissue of interest</td>
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<tr>
<td>TR</td>
<td>repetition time</td>
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<tr>
<td>VFA</td>
<td>variable flip angle</td>
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<td>WM</td>
<td>white matter</td>
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Introduction

Magnetic resonance imaging (MRI) is a modality developed in the 1970s. It has since become essential to the diagnosis and follow-up of many afflictions and pathologies, at any body site. Multiple sclerosis (MS) is one of them. MRI is the only means of visualizing MS lesions in the brain and spinal cord in vivo. In particular, new lesions, which are associated with inflammatory processes and blood-brain barrier (BBB) permeabilization, appear as hyperintense on contrast enhanced T$_1$-weighted scans. They are therefore referred to as “enhancing” lesions.

Because MS enhancing lesions are a reliable marker of disease activity, many studies have been performed to assess the effect of MS therapies on the evolution of such lesions [1] [2]. More importantly, the impact of MS therapies on both enhancing lesions and relapse rates has been evaluated, in an attempt to define MRI as a surrogate outcome for MS relapses in clinical trials. In most studies, the sought correlation between enhancing lesions and relapses was however not found [3] [4].

One difficulty in evaluating the effect of a drug from the evolution of enhancing lesion counts, volumes and durations is that these three indicators are sensitive to the parameters of the contrast-enhanced imaging protocol. Studies have clearly shown that the sensitivity to inflammation is improved at 3T vs 1.5T, with a quoted increase in detected enhancing lesions of about 20% [5]. The dose of contrast injected has an even greater impact: the number of detected enhancing lesions increases by about 66% when a triple dose is injected, vs a standard dose [6]. The wait time between injection and imaging was also found to influence the outcome, with low-permeability lesions needing more time to enhance than high-permeability ones [7] [8]. The standard wait time in clinical enhancement protocols is 10 minutes, but the latter studies show that a prolonged wait time of 30–40 min allows for more enhancing lesions (or higher enhancing volume) to be detected.

A recent study, dubbed BECOME for “Betaseron vs Copaxone in Multiple Sclerosis with Triple-Dose Gadolinium and 3-Tesla MRI Endpoints”, aimed at comparing the effects of two
different treatments on enhancement and formation of new lesions [9]. In order to maximize the sensitivity to inflammation, they used a so-called “optimized” protocol for Gadolinium (Gd)-enhanced MRI, consisting in:

- Triple dose Gd-DTPA, administered as a single dose, followed by an extra double dose 20 min later;
- Delayed imaging: 20 min after the second injection, and therefore 40 min after the first injection;
- 3 T field strength.

The results of this study showed no difference in the effect of Betaseron compared with Copaxone in terms of decreasing the number of enhancing lesions. It also showed that neither therapy actually decreased the counts to a high extent. This was in direct contradiction with previous studies performed using a “standard” protocol (i.e. 1.5 T field strength, single dose Gd-DTPA and 5–10 min delay), which had shown that Betaseron was more efficient at reducing the number of enhancing lesions, and that overall both therapies performed well in that respect.

In order to explain these different conclusions, one hypothesis is to view enhancement as a continuous, rather than binary, phenomenon. Each Gd-enhanced protocol can be associated with a BBB permeability threshold of detection: voxels where the BBB permeability is below the threshold do not appear as enhancing, while those where the permeability is above the threshold appear as enhancing.

If the MS therapies do not remove inflammation completely, but rather lower the level of BBB permeability below the threshold of the standard protocol but not below that of the optimized protocol, this could explain why these therapies were found to reduce counts of enhancing lesions with the standard protocol and less so with the optimized one.

Also, BBB permeability of enhancing lesions in patients on Copaxone is thought to be generally higher than in patients on Betaseron. This could in turn explain why there was little difference found between the effects of these two therapies on lesion counts in the BECOME study, when studies using the standard protocol outlined a better efficiency of Betaseron at reducing the number of enhancing lesions.

The work presented in this thesis is part of a larger study that aims at testing the above hypotheses. In practical terms, the study consists of scanning patients with active relapsing-remitting MS and on either interferon or glatiramer acetate therapy, using both protocols and repeated at two different timepoints, for comparison. Each acquisition performed on the 3T scanner is ac-
companied by a dynamic contrast enhanced (DCE)-MRI acquisition allowing the creation of a parametric map of BBB permeability at that timepoint.

At a given timepoint, more lesions and a larger lesion volume are expected with the optimized vs the standard protocol. The discrimination between voxels that enhance on both protocols vs voxels that enhance on the optimized protocol only can hopefully be explained by the BBB permeability map, in terms of sensitivity thresholds. The evolution of lesion counts and volume between two timepoints (typically one month apart) should allow to draw conclusions with respect to the effect of each therapy on the actual BBB permeability level and to explain why enhancing lesions seem to persist longer with the optimized protocol than with the standard one.

In order for this study to be meaningful, the first step is to set up a dynamic imaging protocol that allows an accurate and precise quantitative measurement of the BBB permeability. Most of the work presented in this thesis is related to this first step.

The background chapter briefly goes through the physics of MRI and of DCE-MRI and presents only those concepts that are needed to understand the present work. It also provides some background information on multiple sclerosis and dwells on the multiple roles of MRI in its diagnosis and follow-up. Chapter 2 constitutes a comprehensive literature review on the measurement of BBB permeability and explains the methodological choices made in this work. The following chapters are organized in the classical format: methods, results, discussion and conclusion.
Chapter 1

Background

1.1 A brief introduction to MRI

The development of MRI was a two-step process: the first step was the discovery of the nuclear magnetic resonance (NMR) phenomenon and its application to liquids and solids by Bloch and Purcell in 1946. The second step was taken in 1973 by Lauterbur and Mansfield, who developed the idea of using magnetic field gradients to spatially encode the signal and produce an NMR image. The first duo of scientists was awarded the Nobel Prize in physics in 1952, while the second duo received the Nobel Prize in Physiology or Medicine in 2003. The first paper demonstrating MRI on humans dates back to 1974, when Damadian realized the potential of this technique to distinguish cancerous from normal tissue.

This section will very briefly present the principles behind NMR and MRI. The concept of contrast in an MR image will also be explained, as well as a few basic sequences that have been used for this work. For a more detailed description of NMR and MRI, one can refer to the Principles of Magnetic Resonance Imaging by D. G. Nishimura [10]. The last part deals with concepts specific to DCE-MRI, since it is the main focus of the project.

1.1.1 Basics of NMR physics and image acquisition

NMR

NMR is a quantum phenomenon that can be observed in nuclei with an odd number of protons and/or neutrons, which possess a non zero spin angular momentum $\vec{S}$, usually simply referred to as “spin”. In the human body, the most common elements with a non-zero nuclear spin are hydrogen ($^1$H), sodium ($^{23}$Na) and phosphorus ($^{31}$P). Hydrogen nuclei obviously outnumber the others by far, since our tissues are mainly made of water.

A charged particle with a spin angular momentum also possesses a small magnetic moment
1.1 A brief introduction to MRI

\(\vec{\mu}\). These two quantities are related by a proportionality constant, called the gyromagnetic ratio \(\gamma\). The latter is specific to a given nucleus and is expressed in Hz/T for a reason that will become clear shortly.

\[\vec{\mu} = \gamma \vec{S}\] (1.1)

In the absence of any external magnetic field, the orientation of each of the magnetic moments in a sample of nuclei is arbitrary, and the net macroscopic magnetization of the sample is therefore zero. When an external magnetic field \(\vec{B}_0\) is applied, the distribution of these orientations is no longer random. More specifically, for a spin \(\frac{1}{2}\) particle (such as \(^1\)H), the individual magnetic moments tend to align either parallel or anti-parallel to \(\vec{B}_0\). The parallel state corresponds to the lower energy state, and its population therefore slightly exceeds that of the anti-parallel state, thus creating a net macroscopic magnetization \(\vec{M}\) in the sample. This excess is a function of temperature, field strength and type of nucleus, but at body temperature and in magnetic fields common to MRI (1.5 T – 3 T), it is of a few parts-per-million.

The macroscopic magnetization \(\vec{M}\), which is the sum of the individual magnetic moments \(\vec{\mu}\), precesses around the axis of the magnetic field, as expressed in the following equation:

\[\frac{d\vec{M}}{dt} = \vec{M} \times \gamma \vec{B}\] (1.2)

The frequency of this precession is called the resonant, or Larmor, frequency. It is specific to the nucleus via the gyromagnetic ratio, but also depends on the intensity of the magnetic field:

\[f_{\text{Larmor}} = \frac{\gamma}{2\pi} \cdot B\] (1.3)

The reduced gyromagnetic ratio of the hydrogen nucleus is \(\frac{\gamma}{2\pi} = 42.575\) MHz/T. The resonant frequency at typical MR field strengths is therefore in the radiofrequency (RF) range. It is about 64 MHz at 1.5 T and 128 MHz at 3 T.

Equation (1.2) implies that the magnetization vector maintains the same angle with respect to the axis of the magnetic field indefinitely in time. Of course in practice there are relaxation processes that allow the magnetization vector to gradually reach its equilibrium position of minimum energy. The configuration of minimum energy is one where the spin occupancy of the parallel and anti-parallel states follows the Boltzmann distribution:

\[\frac{n_{\uparrow\downarrow}}{n_{\uparrow\uparrow}} = e^{-\frac{\gamma B_0}{kT}}\] (1.4)

At equilibrium, the global macroscopic magnetization is therefore aligned with the magnetic
Background

In NMR, there are two separate relaxation processes that govern the gradual alignment of the magnetization along the magnetic field, one for each of the two components of the magnetization vector $\vec{M}$: the “longitudinal” component, along $\vec{B}$, and the “transverse” component, in the plane transverse to $\vec{B}$.

The first process is referred to as spin-lattice, longitudinal or $T_1$ relaxation. It consists in the gradual increase of the longitudinal component $M_z$ of $\vec{M}$, empirically approximated to an exponential recovery with a time constant $T_1$ (see Figure 1.1(a)). This relaxation is due to exchanges of energy between each individual spin and the surrounding lattice. The time $T_1$ is therefore dependent on the chemical and physical properties of the spins’ environment – and from a human body perspective on the type of tissue they are part of. $T_1$ increases with the magnetic field strength.

The second process is referred to as spin-spin, transverse or $T_2$ relaxation. It consists in the gradual decrease of the transverse component $M_{xy}$ of $\vec{M}$, empirically approximated to an exponential decay with a time constant $T_2$ (see Figure 1.1(b)). This relaxation is due to both spin-lattice interactions (the same that allow $M_z$ to increase) and to interactions between neighbouring nuclei, but the latter typically dominate the transverse relaxation process in biological tissues. Therefore $T_2 \leq T_1$. The time $T_2$ also depends on the chemical and physical properties of the sample, but it is largely independent on the magnetic field strength.

For convenience, the inverse of relaxation times are sometimes used. They are naturally referred to as $R_1$ and $R_2$ “relaxation rates”.

\begin{figure}[h]
\centering
\begin{subfigure}{0.45\textwidth}
\centering
\includegraphics[width=\textwidth]{T1}
\caption{$T_1$ relaxation. The longitudinal component of the magnetization increases from zero to the equilibrium maximum value $M_0$ with a time constant $T_1$.}
\end{subfigure}
\hfill
\begin{subfigure}{0.45\textwidth}
\centering
\includegraphics[width=\textwidth]{T2}
\caption{$T_2$ relaxation. The transverse component of the magnetization decreases from its initial value back to zero with a time constant $T_2$.}
\end{subfigure}
\caption{\textbf{T}_1 recovery and \textbf{T}_2 decay.} Assuming at time $t=0$ the magnetization is fully transverse to the magnetic field, it will precess at the Larmor frequency while gradually aligning itself with this field. This causes the longitudinal component to increase and the transverse component to decrease, but with two different time constants. \textit{Illustrations from [11].}
\end{figure}
To carry out a proton NMR experiment, the following are necessary:

- A main static magnetic field \(\vec{B}_0\) of high strength and uniformity, to produce a sufficient macroscopic magnetization of the sample. Its orientation is traditionally referred to as the z-axis. The macroscopic magnetization \(\vec{M}\) produced reaches equilibrium (aligned with \(\vec{B}_0\)) with a time constant \(T_1\), where it stays until it is excited by a change in magnetic field;

- A transient magnetic field \(\vec{B}_1\) applied in the transverse direction (xy-plane) by an RF emitter, oscillating at the Larmor frequency. The amplitude of this field is much smaller than \(B_0\) but it tilts the magnetization \(\vec{M}\) away from its equilibrium position precisely because it is tuned close to the intrinsic resonant frequency of the proton. This step is called **excitation** and is illustrated in Figure 1.2. The angle between \(\vec{M}\) and \(\vec{B}_0\) is proportional to the \(\vec{B}_1\) amplitude and to the duration for which it is applied. The final angle at the end of the excitation (i.e. when \(\vec{B}_1\) is turned off) is called the **flip angle**;

- A receiver coil, picking up changes of magnetic flux in the transverse plane in the form of current. After \(\vec{B}_1\) is turned off, the magnetization \(\vec{M}\) will precess about the z-axis at the Larmor frequency, producing an oscillating magnetic flux in the transverse receiver coil, until its transverse component decays to zero with a time constant \(T_2\). This step is called **relaxation**. The initial amplitude of the signal in the receiver coil is proportional to the equilibrium magnetization \(M_0\). The time constant of decay of the signal amplitude (given by the envelope of the signal) corresponds to the \(T_2\) of the sample.

It is essential to bear in mind that the NMR received signal comes solely from the transverse component of the magnetization. Starting from equilibrium, a 90° flip angle for instance rotates all of the magnetization into the transverse plane and provides the maximum possible signal. Any other flip angle \(\alpha\) will only rotate part of \(\vec{M}\) into the transverse plane and the measured signal amplitude will be proportional to \(M_0 \sin \alpha\).

**NMR Imaging**

In the case of a non-uniform sample (such as a human brain) it would be interesting to differentiate the contributions of different locations in the sample to the overall signal, as they may have different water proton density \(M_0\) and relaxation times \(T_1\) and \(T_2\).

The idea used to achieve this is to apply gradients of magnetic field on top of the main constant \(\vec{B}_0\), in each of the three spatial directions.

The first step is to apply a constant gradient along one spatial direction, e.g. the x-axis, while the relaxation signal is being received. This direction is called the **read-out direction**. With that gradient on, protons at different x locations will experience a different magnetic field \(B(x)\) during
Figure 1.2: When the field $\vec{B}_1$ is applied, the magnetization $\vec{M}$ gradually moves away from its equilibrium orientation along the z-axis while precessing around the axis of the effective field $\vec{B}_0 + \vec{B}_1$. The flip angle between $\vec{B}_0$ and $\vec{M}$ increases as long as the $B_1$ field is on. *Illustration from [10].*

relaxation and will therefore precess at different frequencies $f(x)^1$. By associating spatial location to frequency, the 1-D Fourier transform of the received signal will then allow the restoration of signal contributions from each of the x-locations, and will therefore represent a projection along the read-out axis of signal amplitudes in the sample.

For imaging to be possible, it is necessary to somehow restore spatial information along the other two directions as well. In 3D acquisitions, which will be used during this work, the two remaining directions play identical roles. The way to encode spatial information in a direction other than the read-out (e.g. the y-axis) is to apply a gradient for a fixed duration after excitation and prior to read-out. While this gradient is on, the spins at different y locations will naturally precess at different frequencies $f(y)$. When the gradient is turned off, they will be in different phases $\phi(y)$ relative to each other before the read-out starts. This procedure is called **phase-encoding**. If n locations need to be resolved along the phase-encode direction, the experiment (excitation – phase-encoding – read-out) needs to be repeated n times, each time incrementing the amplitude of the phase-encode gradient to produce a different phase distribution than before.

The sampled signals acquired during read-out and for each phase-encode step are placed in a 2D-grid, referred to as “k-space” and a 2D Fourier transform is applied to obtain the 2D

\[ f = \frac{\gamma}{2\pi} B \]
projection of the sample across the xy-plane. This concept extends easily to 3D by applying a phase-encode gradient along the z-axis as well, and taking the 3D Fourier transform of the cuboid k-space thus filled. This ultimately produces a 3D representation of the NMR signal amplitude coming from each voxel.

1.1.2 Image contrasts and imaging sequences of interest

Sequence parameters and choice of contrast

The beauty of MRI – among other things – is that the signal amplitude recorded in a voxel is a function of many parameters, intrinsic and extrinsic. The main intrinsic parameters are the free water proton density PD, and the two relaxation times $T_1$ and $T_2$. The main extrinsic parameters are related to sequence settings, among which are the:

- Excitation flip angle $\alpha$, which determines how much of the longitudinal magnetization will be flipped in the xy plane to be read;
- Repetition time TR, defined as the time between two successive excitations and therefore between the acquisition of two encoding steps;
- Echo time TE, defined as the time between the excitation and the centre of the read-out block.

The extrinsic parameters can be chosen so that the signal is more or less weighted by each of the intrinsic parameters. Free water proton density (PD) varies little across the human body and is not the best source of contrast between tissues, but the $T_1$ and $T_2$ are much more variable across tissues and are therefore better candidates for image contrast. Figure 1.3 shows the same brain slice in a PD-weighted, $T_2$-weighted and $T_1$-weighted image respectively.

Assuming a basic sequence with a 90° flip angle and a long TR allowing the magnetization to fully relax between excitations (i.e. $TR \gg T_1$), a choice of short TE (i.e. $TE \ll T_2$) will produce a PD-weighted image, because the signal intensity will barely have had time to decay and will just reflect the amplitude of the equilibrium magnetization, which is proportional to the PD. In the same conditions, a choice of longer TE (i.e. comparable to the various $T_2$ values across the sample) will produce a $T_2$-weighted image, because the amount of signal in each voxel at the time of read-out will have decreased to an amount dependent on the $T_2$ of the tissue at that location. On a $T_2$-weighted image, bright voxels correspond to tissues with long $T_2$ and darker voxels to tissues with shorter $T_2$.

Achieving $T_1$-weighting is somewhat more complex because again the only measurable signal in NMR comes from magnetization in the transverse plane. The idea is then to use a TR
Background

(a) PD-weighting. The contrast between brain structures (GM, WM and CSF) is not remarkable.

(b) T\textsubscript{2}-weighting. The contrast is much more pronounced between GM, WM and CSF. The latter comes out very bright, while WM is very dark.

(c) T\textsubscript{1}-weighting. The contrast is also very pronounced but the brightness is reversed, with CSF giving low signal and WM highest signal.

Figure 1.3: Axial slice of a healthy brain, as showing on a PDw, T\textsubscript{2}w and T\textsubscript{1}w image. GM = Grey matter; WM = White matter; CSF = Cerebrospinal fluid. Data courtesy of I. R. Levesque.

shorter than the typical T\textsubscript{1}’s so that, before each new excitation, the amount of longitudinal magnetization ready to be flipped and read-out is that which had time to recover within TR, and therefore depends on T\textsubscript{1}. Combined with a short TE to reduce T\textsubscript{2} effects, the signal intensity will be weighted by the T\textsubscript{1} in that voxel. On a T\textsubscript{1}-weighted image, bright voxels correspond to tissues with short T\textsubscript{1} (fast longitudinal recovery makes more initial magnetization available and higher signal) and darker voxels to tissues with shorter T\textsubscript{1}.

Main sequence used in the present work

The core of the MRI acquisitions performed during this study is based on fast T\textsubscript{1}-weighted sequences, with some light variations. The main pattern sequence used is called SPGR, for SPoiled GRadient echo. It is based on short TR and TE values to ensure T\textsubscript{1} weighting, relatively low flip angles, and it uses RF and gradient spoiling before each new excitation pulse to remove any contributions from remaining transverse magnetization to following repetitions. Assuming perfect spoiling before each new pulse, the SPGR signal equation is written:

\[
S_{SPGR} = M_0 \cdot \frac{1 - E_1}{1 - \cos \alpha \cdot E_1} \cdot \sin \alpha \cdot E_2^\ast \quad (1.5)
\]

where

- \( M_0 \) is the constant incorporating the proton density PD and the scanner gain;

- \( E_1 = e^{-\frac{TR}{T_1}} \), with TR being the repetition time;
1.1 A brief introduction to MRI

- $\alpha$ is the flip angle;
- $E_2^* = e^{-\frac{TE}{T_2^*}}$, with TE being the echo time.

The approximation $TE \ll T_2^*$ is often valid given the sequence parameters, and so what is referred to as the SPGR signal equation is:

$$S_{SPGR} = M_0 \cdot \frac{1 - E_1}{1 - \cos \alpha \cdot E_1} \cdot \sin \alpha$$  \hspace{1cm} (1.6)

1.1.3 (Dynamic) Contrast enhanced MRI

The previous section has shown that the contrast of an MR image is a function of many parameters (intrinsic and extrinsic), making MRI a very flexible imaging modality. The extrinsic parameters can be adjusted to best highlight what is sought to be seen in the image. However, some pathologies require the use of a contrast agent (usually injected intravenously) in order to discriminate between healthy and diseased tissue. Contrast agents (CA) in MR are usually paramagnetic or superparamagnetic compounds that locally modify the magnetic environment of the protons and thus change their longitudinal and transverse relaxation rates. They are therefore labelled as indirect CA because they are not themselves visible on the MR image, but rather the effect of their presence is seen through the modified relaxation rates of the hydrogen nuclei in the tissues [12].

Most current MR CA’s are not pathology-specific, but are rather evidence of the anatomy and physiological functioning of circulatory systems, organs or tissues at stake. A typical example of the use of CA in the diagnosis of brain pathology for instance is the evaluation of the integrity of the blood-brain barrier (BBB). In order to protect brain tissue from toxins circulating in the blood, the BBB provides very selective filtering in normal brain tissue. MR CA molecules, although relatively small in size, are already too large to cross it and pass from the blood/plasma pool into the extravascular extracellular space (EES) of brain tissue. However, some pathologies – most predominantly brain tumours, but also inflammatory lesions in MS – are characterized by the local loss of integrity of the BBB, which becomes permeable to the CA. The leakage of CA in a diseased region of the brain can be visualized on contrast enhanced MRI, which helps outline the extent of pathology involving BBB disruption.

The efficiency of a CA to locally alter the $T_1$ and $T_2$ of protons is given by its typical longitudinal ($r_1$) and transverse ($r_2$) relaxivities. Relaxivity is expressed in s$^{-1}$mM$^{-1}$, and measures
the increase in the relaxation rate $R$ of protons at a CA concentration of 1 mM. More explicitly, for CA concentrations of up to 10 mM, the following relationship holds:

$$R_{i, \text{current}} = R_{i, \text{initial}} + r_i \cdot [\text{CA}]$$

where:

- $i = 1$ or $2$
- $R_i$ is the relaxation rate (in $s^{-1}$)
- $r_i$ is the relaxivity (in $s^{-1}\text{mM}^{-1}$)
- $[\text{CA}]$ is the current CA concentration (in mM)

Most paramagnetic CAs used in MRI are complexes of gadolinium (Gd). Their predominant effect is to shorten the $T_1$. This accelerated recovery of longitudinal magnetization results in higher signal intensity on a $T_1$-weighted image. These CAs are therefore referred to as positive contrast media and used in (D)CE-MRI. The details of the paramagnetic relaxation mechanisms are beyond the scope of this thesis, but the phenomenon is classically explained as the added contributions from two spheres of influence of the paramagnetic centre on neighbouring protons: an “inner sphere” involving chemical exchanges and water molecule mobility, and an “outer sphere” involving long-distance dipolar interactions [13].

The superparamagnetic CAs used in MRI usually consist of iron oxides. Their predominant effect is to shorten the $T_2$ and $T_2^*$, which results in reduced signal intensity. These CAs are therefore referred to as negative contrast media and the techniques using them as dynamic susceptibility contrast (DSC)-MRI, rather than DCE-MRI.

The typical protocol to observe enhancing tissues is to image the subject pre-contrast, inject a dose of CA into the subject’s blood system, wait a sufficient amount of time (typically 10–20 min) for the uptake of CA in the tissues to happen, and then run the same sequence to observe regions of enhancement compared to the pre-contrast scan. In DCE-MRI, the term “dynamic” refers to the possibility of acquiring multiple images across time, while the CA spreads through the body, in order to retrieve a time curve of the CA concentration in a given region. For an image acquired at timepoint $t$ of the dynamic series, the relaxation rate $R_1(t)$ in each voxel is:

$$R_1(t) = R_{10} + r_1 \cdot [\text{CA}](t)$$

(1.8)
The analysis of the \([CA](t)\) curve can then provide useful information, such as measurements of the BBB permeability in the case of brain imaging. This will be explained at length in the next chapter.

### 1.2 MRI in the study of multiple sclerosis

#### 1.2.1 What is multiple sclerosis?

Multiple sclerosis is a disease in which the patient’s own immune system attacks the central nervous system (CNS). The disease was first described and named by French neurologist Jean-Martin Charcot in 1868, and although it has been extensively studied since, its exact causes and mechanisms are still poorly understood. The cure – if any – is yet to be found. This introduction is based on recent comprehensive reviews by Compston and Coles [14], and Noseworthy et al. [15].

MS usually starts off in young adulthood (second or third decade of life). There is a strong female/male bias of 2:1. The average prevalence is of around 120 per 100,000, with a lifetime risk of one in 400. However, its prevalence varies greatly around the world, with the regions of highest rates being northern Europe, southern Australia and the middle part of North America. This disparity of prevalence supports both environmental and genetic factors as causes of MS. The mechanisms of disease onset are very likely a combination of the two.

The large majority of autoimmune damage caused by MS occurs in the white matter (WM), where axons lose part of their protective myelin sheath. Demyelinated axons are unable to conduct nervous impulses properly and communication via those axons is impaired. The extent of the damage produced is spatially limited to a region of the brain, referred to as lesion or plaque, and the neurological function relying on communications in that area is affected. A patient with MS typically accumulates plaques in multiple locations, hence the name “multiple sclerosis” – or in French: “sclérose en plaques”.

There are two typical pathways for the course of the disease.

The most common one (80% of patients) is a relapsing-remitting course (RRMS), typically in three stages. The first stage is a succession of “attacks” with inflammation and demyelination (relapses) which are followed by periods of remyelination (remittance) during which the patient can fully recover from the disabilities caused by the attack. Then comes a second stage of continuous inflammation and relapses leading to persistent demyelination (and hence persistent disability). The third stage is a secondary progressive form of the disease (SPMS) characterized
by infrequent inflammation but chronic axonal degeneration and gliosis.

The other 20% of patients present with a progressive form of the disease from the start, hence the name given to this course: primary progressive (PPMS).

In spite of these known pathways, a central issue is that the course of MS in an individual patient is highly unpredictable. Even the most recent diagnostic and follow-up advances using MRI (as detailed in the next section) fail to provide reliable predictions in terms of risk of relapse, eventual disability level and entrance into the progressive phase of the disease.

Existing treatments mainly aim at reducing the frequency of relapses and limiting their lasting effects, but their efficacy is not guaranteed. Clinical trials are challenging because of the unpredictable course of MS, which makes it difficult to assess the success of a drug on the long-term based on short-term observations.

Nonetheless, patients are expected to live at least another 25 years from disease onset, with most of them dying from unrelated causes.

1.2.2 MRI as a diagnostic and follow-up tool in MS

As explained in the introductory section on MRI, $T_1$ and $T_2$ relaxation times are representative of the chemical and microstructural environment of the proton. The processes associated with MS lesion formation or permanency – inflammation, demyelination, axonal degeneration, gliosis... – all translate into changes of the protons’ environment at the site of the lesion. Therefore, an MRI conventional scan, be it $T_1$- or $T_2$-weighted, will show MS lesions as regions of different signal intensity than in the surrounding normal WM.

The sensitivity of this modality is such that conventional MR imaging highlights CNS abnormalities in 95–100% of patients with clinically definite MS [16]. This imaging technique has even made its way into the diagnostic criteria for MS: assessment of clinically definite MS should be based on the occurrence of two attacks and either clinical evidence of two lesions or clinical evidence of one lesion plus paraclinical evidence of a second lesion. MRI data is regarded as paraclinical proof of a lesion. However, CNS abnormalities as detected on MRI are not MS-specific, therefore the diagnosis of the disease should ultimately still be based on clinical evidence [17].

Among the “conventional” methods, $T_2$-weighted scans are considered most sensitive in the detection of MS lesions. The latter appear as hyperintense on the image, due to the prolonged $T_2$ compared to normal WM (see Figure 1.4(a)). The drawback associated with this sensitivity is however the lack of specificity of $T_2$ hyperintense lesions. Not only are they markers of many processes associated with MS, but they are also encountered in numerous other WM pathologies.
1.2 MRI in the study of multiple sclerosis

(a) $T_2$-weighted lesions. The arrows point to the $T_2$ hyperintense lesions. The areas of WM abnormality highlighted on this type of scan are often extensive.

(b) $T_1$-weighted lesions. The arrows point to the $T_1$ hypointense lesions. When chronic, the areas of WM abnormality highlighted on this type of scan are specific markers of tissue destruction.

Figure 1.4: Axial slice of an MS patient brain as showing on a $T_2$-weighted and $T_1$-weighted image, respectively. Data courtesy of I. R. Levesque.

Nonetheless, in patients with clinically definite MS, the evolution of $T_2$ lesion load in time is a reasonable indicator of disease activity and/or response to treatment [15].

Hypointense lesions on $T_1$-weighted scans – also due to the prolonged $T_1$ compared to normal WM – are evocative of either acute edema or tissue destruction (see Figure 1.4(b)). Their extent is more restricted compared to $T_2$ lesion load but chronic “black holes” (hypointensities on $T_1$-weighted scans) are a more specific marker of permanent tissue destruction than $T_2$-weighted lesions [17].

As mentioned in the introduction, hyperintense lesions on contrast enhanced $T_1$-weighted scans are very specific markers of inflammation and activity of the disease. Indeed, the contrast agent is able to leave the blood/plasma and enter the EES in the WM wherever the BBB is disrupted, thus making the regions of inflammation visible with (D)CE-MRI. These so-called “enhancing lesions” last for a brief period of time, usually four to six weeks. They may or may not evolve into permanent $T_2$-lesions. Patients with a recent or current relapse will usually display enhancing lesions, but the latter can be found without any clinical evidence of a relapse. In fact, there is five to ten times more activity detected with Gd-enhanced scans than on clinical assessments [18]. The characterization of these enhancing lesions in terms of number and volume,
and the more challenging measurement of the associated BBB permeability through DCE-MRI are the main focus of this work.

Aside from these “conventional” imaging methods, MRI bears the promise of new semi-quantitative or quantitative methods that would provide more specific and accurate estimates of the extent and the severity of various damages caused by MS, as reviewed by Filippi and Grossman [19].

**Magnetization transfer (MT) MRI** in the CNS is based on the interaction between protons from the tissue water (considered as free) and protons from the macromolecules of myelin (considered as bound, thus having a much broader resonance). These two pools constantly exchange magnetization and therefore saturating the bound protons with an off-resonance pulse impacts the overall signal. The amount of signal reduction is given by the MT Ratio (MTR) and is an indirect measurement of the amount of macromolecules in a given voxel. In the case of MS, it is therefore an indicator of myelin loss and reduced axonal density.

**Diffusion-weighted (DW) MRI** also has the potential to measure structural breakdown in the WM. Diffusion in the normal WM is highly anisotropic since it is very restricted transverse to the axons and almost free along the axons. Myelin loss and axonal degeneration therefore result in locally increased isotropy on DW-MRI.

**Magnetic resonance spectroscopy** (MRS) can provide information on a number of metabolites involved in MS processes, such as choline, lactate and N-acetylaspartate. Lipids, which are normally invisible to MRS due to extremely fast relaxation in a restricting environment, can become observable on spectra precisely if the macromolecular structure of membranes is damaged by the disease and they become free.

MRI offers a wide range of possibilities for detecting abnormalities in the CNS caused by MS. Most of these methods are summarized in Table 1.1. Unfortunately, the correlation between MR images and clinical observations is variable [16]. For instance, new active lesions can be detected on MRI without any corresponding clinical signs. There is also no close correlation between the clinical disability status scale and the burden of disease as measured on MRI. Neither does the latter correlate well with duration of disease.

Although MR images present themselves as an appealing outcome of MS clinical trials, they have therefore not been validated yet as primary outcome measures for phase III trials [17]. More investigations need yet to be done to understand the correlation between the effects of a treatment on MR measures on the one hand, and on the actual evolution of the disease in the patient on the other hand.
### Table 1.1: Conventional and advanced MRI techniques and MS measures.

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<th>MRI sequence</th>
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<th>Advantages</th>
<th>Disadvantages</th>
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<td>PD/T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Lesions, disease burden</td>
<td>Robust across different scanners, assessed in most trials</td>
<td>No pathology specificity, periventricular lesions difficult to see</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Lesions, disease burden</td>
<td>Lesion conspicuity and lesion-to-CSF contrast</td>
<td>No pathology specificity</td>
</tr>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Structural integrity</td>
<td>Overall structural information, atrophy</td>
<td>Insensitive to many aspects of MS pathology</td>
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<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt; Gd-enhanced</td>
<td>BBB breakdown in earlier active lesions</td>
<td>Assessment of disease activity</td>
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<td>T&lt;sub&gt;1&lt;/sub&gt; hypointensity</td>
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</tr>
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</table>

*PD = proton density; FLAIR = fluid-attenuated inversion recovery; BBB = blood-brain barrier; MRS = magnetic resonance spectroscopy.*
Measuring blood-brain barrier permeability

2.1 T₁ relaxometry

The background chapter briefly explained how the concentration of contrast agent as a function of time in a voxel, \([CA](t)\), can be derived from the change in the longitudinal relaxation rate in that same voxel, using:

\[ [CA](t) = \frac{\Delta R_1}{r_1} = \frac{R_1(t) - R_{10}}{r_1}, \]  

(2.1)

where \(r_1\) is the relaxivity of the contrast agent for the given set of experimental parameters: magnetic field strength, pH and temperature. \(R_{10}\) is the initial longitudinal relaxation rate, before the injection of CA.

The time curve of CA concentration is needed to estimate the BBB permeability, as will be explained in the next section. In order to obtain sufficient sampling of the CA uptake curve, \(T_1\) (or equivalently, \(R_1\)) parametric maps need to be acquired with a temporal resolution sufficient to capture the dynamics of the system.

Several methods have been developed for quantitative \(T_1\) measurements – also called \(T_1\) relaxometry. One of the fastest and most popular for \textit{in vivo} applications with limited time is the variable flip-angle (VFA) method. It consists of multiple (usually two or three) 3D SPGR acquisitions, each using a different flip angle (FA). Rearranging the SPGR signal equation (see Equation (1.6) page 23) for each of the FA \(\alpha_i\),

\[ \frac{S_i}{\sin \alpha_i} = \frac{S_i}{\tan \alpha_i} E_1 + M_0(1 - E_1) \]  

(2.2)

we see that there should be a linear relationship between \(x = \frac{S_i}{\tan \alpha_i}\) and \(y = \frac{S_i}{\sin \alpha_i}\), with a slope \(m = E_1\) and an intercept \(b = M_0(1 - E_1)\).

If data is acquired with at least two flip angles, a linear fit can be performed on Equation (2.2)
2.2 The pharmacokinetic model

Following a CA injection, DCE-MRI allows the measurement of contrast agent concentration across time. The role of MRI stops here. In order to produce quantitative maps of BBB permeability and of the volumetric fraction of EES available to the CA, one needs to use a model that can relate the evolution of CA in time to the physiological parameters sought.

2.2 The pharmacokinetic model

Following a CA injection, DCE-MRI allows the measurement of contrast agent concentration across time. The role of MRI stops here. In order to produce quantitative maps of BBB permeability and of the volumetric fraction of EES available to the CA, one needs to use a model that can relate the evolution of CA in time to the physiological parameters sought.

\[ T_1 = -\frac{TR}{\ln m} \]  
\[ M_0 = \frac{b}{1-m} \]

The higher number of FA’s used, the better the accuracy and precision on \( T_1 \) and \( M_0 \) estimates. But more FA’s also means longer acquisition time in order to produce one set of \( T_1 \) and \( M_0 \) parametric maps. A method was recently developed, using the principles of VFA, that allows \( T_1 \) and \( M_0 \) estimates with approximately 5% standard error, using the minimum of two flip angles. The method was dubbed DESPOT1, for Driven Equilibrium Single Pulse Observation of \( T_1 \) [20]. DESPOT1 includes a method for calculating the two flip angles that will give optimal accuracy and precision, depending on the \( T_1 \) values expected. Thus the acquisition can be optimized for \( T_1 \) measurements in either WM, GM, blood, etc. For \( T_1 \) values outside of the optimized region, the method is expected to perform less well, with systematic – but still acceptable – errors in the relaxation times calculated. Of these two optimized flip angles, one is usually low – producing a PD-weighted image – and the other one relatively large – producing a \( T_1 \)-weighted image.

In the pursuit of minimizing acquisition time to achieve the best temporal resolution possible in a DCE-MRI study, one can also consider that the constant factor \( M_0 \) would not change during the entire procedure, provided that the scanner gain is not readjusted in-between images. If initial maps of \( T_1 \) (i.e. \( T_{10} \)) and \( M_0 \) are acquired right before contrast injection using the DESPOT1 method, the dynamic acquisition during the CA circulation can be a series of 3D SPGR images using a single flip angle (the larger one that gives \( T_1 \) contrast). Each of these \( T_1 \)-weighted images can be made into a \( T_1 \) parametric map using the previously acquired \( M_0 \) map and inverting the SPGR signal equation (1.6):

\[ E_1 = \frac{S - M_0 \sin \alpha}{S \cos \alpha - M_0 \sin \alpha} \]

The temporal resolution of the DCE-MRI acquisition can thus be increased by a factor of 2, because for each \( T_1 \) parametric map, only one SPGR image need be acquired, instead of two.
The most common model used in such studies – including the present work – was described as early as 1951 by Kety [21]. It considers the exchange between two pools separated by a permeable membrane or barrier. A detailed description of this model in the context of DCE-MRI can be found in work by Tofts [22].

Figure 2.1: The two-compartment pharmacokinetic model used for the analysis of DCE-MRI data for the purpose of extracting the physiological parameters $K_{\text{trans}}$ and $v_e$. $K_{\text{trans}}$ is the transfer rate constant between the two compartments, across the BBB. The model assumes equal forward and reverse rates. $v_e$ is the fraction of extravascular extracellular space (EES) volume per unit tissue volume. With fast intravenous CA input, the concentration in the plasma increases rapidly and the CA begins to leak into the EES through the disrupted BBB. Once the concentrations are equal between the plasma and EES compartments, the CA is able to flow back from the EES into the plasma as it is slowly cleared out of the plasma by the kidneys. The CA that penetrates the tissue is confined to the EES and does not enter the cells.

The two pools at stake here are the plasma and the EES of the brain. They are separated by the blood-brain barrier, as illustrated in Figure 2.1. The contrast agent is assumed to be well mixed within each of the pools. Its rate of flow from the plasma to the EES and/or back depends on three parameters: blood flow (supply to the tissue), BBB permeability and surface area available for exchange. Cell membranes are not permeable to the contrast agent, so that CA concentration in the intracellular space – be it brain tissue cells or red blood cells – is zero.

The rate of change of CA concentration in the EES, $C_e$, is written:

$$v_e \cdot \frac{dC_e}{dt} = K_{\text{trans}} \cdot [C_p(t) - C_e(t)] \quad (2.6)$$
• $v_e$ is the volume of EES per unit volume of tissue

• $C_e(t)$ is the CA concentration in the EES at time $t$ (in mM)

• $C_p(t)$ is the CA concentration in the plasma at time $t$ (in mM)

• $K_{trans}$ is the transfer constant (in $s^{-1}$ or $min^{-1}$)

MS inflammatory lesions are associated with only mild BBB disruption (compared with cases of more severe disruption that can occur in brain tumours for example) which, combined with a bolus injection of CA, makes it reasonable to assume that the leakage from the plasma to the EES is permeability-limited. That is to say that the transfer constant between the two compartments is dominated by the barrier permeability\(^1\). In the permeability-limited regime, the transfer rate can be expressed as:

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

• $P$ is the barrier permeability (in cm\(^{-2}\)s\(^{-1}\))

• $S$ is the exchange surface area per unit mass density of tissue (in cm\(^5\)g\(^{-1}\))

• $\rho$ is the tissue density (in g cm\(^{-3}\))

In this case, the transfer rate is proportional to the sought BBB permeability. For convenience, $K_{trans}$ is therefore often referred to directly as “permeability”. This lexical shortcut is also adopted in the present work.

Solving the differential equation (2.6) gives the following solution for the concentration in the EES:

$$C_e(t) = \frac{K_{trans}}{v_e} \int_0^t C_p(u) \exp \left( \frac{K_{trans}}{v_e} (t-u) \right) du$$

(2.7)

However, the quantity that is measurable with DCE-MRI is the average CA concentration in the tissue within a voxel, labeled $C_t$. Since the contributions to concentration in tissue are from either plasma or EES, then:

$$C_t(t) = v_e C_e(t) + v_p C_p(t)$$

(2.8)

where $v_p$ is the volumetric fraction of plasma in the voxel.

\(^1\)The opposite extreme case is a flow-limited regime, in which the transfer constant is dominated by the supply of CA to the plasma pool, i.e. by blood flow and CA intake rate.
In a voxel that is purely blood (in an artery or vein), $v_e = 0$ and $v_p = (1 - Ht)$, with $Ht$ referring to the hematocrit. Thus equation (2.8) becomes:

$$C_{\text{blood}}(t) = (1 - Ht) \cdot C_p(t)$$ (2.9)

In a voxel that contains white matter – be it normal tissue or inflammatory lesion – $v_p$ is often assumed negligible\(^2\) and $C_t$ in equation (2.8) can be approximated as:

$$C_t(t) \approx v_e C_e(t)$$ (2.10)

$$C_t(t) = K_{\text{trans}} \int_0^t C_p(u) \exp\left(-\frac{K_{\text{trans}}}{v_e}(t-u)\right) du$$ (2.11)

If $C_t(t)$ and $C_p(t)$ are known, permeability $K_{\text{trans}}$ and fraction of leakage space $v_e$ can be extracted from equation (2.11) using a non-linear least squares fitting algorithm.

From now on, the concentration of CA in the tissue of interest – in our case MS enhancing lesions – will be referred to as $C_t$. Concentration in the plasma and in the blood will be designated by $C_p$ and $C_b$, respectively.

In all DCE-MRI studies, $C_t(t)$ is measured following CA injection, and the literature is relatively consensual regarding the methods to do that. Contrastingly, the approaches to obtaining the plasma curve $C_p(t)$, often also referred to as the “arterial input function” (AIF), are highly debated in the literature. Section 2.3 gives a description of the current various theories on the matter. It also presents the reasons for the choices made in this study with respect to the AIF issue.

### 2.3 The Arterial Input Function (AIF)

There are multiple reasons why a direct measurement of the AIF is challenging and why there is much controversy on the protocol. First of all, a main blood vessel is not always present in the field of view (FOV) of the acquired images. A method to bypass this problem is to physically collect blood samples from the subject at regular timepoints and analyze them afterwards to determine the CA concentration. However this method is invasive and has intrinsic poor temporal resolution and timing accuracy. Second, even if a blood vessel is present to be imaged, the rate of change of CA concentration in the blood in the first minute following injection – the so-called “first-pass bolus” – is so high that imaging techniques were, until recently, not rapid enough to provide appropriate temporal sampling. Moreover, blood vessel MRI images can be corrupted by flow artifacts. Last but not least, it is not certain whether the linear relationship between $R_1$

\(^2\)This is not the case in tumour voxels for instance, where there is a significant amount of vasculature.
relaxation rate and CA concentration holds for the high concentration values encountered in the
blood during the first pass bolus.

There are currently three primary approaches to obtaining an AIF to use in equation (2.11)
and enable estimation of $K_{\text{trans}}$ and $v_e$:

- Use a population-averaged AIF extracted from individual blood vessel AIF measurements
  in one cohort and then apply a model to fit the averaged data, thus producing an analytical
  expression of a “standard” AIF to be used in any other population [23], [24], [25];

- Use an individually measured AIF – acquired simultaneously with the DCE-MRI data in
  the tissue of interest – either in its sampled form or fitting a model to the experimental data
  points [25], [26];

- Avoid the problem by comparing the CA uptake curve in the tissue of interest to that in
  a reference tissue with known permeability and EES fractional space values [27] – e.g. a
  muscle.

2.3.1 Population-averaged AIFs

The main reason for using a population-averaged AIF is that an individual AIF measurement
is not easily obtainable. Studies have shown that it also allows for improved reproducibility of
estimated parameters versus an individual AIF [24], [25]. Other studies have shown however that
when using a population-averaged AIF, the output $K_{\text{trans}}$ does not benefit from sufficient dynamic
range and that the result does not compare favourably with that obtained using an individual
AIF [28].

On the one hand, it is generally thought that, when using a population-averaged AIF, the
observed changes in $K_{\text{trans}}$ and $v_e$ between scans can be attributed to genuine changes in tissue
structure, and that the bias introduced by using a standard AIF instead of a measured individual
one is small and stable between sessions.

On the other hand, the undeniable limitation associated with using a population-averaged AIF
is that it is insensitive to both inter- and intra-patient variability; combining a direct measurement
of the CA uptake curve in the lesion with a standard AIF means that physiology and injection
protocol differences will only be rendered in one of the two curve shapes and will therefore lead
to errors in the estimates of parameters such as $K_{\text{trans}}$ and $v_e$. Moreover, when seeking to com-
pare the sensitivities of two protocols by determining a permeability threshold below which MS
enhancing lesions are visible with one but not the other protocol, this measurement of perme-
ability should be as quantitatively accurate and unbiased as possible.
These model-based AIFs are nonetheless used extensively in numerous DCE-MRI studies. The following two paragraphs describe the earlier model established by Tofts et al. and the more recent models that stem from acquisitions with increased temporal resolution.

**Tofts’ bi-exponential AIF** This AIF model was derived theoretically by Tofts et al. [23] on the basis that the concentration in the plasma decreases with two phenomena: the exchange between the plasma and EES compartments, and the clearance by the kidneys. Hence in Tofts’ vision the plasma curve starts off at its maximum instantaneously with the injection and then decays biexponentially with a fast component (equilibration between plasma and EES concentrations) and a slow component (kidney clearance). It can be expressed analytically as:

\[
C_p(t) = D \cdot [a_1 \exp^{-m_1 t} + a_2 \exp^{-m_2 t}]
\]

where D is the dose of CA injected, expressed in mM/kg.

Tofts then used data acquired by Weinmann et al. after Gd-DTPA injections [29] to estimate the \((a_1, m_1, a_2, m_2)\) parameters through a fitting procedure. The resulting analytical AIF was assumed to be valid for any human subject and subsequently used in BBB permeability measurements with Gd-DTPA in new patients. Figure 2.2 illustrates the shape of this AIF with a standard dose of 0.1 mM/kg of Gd-DTPA and explicits the values of \(a_1, m_1, a_2\) and \(m_2\) parameters.

![Figure 2.2: Theoretical plasma concentration curve (AIF) in the first 20 minutes following a 0.1 mM/kg bolus injection of Gd-DTPA, as modelled by Tofts et al. [23], using averaged data from Weinmann et al. [29].](image)

Although this AIF formula is still used in some recent studies [30], its limitations and sources
of error are obvious:

- It was assumed that the AIF is at its maximum at \( t = 0 \), i.e. at the start of the injection; although the injection is fast, its duration is nonetheless still on the order of 5–10 seconds and the initial increase in the plasma pool is therefore measurable with current temporal resolutions of about 5 seconds. More importantly still, the actual arrival time of the bolus in the plasma pool is unknown with this approach and is arbitrarily set to be the injection start time; again depending on actual experimental conditions (subject’s venous system, injection delays – especially with manual injections, etc.) this very likely leads to erroneous offsets in matching the timing of the plasma curve with that of the uptake curve in the lesion.

- The temporal resolution of the acquisition used at the time of Tofts et al.’ experiments is insufficient to sample the early components of the AIF; later acquisitions with a temporal resolution of 5 s or lower demonstrated that, prior to the biexponential decay modelled by Tofts et al., the AIF displays an extremely sharp rise and drop within the first 40–50 seconds after injection start, corresponding to the first pass of the CA through the circulatory system (the first-pass bolus) before it has time to spread in the tissues. Because the AIF is convolved with the exponential term \( \exp^{-K_{\text{trans}}/v_c} \) to produce \( C_t \) (see equation (2.11)), the correct incorporation of this first-pass peak into the AIF is expected to have non-negligible effects on permeability and leakage space estimates, as will be evaluated later on.

Recent models incorporating the first-pass peak Improved and more efficient MRI sequences now allow for dynamic acquisitions with a temporal resolution of 5 seconds or less. With new data depicting the early part of the plasma curve, new models to be fit to population-averaged curves were proposed.

Parker et al. [24] suggested a model for the AIF fit as the sum of two gaussians (modelling the first and second pass peaks) and of an exponential modulated with a sigmoid function (modelling the “tail” of the AIF). This form of AIF involves 10 independent parameters to be fit to the data. Figure 2.3 illustrates the standard AIF stemming from Parker’s study on 67 acquired and averaged AIFs from 23 cancer patients.

McGrath et al. [25] recently compared this sophisticated model to three simpler ones: Tofts’ bi-exponential model\(^3\), an improved version allowing for a linear upslope before the bi-exponential decay, and a single gaussian combined with an exponential. The shape of each of these models is

---

\(^3\)Although the authors claim that this model is based on Tofts and Kermod’s work, the decay rates of the two exponential components they extract are too high to correspond to what Tofts and Kermode had described as equilibration between the plasma and the tissues and clearance by the kidneys. The acquisition times over which the fit is applied are also very different: 120 min in Tofts and Kermode’s paper and 5 min in McGrath et al.’s
Figure 2.3: Theoretical plasma concentration curve (AIF) in the first 10 minutes following a 0.1 mM/kg bolus injection of Gd-DTPA, as modelled by Parker et al. [24] after averaging data from 67 individually measured AIFs with a 5 s temporal resolution. The time scale is limited to 10 minutes for the first- and second-pass boli to be visible, but note how the decrease is more rapid than in Tofts et al.’s AIF. Also Parker et al. provide an analytical form for the concentration curve in the blood. This graph represents the concentration curve in the plasma, using a female hematocrit value of 0.38.

illustrated in Figure 2.4, but the fit parameters provided are for AIFs in rats and are therefore not directly applicable to human studies. The conclusion of their study was that the biexponential model with a linear upslope, applied to a population-averaged sampled plasma curve, provided best repeatability and sensitivity to genuine pathological change. However, all these studies underline that models applied to an average AIF are recommended only if the individual data suffer from insufficient temporal resolution or low signal-to-noise ratio (SNR), or if no individual data are obtainable.

There might be advantages to fitting a model to an individually acquired AIF over using the raw sampled data, if the data are noisy. If that is done, the model incorporating a linear upslope and a bi-exponential decay indeed seems the most reasonable in terms of providing a close fit to what is observed in practice and keeping the number of fit parameters reasonably low. In that case however, the start time and peak time should also be determined from the fitting procedure, as detailed later on in Section 3.1.2.
2.3 The Arterial Input Function (AIF)

Figure 2.4: Theoretical plasma concentration curve (AIF) in the first 10 minutes following a 0.1 mM/kg bolus injection of Gd-DTPA, as depicted by 4 different models explored by McGrath et al. [25]. These models can be fit either to a population-averaged sampled AIF or to an individual sampled AIF. Model B appeared as the best compromise between quality and robustness of the fit.

2.3.2 The reference region approach

The reference region model was first described by Yankeelov et al. [27]. Unlike the acquisition of an AIF, this approach does not require high temporal resolution images, hence its initial appeal.

The start point is writing the rate equation (see Equation (2.6)) for both the tissue of interest (TOI) and a reference region (RR) – typically a muscle – and then combining the two equations to cancel the plasma concentration $C_p(t)$. This yields:

$$\frac{dC_{TOI}}{dt} + \frac{K_{trans,TOI}}{v_e,TOI} \cdot C_{TOI}(t) = \frac{K_{trans,TOI}}{K_{trans,RR}} \cdot \frac{dC_{RR}}{dt} + \frac{K_{trans,TOI}}{v_{e,RR}} \cdot C_{RR}(t) \quad (2.13)$$

And after integration:
\[ C_{TOI}(t) = \frac{K_{\text{trans,TOI}}}{K_{\text{trans,RR}}} \cdot C_{\text{RR}}(t) + \frac{K_{\text{trans,TOI}}}{K_{\text{trans,RR}}} \left[ \frac{K_{\text{trans,RR}}}{v_{e,RR}} - \frac{K_{\text{trans,TOI}}}{v_{e,TOI}} \right] \cdot \int_0^t C_{\text{RR}}(t) \cdot \exp \left( -\frac{K_{\text{trans,TOI}}}{v_{e,TOI}} (t-u) \right) du \]  

(2.14)

The concentration curves \( C_{TOI}(t) \) and \( C_{\text{RR}}(t) \) are both measured after CA injection. They are assumed to vary slowly enough to be acquired with sufficient sampling by a standard DCE-MRI sequence.

In order to extract \( K_{\text{trans,TOI}} \) and \( v_{e,TOI} \) from Equation (2.14) using a non-linear least squares algorithm, values for \( K_{\text{trans,RR}} \) and \( v_{e,RR} \) should be input as known parameters. Alternatively, only one of the two can be input as a known parameter (usually \( v_{e,RR} \)) and a three-parameter fit run on Equation (2.14).

The main issue with this method is therefore assigning \( K_{\text{trans,RR}} \) and \( v_{e,RR} \) values. Although it may be reasonable to believe that permeability and EES volume fraction suffer from little inter- and intra-patient variability in a healthy well defined tissue, assuming incorrect values to start with has been shown to lead to significant errors on \( K_{\text{trans,TOI}} \) and \( v_{e,TOI} \). Moreover, Vincensini et al. [31] have shown that permeability and EES volume fraction vary among different types of muscle fibres. In our particular study, obtaining data on permeability and EES volume fraction for a muscle that would be in the FOV with the brain seemed like a difficult, if not impossible, task. Although the cheek muscle might have been a candidate, it would have required enlarging the FOV of the acquisition, with loss in either scan time or spatial resolution. Also, reliable data on the characteristics of cheek muscle were not found. Finally, the cheek muscle often shows movement artifacts due to patient swallowing during the scan.

Yankeelov et al.’s later work on carcinomas in rats [28] highlighted that parameter values extracted using the RR method were much less precise than using the individual AIF method.

In the current study, because we were seeking to produce quantitatively accurate and precise measurements of \( K_{\text{trans}} \) and \( v_e \) values in MS enhancing lesions, we decided to perform the analyses using an individual AIF measured on each scan. This choice was supported by the fact that we could obtain a temporal resolution of 5 s, deemed sufficient to accurately sample the first-pass bolus in the AIF. The second argument in favour was the lack of requirement of a power injector, since the measurement allowed to retrieve any variations in terms of CA arrival time, injection rate and duration. We chose to estimate the AIF from the sagittal sinus vein located at the back of the head. It appeared as the best choice because of its large size (to avoid partial volume effects (PVE)) and because flow artifacts in veins are much less pronounced than in arteries. Also, neglecting the dispersion between arterial and venous concentrations in the head is a reasonable
approximation.

2.4 Assumptions and approximations

Before moving on to describing the experimental methods used in this work, it is essential to highlight all the assumptions and approximations made in the various methodological blocks described above: $T_1$ relaxometry, the pharmacokinetic model and the AIF measurement.

2.4.1 $T_1$ parametric maps

The use of the SPGR signal equation (Equation (1.6)) intrinsically assumes that the sequence provides perfect spoiling of magnetization between applied RF pulses. In practice, spoiling is never perfect – and not even optimal – on 3D SPGR sequences readily available from the scanner library. The level of spoiling in these sequences is sufficient to produce $T_1$-weighted images free of spurious patterns of signal increase or loss, but may be insufficient to allow accurate $T_1$ relaxometry to be performed. Recent works [32], [33] have attempted to quantify the error in $T_1$ estimates produced by using a suboptimally spoiled sequence, as well as to describe efficient combinations of spoiling RF incrementation and crusher gradient moments to be used when doing VFA relaxometry. But these modified SPGR sequences were not evaluated and implemented for our work. We assume that in the range of low FA used here ($< 20^\circ$) the remaining magnetization before each new RF pulse is small enough to introduce negligible error in the $T_1$ calculation. This remaining magnetization was however not measured with the specific scanner and sequence used.

At high fields, the inhomogeneity of RF excitation across the FOV becomes non negligible. The RF inhomogeneities expected at 3T would typically give flip angles varying from 70% to 120% of the theoretical value across the FOV. The calculation of $T_1$ and $M_0$ in a given voxel from the SPGR signal equation requires the knowledge of the actual flip angle applied at that location, which may therefore be quite different from the theoretical flip angle. Accurate $T_1$ relaxometry at 3T would therefore require the acquisition of a $B_1$ map to correct for variations in the flip angle. Rapid methods for $B_1$ mapping are proposed and discussed in the recent literature [34], [35], [36], [37] but they were not implemented for use in the current study. The $T_1$ and $M_0$ maps produced will therefore necessarily be biased by RF excitation inhomogeneities. However, we note that $B_1$ mapping can be easily applied to our protocol without affecting temporal resolution or other processing steps.
2.4.2 The pharmacokinetic model and AIF measurement

The linear relationship between CA concentration and change in the longitudinal relaxation rate (see Equation (2.1)) is widely used in DCE-MRI data analysis. It is important nonetheless to bear in mind its two underlying assumptions, that may be invalid in some cases.

The first major assumption is that within a given voxel, water protons are in the fast exchange limit, so that the whole voxel relaxes at a single rate (which is then the volume weighted average of various compartment rates). A very comprehensive study of the influence of water diffusion and exchange on contrast enhancement was carried out by Donahue et al. [38]. The assumption that water diffuses freely within one compartment on the time scale relevant to MRI (millisecond) is reasonable enough. However, the stronger assumption that there is fast proton exchange between various compartments contained in a single voxel is not always valid. Indeed, one voxel usually contains several different compartments between which diffusion experiences some form of hindrance (e.g. plasma, red blood cells (RBC), extravascular extracellular space and extravascular intracellular space).

The fast-exchange limit is valid between the two most important pairs of compartments (plasma-RBC and cellular-interstitial spaces), for most sets of parameters used (CA dose, sequence timings, physiological times). However, care must be taken when considering water exchange between vascular and extravascular spaces because it is usually in the slow- to intermediate-exchange regime. In this study on enhancing lesions in the WM, we assumed that the plasma compartment inside a WM voxel was negligible, and reciprocally that the voxels segmented in the sagittal sinus were free of PVE, hence little cohabitation between the vascular and extravascular spaces within one voxel.

The second assumption made in most DCE-MRI studies is that the relaxivity value $r_1$ is the same in all tissues. It is well known that the relaxivity of a contrast agent depends on magnetic field strength, temperature and pH. Producing a table of relaxivity values for different sets of these parameters is not unfeasible since those parameters are easy to manipulate. However, relaxivity also depends on the macromolecular content of the sample of interest [39], a range of possibilities which is less obvious to cover in a look-up table. An accurate study in our case would require relaxivity values for Gd-DTPA at 3T, and for Gd-BT-DO3A at 1.5T and 3T, at 37°C and neutral pH, in: plasma, blood, normal WM and diseased WM. To underline the degree of variability of the relaxivity with medium, Table 2.1 provides a few reference values for the relaxivity $r_1$ of Gd-DTPA and Gd-BT-DO3A.

The values for WM are not readily found in the literature to the best of our knowledge, and in this study are approximated to those in plasma, as presented by Rohrer et al. [40].
### 2.4 Assumptions and approximations

<table>
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<tr>
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<th>Gd-DTPA</th>
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<th>Gd-BT-DO3A</th>
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<td></td>
<td>Water</td>
<td>Plasma</td>
<td>Blood</td>
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<tr>
<td>1.5 T</td>
<td>3.3 (±0.2)</td>
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<td>3 T</td>
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**Table 2.1:** Relaxivity values of Gd-DTPA and Gd-BT-DO3A at 37°C and pH = 7, in two common field strengths and in three different media, as provided by Rohrer *et al.* [40]. The relaxivity values are expressed in units of mM$^{-1}$s$^{-1}$.

Other assumptions more intimately related to the two-compartment pharmacokinetic model used to extract BBB permeability and EES fraction from DCE-MRI data have already been suggested but are once more listed below:

- We are in a permeability-limited regime in which blood supply is not considered, hence the rate of CA exchange between the plasma and the EES is strictly governed by the permeability of the BBB;

- The transfer constant $K_{\text{trans}}$ between plasma and EES is the same in both directions (influx and efflux);

- Each of the compartments is well mixed, i.e. the CA concentration at a given timepoint is the same anywhere in the blood, or the plasma, or the EES;

- Concentrations in the plasma and blood are related through the hematocrit value;

- The dispersion kernel between arterial and venous concentrations is neglected, and the AIF is measured as CA concentration in a vein, and rescaled to concentration in the plasma using the hematocrit;

- Contributions to the overall CA concentration measured in a voxel in the WM (enhancing due to BBB disruption) are limited to CA present in the EES: the contribution from blood or plasma present in that voxel is negligible.
Methods

The research plan for this project consisted of two objectives. The first objective was the development of a protocol that allows for accurate measurement of BBB permeability in the brain of an MS patient. The first section of this chapter describes how the protocol was established, tested on patients for feasibility and evaluated through simulations. The second objective was the initiation of a comparative study of enhancement between the optimized and the standard non-dynamic protocols and the analysis of preliminary results. The methods involved in this step are described in the second section of the chapter.

Patient recruitment  Recruiting patients with enhancing lesions is not an easy task, because the presence of these lesions is not known a priori. Indeed, Gd-enhanced scans are not performed routinely in MS follow-ups, so the recent history of enhancement of a patient is not always available. Moreover, even if that information is available, the presence of enhancing lesions on an earlier (albeit recent) scan does not guarantee that the subject will show enhancement when actually scanned for the purposes of our study. Indeed, as underlined earlier in the background chapter, inflammatory lesions usually only last up to six weeks, so their “disappearance” between two scans is very likely.

A recent relapse (i.e. within the past 12 months) is a reasonable criterion to start with, as this indicates potential disease activity – and therefore inflammation.

Because the ratio of enhancing lesions to number of subjects scanned turned out relatively poor at first, recruitment criteria were refined along the way. A recent paper by Barkhof et al [41] suggested additional predictors of enhancement: higher T2 burden of disease, shorter disease duration and younger age at onset. The T2 burden of disease is not readily and systematically available for all MS patients, but the disease duration and patient age at onset are. The latter two criteria were therefore also incorporated for patient recruitment, along with the evidence of a recent relapse.
3.1 Development of an accurate BBB permeability measurement protocol for MS patients

3.1.1 Experimental study

The purpose of this study was to test the new BBB permeability measurement method designed for MS enhancing lesions. This new method of measurement incorporates the following constraints:

- the AIF should be measured in each subject since it has high inter-subject variability;

- the AIF should be measured upon each new contrast-enhanced scan, as it is sensitive to the dynamics of the injection and to the subject’s physiology at the time of injection (e.g. heart rate);

- the minimum temporal resolution required to accurately sample the AIF during the first pass bolus (50 – 60 s following the injection) is 5 seconds because Gd concentration variations in the blood and plasma are very rapid at that time; a 30 s resolution is sufficient at later times for AIF sampling and at any time for the sampling of the slow CA uptake in MS enhancing lesions;

- the minimal spatial resolution required to reliably detect and segment MS enhancing lesions is 1x1x3 mm$^3$; a 2x2x6 mm$^3$ resolution is sufficient for segmentation of sagittal sinus voxels with almost no PVE.

The method therefore consists of a “dual temporal resolution” dynamic acquisition during and following contrast injection: because the high temporal resolution is only required in the first 50 – 60 seconds after injection, prior to any measurable uptake in the lesions, one can take advantage of this timing difference to acquire DCE-MRI data with high temporal resolution (5 s) and lower spatial resolution in the first minute after injection, and lower temporal resolution (32 s) but high spatial resolution after on. This dual-temporal resolution acquisition will be referred to as “5 s + 32 s” from now on. The data acquired in the first minute is used to calculate concentrations in the sagittal sinus only, and not in the lesion areas.

The method also rests on all the assumptions and approximations detailed earlier in Section 2.4. One additional approximation specific to our method is that there is no detectable Gd uptake in the MS enhancing lesions within the first 50 – 60 s post-injection.
Acquisition parameters and protocol

Four MS patients were scanned on a 3T TIM-Trio (Siemens Medical Systems, Erlangen, Germany) using the whole body transmission coil and a 32-channel receive-only head coil. The subjects were all female, with an average age of 37.5 (range: 30–44). The study was approved by the Research Ethics Board of the Montreal Neurological Institute and written consent was obtained from all subjects prior to the scan.

The contrast agent used was Gd-DTPA (Magnevist®, Bayer, Canada) in three patients, and Gd-BT-DO3A (Gadovist®, Bayer, Canada) in one patient.

Basic sequence parameters, such as TR, TE and FOV needed to be consistent between all 3D-FLASH acquisitions performed, whether they were acquired for T₁₀ and M₀ mapping or as part of the dynamic measurement of CA concentration. Because fast imaging was required for the dynamic measurements, repetition time was made as short as possible (TR = 5.6 ms) and the excited slab was slanted and reduced to the minimum number of slices that allowed for brain and sagittal sinus coverage (FOV = 256x192x120 mm³). The echo time was also kept short (TE = 2.61 ms) to avoid T₂ weighting of the SPGR signal (see Equations (1.5) and (1.6) page 23).

The DESPOT1 technique [20] was used to produce pre-contrast T₁₀ and M₀ maps with a 1x1x3 mm³ voxel size, typical for MS clinical data. The acquisition consisted of two 3D-FLASH images with different flip angles. The two flip angles chosen (3° and 15°) were optimized for the range of T₁ values expected in white matter at 3T (≈ 1000 ms). This choice of flip angles also provided T₁ estimates in the blood (T₁ ≈ 1900 ms at 3T) with acceptable accuracy. Two serial measurements were averaged to increase the SNR. The scan duration to acquire the two raw images was 3 minutes.

With no adjustment to the scanner gain, the series of 3D-FLASH dynamic acquisitions was started. The flip angle was increased to α = 20° to compensate for the shortening of T₁ in the presence of the CA. Prior to contrast injection, five baseline measurements were performed (voxel size = 1x1x3 mm³). The standard dose of contrast agent (0.1 mmol/kg) was then injected intravenously, followed by 20 cc of saline. During and right after contrast injection, 13 images were acquired at high temporal resolution (5 s), using parallel imaging (GRAPPA factor 2) and low spatial resolution (2x2x6 mm³) to increase acquisition speed. The acquisition then continued with 36 additional images at lower temporal resolution (32 s), but high spatial resolution (1x1x3 mm³). Scan duration was 2:41 minutes for baseline and 20 minutes in the presence of Gd.

High SNR and spatial resolution standard anatomical 3D-FLASH T₁-weighted scans pre- and post-Gd were also acquired to allow reliable segmentation of enhancing lesions and blood
vessels ($\alpha = 27^\circ$ / TR = 28 ms / TE = 5 ms / FOV = 256x192x180 mm$^3$ / voxel size = 1x1x3 mm$^3$ / duration = 5:24 min).

A recapitulative timeline of the protocol is shown in Figure 3.1.

![Figure 3.1: Timeline of protocol for BBB permeability measurement.](image)

**Figure 3.1: Timeline of protocol for BBB permeability measurement.** The DESPOT1 block produces HSR pre-Gd $T_{10}$ and $M_0$ maps using FA = 3°,15°. The baseline block provides HSR pre-Gd signal levels with identical image contrast as after CA injection: FA = 20°. The “bolus” block allows to track very rapid changes of Gd concentration in the venous blood with HTR but LSR. The “uptake” block allows to track smoother changes of Gd concentration in the venous blood and in the lesions with LTR but HSR. The pre- and post-Gd anatomical images are clinical standards used for reliable structure segmentation. *The time axis is to scale.* HSR: High Spatial Resolution; LSR: Low Spatial Resolution; HTR: High Temporal Resolution; LTR: Low Temporal Resolution.

**Data analysis**

All data were viewed, registered and segmented using previously developed in-house software (MINC Tools$^1$). Additional processing and computing was performed using custom-written programs in Matlab (The MathWorks™) and Perl.

**Registration and resampling** Since voxel values were to be compared at different time points, proper registration of images was crucial to limit the effects of patient motion. Each short-TR 3D-FLASH image was registered to the last frame acquired, which in turn was also registered to the post-Gd anatomical scan used for segmentation.

High spatial resolution (HSR) images from the “uptake” block were used to produce Gd concentration-time curves in the enhancing lesion voxels as detailed further below.

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$^1$http://packages.bic.mni.mcgill.ca/tgz
These images were also resampled to the lower spatial resolution to match the data acquired during the “bolus” block, and low spatial resolution (LSR) data from both blocks were then used to produce Gd concentration-time curves in the venous voxels.

Figure 3.2: Going from the raw data to parametric maps of BBB permeability and leakage space. Concentration maps were calculated at each timepoint and then concatenated together to give CA concentration curves across time in each voxel of the FOV. They were produced in both LSR and HSR. The LSR maps were used to extract concentration-time curves in sagittal sinus voxels and estimate the AIF by averaging the individual curves together. The HSR maps were used to extract concentration-time curves in the enhancing lesion voxels. For each latter voxel, $K_{\text{trans}}$ and $v_e$ were estimated by inputting the corresponding concentration curve and the AIF in the pharmacokinetic model equation and running a non-linear least squares fit.

**BBB permeability and leakage space calculation** $M_0$ and pre-contrast $T_1$ (referred to as $T_{10}$) maps were first produced by inputting the raw DESPOT1 data into Equation (2.2), page 30.

$T_1$-weighted images from the dynamic series were used together with the $M_0$ map to generate quantitative $T_1$ maps at each time point by inverting the SPGR signal equation (see Equation (2.5)
The five baseline raw images were registered and averaged together for improved SNR and the resulting image was also converted to a quantitative T$_1$ map.

Quantitative T$_1$ maps were further converted to CA concentration maps using the T$_{10}$ map, the value for CA relaxivity in plasma and Equation (2.1) page 30.

Two sets of CA concentration maps in time were then available: one set at LSR to be used for plasma concentration curve extraction and another at HSR, to be used for the extraction of concentration curves in the lesions.

The LSR set corresponded to data acquired during the first pass bolus and spatially resampled data acquired afterwards. These CA concentration maps were concatenated along the time dimension, each image being associated with the time at which the centre of k-space was acquired. An image that took 5 s to acquire and started at time t=0 was for instance associated with timepoint t=2.5 s, while an image that took 32 s to acquire and started at time t=60 s was associated with timepoint t=76 s.

The HSR set corresponded to data acquired during the “uptake” block. Compared to the previous concentration-time curves at LSR, it was short of the 13 frames acquired at LSR during “bolus” block. Since no detectable increase in CA concentration was expected in the lesions during the bolus, the averaged baseline concentration map was replicated 13 times and then concatenated along the time dimension with the HSR concentration maps from the “uptake” block. The number of timepoints of the concentration-time curve in an enhancing lesion voxel could then match that of the AIF. The timings associated with each image were calculated as previously.

Enhancing voxels in the sagittal sinus and in lesions were manually segmented on LSR and HSR data respectively, to produce regions of interest (ROIs) in the blood and in the inflammatory WM tissue.

Among the venous voxels segmented, only those with a peak concentration within 90% of the global maximum over the ROI were selected to contribute to the AIF, in order to limit PVE. The voxels that passed the criterion were averaged together to render a smooth AIF. The use of the 90% threshold is a good compromise as it filters out voxels with a peak concentration clearly corrupted by PVE, while still producing a high SNR AIF through the averaging of the remaining voxels. It involves however the use of an arbitrary (albeit sensible) threshold and could potentially introduce a bias, not so much in the tail of the AIF as in its peak value. No further fitting to a model was performed, so the AIF was used as a sampled function.

Within the enhancing lesion ROIs, the voxels were filtered using a concentration detection threshold. Only those voxels in which the measured concentration level could not be the product
of noise were kept. The threshold was calculated with our sequence parameters and characteristics, using a formula from Schabel and Parker [42]:

$$C_{\text{det}} \approx \frac{1}{\text{SNR}} \sqrt{\left(1 + \frac{1}{N_B}\right) (T_{10} \cdot r_1)^{-2}},$$

(3.1)

where $N_B$ is the number of baseline images acquired prior to the injection. A window corresponding to $\pm 2C_{\text{det}}$ was used to filter the voxels in the enhancing lesion ROIs.

In each of the enhancing voxels that passed the filtering, $K_{\text{trans}}$ and $v_\text{e}$ were fit using the two-compartment model [43], summarized by Equation (2.11) page 34, and a non-linear least squares algorithm. The input concentration curves $C_r(t)$ and $C_p(t)$ required in Equation (2.11) were of course the concentration curve in the voxel of interest and the averaged AIF, respectively. The sampled AIF was approximated to a piecewise constant function in order to be inserted in the convolution product, as explained by Horsfield and Morgan [44]. Parametric maps of $K_{\text{trans}}$ and $v_\text{e}$ were thus produced in each enhancing lesion.

Figure 3.2 illustrates the different steps described so far.

The same analysis was then re-run on the data (AIF and uptake curves in lesions) after temporal down-sampling of the AIF to mimic a plain 32 s resolution (as opposed to our dual-temporal resolution acquisition), in order to estimate the change in the $K_{\text{trans}}$ and $v_\text{e}$ fit results with sampling rate. Of course the outcome was not identical to what would have been obtained experimentally with a 32 s resolution acquisition. Indeed, if we examine closely the first minute of acquisition, a 32 s temporal spacing would yield two datapoints and be influenced by all the concentration levels reached during times $t=0$ to 32 and $t=32$ to 64. However, the main contribution to the signal intensity comes from the centre of k-space, which would be acquired at times $t=16$ and $t=48$. For this reason, we mimicked a 32 s resolution from a 5 s resolution acquisition by averaging the data points at times $t=12.5$ and $t=17.5$ as well as those at times $t=47.5$ and $t=52.5$. This still provided a good approximation of the experimental result. The gain in SNR brought by averaging timepoints together to produce a lower temporal sampling in post-processing was also estimated to be comparable to the gain brought in a real acquisition by increasing the time from 5 to 32 s while reducing the voxel size by a factor of 8 (going from LSR to HSR).

### 3.1.2 Simulations

Successfully testing the protocol on patients and using the data to produce $K_{\text{trans}}$ and $v_\text{e}$ parametric maps was an important step. However, in order to compare this new dual-temporal resolution protocol to the conventional one (i.e. acquiring at 32 s temporal resolution throughout, with HSR) and determine whether it actually improves the accuracy and/or precision of parameter
estimates, simulations had to be performed. This section describes how these simulations were designed, tested and used.

Simulation validation

In order to assess whether simulation results were reliable in terms of correspondence with experimental findings, the simulation was first set up to reproduce as closely as possible the experiments performed in the study described in section 3.1.1.

For each of the four subjects scanned, the acquired AIF was first fit to a biexponential model with an initial linear upslope, which according to McGrath et al. [25] provides an adequate fit with a reasonably low number of independent parameters. The bolus arrival time (BAT) and peak time were also included as fit parameters and therefore automatically determined, to account for inter-experiment variability of actual injection time and inter-subject variability in physiology [45]. We thus obtained an analytical expression of the AIF for each subject, of the form:

\[
\begin{align*}
t & \leq \alpha, \quad C_p(t) = c \\
\alpha < t & \leq \beta, \quad C_p(t) = c + (a_1 + a_2) \frac{t - \alpha}{\beta - \alpha} \\
t & > \beta, \quad C_p(t) = c + a_1 \cdot e^{-m_1(t-\beta)} + a_2 \cdot e^{-m_2(t-\beta)}
\end{align*}
\]

where \(\alpha, \beta, c, a_1, a_2, m_1, m_2\) were parameters estimated in the fitting procedure.

This model-based AIF was then input into Equation (2.11) (p.34) along with a set of \((K_{\text{trans}}, v_{\text{e,th}}, v_{\text{th}})\) values close to those evaluated experimentally in the lesions. This step generated a theoretical contrast agent concentration over time \(C_r(t)\) in a lesion voxel governed by \((K_{\text{trans}}, v_{\text{e,th}}, v_{\text{th}})\). The AIF – which represents Gd concentration in plasma over time – was also scaled by \((1 - H_t)\) to simulate concentration in the blood \(C_b(t)\).

Working backwards, both \(C_b(t)\) and \(C_r(t)\) curves were converted into \(T_{1,b}(t)\) and \(T_{1,r}(t)\) curves using Equation (1.8) (p. 24) as well as the value of CA relaxivity and realistic initial \(T_{10}\) values for blood and white matter, respectively.

The \(T_1(t)\) curves further generated MR signal amplitude curves \(S(t)\), using the SPGR signal equation (p. 23) and the experimental imaging parameters (TR and flip angle). \(M_0\) was attributed a random value that was assumed to be known with infinite accuracy, although experimentally it is not. These theoretical MR signals were then sampled to match the two temporal resolution patterns considered: \(5 \text{s} + 32 \text{s}\) and \(32 \text{s}\). Again, the main contribution to the intensity in an image that took \(T\) seconds to acquire was assumed to be the signal level at the time the centre of k-space
was acquired, i.e. T/2.

SNR was estimated from the experimental data in the presence of CA, both in the sagittal sinus and in the white matter, by measuring the ratio of the mean signal to its standard deviation in structurally uniform regions of interest. Noise was then added to the simulated signals to match the experimental SNRs.

These noisy simulated signals were finally processed exactly as the raw experimental data to generate \( (K_{\text{trans,est}}, v_{e,est}) \) values.

The whole process was run for 1000 iterations, in order to extract mean values and standard deviations for \( (K_{\text{trans,est}}, v_{e,est}) \). Because in simulations the “true” values of \( K_{\text{trans}} \) and \( v_e \) are known, root mean square error (RMSE) on the estimates were calculated. The quality of fit (through the coefficient of determination \( R^2 \)) of the two-compartment model on the noisy CA uptake curve was also recorded.

Comparing the relative changes in \( (K_{\text{trans,est}}, v_{e,est}) \) with the relative changes in the experimental \( (K_{\text{trans,exp}}, v_{e,exp}) \) when the temporal sampling pattern was modified from 5 s + 32 s to 32 s, provided a reasonable method to evaluate how realistically the simulation performed.

## Predicting performance from simulations

The main purpose of these simulations was to test the performance of the dual-temporal resolution protocol developed, in comparison to the more conservative approach of acquiring at lower temporal resolution (32 s) and HSR (1x1x3 mm\(^3\)) throughout, and to determine whether it indeed allows a more accurate and precise measurement of BBB permeability. Once validated, the simulation method described in the previous section was therefore used to evaluate the accuracy and precision of \( (K_{\text{trans,est}}, v_{e,est}) \) estimates with respect to the theoretical inputs \( (K_{\text{trans,th}}, v_{e,th}) \) for the two different temporal resolution patterns, and in various conditions:

- The time delay between acquisition start and injection start was allowed to vary from 0 to 45 s, in steps of 1 second. This was done by changing the \( \alpha \) and \( \beta \) values in the linear bi-exponential expression of the AIF to the desired delay. In the 5 s + 32 s acquisition scheme, the HTR part lasts 60 seconds, such that a delay exceeding 45 seconds would defeat its purpose. But delays in the 0 – 45 s range are possible due to the variability associated with the manual injection procedure;

- The shape of the AIF varied, from a wide and low first-pass peak to a narrow and high one. This is likely allowing for inter- and intra-patient variability;

- \( K_{\text{trans,th}} \) covered a broad range of values quoted in the MS literature [23], from 0.01 min\(^{-1}\) to 0.07 min\(^{-1}\) in steps of 0.02 min\(^{-1}\), while the theoretical EES fraction was maintained
3.2 Comparative study of enhancement at “3T–triple dose” vs. “1.5T–single dose” constant;

• $v_{e,th}$ covered a broad range of values quoted in the MS literature [23], from 15% to 45% in steps of 10%, while the theoretical BBB permeability was maintained constant.

The output parameters of interest after 1000 simulation iterations were the mean estimated $K_{trans}$ and $v_e$, along with the corresponding standard deviations and RMSE.

3.2 Comparative study of enhancement between the “3T–triple dose” and the “1.5T–single dose” protocols

Once the dual-temporal resolution protocol for accurate BBB permeability mapping was validated, it was used as a tool for a comparative study of sensitivity to BBB disruption of two different Gd-enhanced protocols (presented in the introduction, page 13).

This comparative study was based on the following acquisitions:

• First session: contrast enhanced MRI acquisition using the optimized (3T–triple dose) protocol, as well as BBB permeability mapping using the dual-temporal resolution protocol;

• Second session 3 – 4 days later, if enhancement was found on the 3T scan: contrast enhanced MRI using the standard (1.5T–single dose) protocol;

• Both sessions are repeated after one month.

A schematic representation of the scans timeline is shown in Figure 3.3. The comparative study was carried out with Gadovist®.

3.2.1 Acquisition protocol

To date, three MS patients with a recent relapse were screened and two were enrolled in the study. Both subjects were female, aged 30 and 32. Written consent and creatinine levels, to assess kidney function (because of the triple dose injection), were obtained for both subjects prior to the scans.

The triple-dose scans were performed using the same hardware as previously described: a 3T TIM-Trio scanner (Siemens Medical Systems) with a whole body coil for transmission and a 32-channel receive-only head coil.

The scan started with a standard clinical FSE PD/T$_2$ sequence to evaluate the burden of disease ($\alpha = 120^\circ$ / TR = 2100 ms / TE$_{1/2}$ = 16/80 ms / FOV = 256x192x180 mm$^3$ / voxel size.
Figure 3.3: Timeline of scans that enable comparison of enhancement with the standard vs the optimized protocols and correlation (if any) of the enhancement differences with permeability values. The pair of scans was also repeated after one month.

= 1x1x3 mm\(^3\) / duration = 7:02 min). This was followed by a pre-Gd T\(_1\)-weighted anatomical sequence with an MT pulse for tissue attenuation (\(\alpha = 27^\circ\) / TR = 30 ms / TE = 6.15 ms / FOV = 256x192x180 mm\(^3\) / voxel size = 1x1x3 mm\(^3\) / duration = 4:32 min). The role of the MT pulse is to bring down the overall signal level and thus allow enhancing voxels to be imaged with increased contrast to noise ratio.

The entire “permeability measurement” block (see Figure 3.1) was then performed while the first dose of Gadovist was injected.

Following the 20 minutes of dynamic acquisition required for permeability measurements, an extra double dose of Gadovist was injected intravenously into the patient. After another 15 min delay, a post-Gd T\(_1\)-weighted anatomical sequence with an MT pulse for tissue attenuation was finally acquired. The 15 minute wait between the second injection and the post-Gd T\(_1\) weighted imaging was used to acquire a FLAIR sequence (TI = 1800 ms / TR = 5000 ms / TE = 397 ms / FOV = 256x256x156 mm\(^3\) / voxel size = 1x1x3 mm\(^3\) / GRAPPA fact. 2 / duration = 3:52 min), which was not affected by the presence of the CA and allowed better distinction between periventricular lesions and CSF than the PD/T\(_2\) sequence.

The single-dose scans were performed on a 1.5T Siemens Sonata scanner (Siemens Medical Systems) using a whole body coil for transmission and a circularly polarized receive-only head coil.
3.2 Comparative study of enhancement at “3T–triple dose” vs. “1.5T–single dose”

The scan also started with a standard clinical FSE PD/T$_2$ sequence to evaluate the burden of disease ($\alpha = 180^\circ / TR = 2070 \text{ ms} / TE_{1/2} = 12/83 \text{ ms} / FOV = 256x256x180 \text{ mm}^3 / \text{ voxel size} = 1x1x3 \text{ mm}^3 / \text{ duration} = 5:33 \text{ min}$). This was followed by a standard pre-Gd T$_1$-weighted anatomical sequence ($\alpha = 30^\circ / TR = 30 \text{ ms} / TE = 11 \text{ ms} / FOV = 256x256x180 \text{ mm}^3 / \text{ voxel size} = 1x1x3 \text{ mm}^3 / \text{ duration} = 4:32 \text{ min}$). One dose of Gadovist was then injected intravenously. A post-Gd T$_1$-weighted anatomical sequence was then acquired 10 min after the injection. A FLAIR sequence was also acquired between the injection and the post-Gd image ($TI = 2500 \text{ ms} / TR = 9360 \text{ ms} / TE = 66 \text{ ms} / FOV = 333x192x180 \text{ mm}^3 / \text{ voxel size} = 1.3x1x3 \text{ mm}^3 / \text{ duration} = 5:20 \text{ min}$).

3.2.2 Data analysis

All data were viewed, registered, resampled and processed using the same tools and methods as previously. After each pair of scanning sessions, all images were registered to the post-Gd image acquired on the 3T. Enhancing lesions were segmented by a radiologist on each post-Gd image (one on the 3T and one on the 1.5T) and labelled.

The data acquired on the 3T scanner for permeability measurements was then used to produce parametric maps of BBB permeability ($K_{\text{trans}}$), EES voxel fraction ($v_e$) and quality of fit ($R^2$ coefficient of determination) in the voxels segmented as enhancing on the 3T scan. The methods were identical to those described previously on page 48. The only difference in procedure was that the concentration detection threshold (see Equation (3.1) page 50) was not used to discard any voxels prior to a fit attempt. The rationale for this was that we were particularly interested in looking at voxels that enhanced on the 3T scan only (and not on the 1.5T one), in which very subtle enhancement and low $K_{\text{trans}}$ values were expected. The $R^2$ map allowed the assessment of fit reliability instead, with some voxels still being discarded as explained later on.

The co-registered ROIs drawn on the post-Gd 3T and 1.5T scans were then compared in terms of number of enhancing lesions and enhancement volume. In particular, voxels were separated into two categories:

- those that enhanced with both protocols constituted the “overlapping” group;
- those that only enhanced with the 3T-triple dose protocol constituted the “non-overlapping” group;

Using the parametric maps, histograms of $K_{\text{trans}}$, $v_e$ and $R^2$ were then produced to examine the distribution of parameter values within each of the two groups. We expected that the mean
The permeability value distribution in each of the two pools of voxels was also plotted in terms of percentiles. This allowed a more robust and quantitative method for the extraction of a sensitivity threshold between the two protocols.

The same analysis was performed on the second pair of scans acquired one month later.

The two pairs of scans were also compared between each other. In particular, the evolution within one month of the number of enhancing lesions and their volume on the 3T–triple dose scan was compared to the evolution of the same parameters on the 1.5T–single dose scan. We expected that the number and volume of enhancing lesions persistent at one month would be larger with the optimized than with the standard protocol.
Results

4.1 Development of an accurate BBB permeability measurement protocol for MS patients

4.1.1 Experimental study

Of the three patients scanned with Gd-DTPA, only one turned out to have an enhancing lesion at the time of the scan. This subject is referred to below as Subject #1. The other two patients, referred to as Subject #2 and Subject #3, showed no enhancing lesions. Since their AIF measurements were nonetheless available, they were used as inputs for simulations, as previously explained in Section 3.1.2. Subject #4, scanned with Gadovist, showed 4 enhancing lesions.

One slice of the pre-Gd $T_{10}$ and $M_0$ maps obtained for Subject #1 are shown in Figure 4.1. The enhancing lesion can be seen on the raw $T_1$-weighted image in Figure 4.2 and on the resulting Gd concentration map in Figure 4.3.

The AIF extracted from Subject #1 was the average of four enhancing voxels in the sagittal sinus (voxel size: 2x2x6 mm$^3$). The curves for each voxel and the resulting average are represented in Figure 4.4, as an example.

In the enhancing lesions, the minimum detectable concentration (see Equation (3.1), p. 50) with our imaging parameters was calculated to be $C_{det} = 0.02$ mM for Magnevist and $C_{det} = 0.015$ mM for Gadovist. All the voxels in which the Gd concentration remained below $2C_{det}$ were discarded. Table 4.1 provides the number of voxels remaining to be analyzed in each lesion, as well as average fit results from the directly acquired data (i.e. a 5 s + 32 s sampling pattern). Figure 4.5 shows the resulting $K_{trans}$ and $v_e$ parametric maps in one slice of the lesion, from Subject #1.

The AIFs from Subjects #1 and #4 were also resampled to simulate a 32 s resolution through-
“Black hole”-type lesions are visible on the frontal part of the brain: the hypointensities in $T_1$-weighted raw images translate into longer $T_1$ and therefore appear brighter than surrounding WM on $T_1$ parametric maps. Grey scale boundaries: 0 – 5 seconds.

(a) $T_{10}$ map.  (b) $M_0$ map. The $B_1$ inhomogeneities are somewhat apparent, especially in the lower left-hand side of the image. Grey scale boundaries: 500 – 7000 a.u.

Figure 4.1: One axial slice of the pre-Gd $T_{10}$ and $M_0$ 3D-maps obtained in Subject #1 using the DESPOT1 method.

out and processed along with the original uptake curves in the enhancing lesions to output new pharmacokinetic parameter estimates in each of the 529 enhancing voxels.

Figure 4.6 shows the two AIFs in the first 3 minutes of acquisition, as produced by the two different resolution patterns. Depending on the time delay between acquisition start and injection, the 32 s acquisition timing can allow the sampling of the AIF to be satisfactory (Subject #1) or not (Subject #4). This aspect will be further investigated through simulations.

The changes in estimated $K_{trans}$ due to temporal sampling of the AIF are plotted in Figure 4.7 for all 529 voxels. The difference is significant and increases with permeability. It goes up to 33% in the case of a high permeability value (around 0.03 min$^{-1}$). For a given permeability value, the data points show some spreading related to noise but also to the EES fraction $v_e$ in each voxel, which varies among the data and impacts the robustness of the fit.

These findings underline that the temporal sampling of the AIF does have a non negligible impact on the estimated BBB permeability, and that although the effect is more pronounced with higher permeability (less often encountered in MS enhancing lesions) it can already be quite distinct at typical MS permeability values (i.e. $K_{trans} = 0.01$ min$^{-1}$).
4.1 Development of an accurate BBB permeability measurement protocol

Figure 4.2: Last T1-weighted axial image of the dynamic acquisition (∼ 20 minutes after contrast injection), showing the enhancing lesion as a bright oval spot.

Figure 4.3: Same slice as in Figure 4.2, converted to a Gd-DTPA concentration map. The region of BBB disruption comes out very sharply from the background (yellow arrow), as well as the sagittal sinus (green arrow) and other small blood vessels. Metal color scale boundaries: 0 – 0.2 mM.

The simulation results presented in the following section allowed us to quantify the error in $K_{\text{trans}}$ introduced by adopting a 5 s + 32 s vs. a 32 s sampling scheme.

AIF fits

The AIFs from the three subjects scanned with Gd-DTPA were successfully fit to a bi-exponential model with a linear upslope (see Equations (3.2),(3.3) and (3.4)). They are referred to as AIF1, AIF2 and AIF3 further on in the text. Figure 4.8 shows the experimental sampled curves and their corresponding fits, along with the parameters output by the fit. These analytical expressions of the AIFs were used as input AIFs for simulations, with results presented in Section 4.1.2.

The second exponential decay rate $m_2$ is very similar among the three AIFs. However, the amplitude and width of the first-pass peak are highly variable. AIF2, in particular, displays a peak that is approximately half the amplitude and twice the width of the other two. The injection procedure in that case was indeed slowed down by the patient’s atrophied venous system in the
Figure 4.4: Plasma concentration curves measured in four sagittal sinus voxels and averaged to produce the AIF of Subject #1. The temporal resolution of the sampling is 5 s in the first 50 s and 32 s thereafter. The high temporal resolution in the first part allows one to clearly detect the start time of the injection and accurately sample the first-pass bolus.

The effects of injection variability on the shape of the AIF – especially when the procedure is manual – are very well illustrated through these 3 examples. The necessity to sample the AIF at a high rate in the first minute post-injection is made very clear. It will be shown later on in this work that the initial shape of the AIF impacts the fit parameters $K_{\text{trans}}$ and $v_e$ to a non negligible degree even in the case of MS, where the detectable CA uptake in the enhancing lesions happens at a later time and is very slow$^1$.

$^1$The need for high sampling rates in tumour CA uptake has been demonstrated in the literature already.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Lesion #</th>
<th># Voxels</th>
<th>$K_{\text{trans}}$ (min$^{-1}$)</th>
<th>$\sigma(K_{\text{trans}})$ (min$^{-1}$)</th>
<th>$v_e$ (%)</th>
<th>$\sigma(v_e)$ (%)</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>62</td>
<td>0.0097</td>
<td>0.0045</td>
<td>14.4</td>
<td>6.5</td>
<td>0.91</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>403</td>
<td>0.0089</td>
<td>0.0044</td>
<td>10.5</td>
<td>6.2</td>
<td>0.91</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>40</td>
<td>0.0107</td>
<td>0.0055</td>
<td>7.1</td>
<td>2.7</td>
<td>0.89</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>18</td>
<td>0.0065</td>
<td>0.0031</td>
<td>8.1</td>
<td>3.2</td>
<td>0.90</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
<td>0.0104</td>
<td>0.0027</td>
<td>3.8</td>
<td>1.0</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Table 4.1: Statistics on each of the 5 enhancing lesions found: number of voxels, mean and SD of $K_{\text{trans}}$ and $v_e$ across the lesion, mean quality of fit $R^2$. Data sampling: 5 s + 32 s pattern.
4.1 Development of an accurate BBB permeability measurement protocol

(a) $K_{\text{trans}}$. The metal color scale boundaries are 0 – 0.215 min$^{-1}$.

(b) $v_e$. The metal color scale boundaries are 0 – 30%.

**Figure 4.5:** $K_{\text{trans}}$ and $v_e$ parametric maps of the enhancing lesion in Subject #1.

(a) AIF in Subject #1

(b) AIF in Subject #4

**Figure 4.6:** The AIF in Subjects #1 and #4 as acquired, and resampled in post-processing to a 32 s resolution. Depending on the time delay between acquisition start and injection, the 32 s acquisition can allow the sampling of the AIF to be satisfactory (Subject #1) or not (Subject #4).
Figure 4.7: Each of the 529 voxels was analyzed using an AIF sampling of 5 s + 32 s and 32 s, and the difference in the resulting $K_{\text{trans}}$ plotted against $K_{\text{trans,5s+32s}}$. The permeability estimate with an undersampled AIF is systematically higher, and the difference increases with higher permeability. The data points represented have various EES fractions, which also impact the error in the estimates, hence the spread for a given permeability value.
Figure 4.8: AIFs measured on three subjects and fit to a bi-exponential function with a linear upslope. The analytic expressions of the AIFs are used as input AIFs for simulations.
4.1.2 Simulation results

Simulation validation

Voxels with an experimentally measured $v_e$ between 9% and 11% were extracted from the dataset of Subject #4. Their associated permeability values covered a wide range, between $0.004 \text{ min}^{-1}$ and $0.02 \text{ min}^{-1}$.

Simulation parameters were then chosen to match as closely as possible the case of Subject #4. The main simulation inputs are as follows:

- $AIF = AIF4$
- $K_{trans,th} = 0.002–0.02 \text{ min}^{-1}$
- $v_{e,th} = 10\%$
- $M_0 = 1$ (arbitrary)
- $\alpha = 20\°$
- Number of iterations = 1000.

The SNR levels as estimated from the data and used to simulate noisy signals are provided in Table 4.2.

<table>
<thead>
<tr>
<th>Temporal resolution</th>
<th>5 s</th>
<th>32 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>In sagittal sinus</td>
<td>$\text{SNR}_{HSR}$</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>$\text{SNR}_{LSR}$</td>
<td>170</td>
</tr>
<tr>
<td>In lesion</td>
<td>$\text{SNR}_{HSR}$</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 4.2: Post-Gd SNR levels in the sagittal sinus and in the enhancing lesion, as estimated from the acquired data and used as inputs for the simulations. Values for the 5 s and 32 s resolutions are measured directly on the images. $HSR$: High Spatial Resolution ($1\times1\times3 \text{ mm}^3$); $LSR$: Low Spatial Resolution ($2\times2\times6 \text{ mm}^3$).

As with the real data, permeability and EES fraction were estimated using two different sampling patterns for the AIF: 5 s + 32 s and 32 s. Figure 4.9 shows the mean difference and associated standard deviation between $K_{trans,32s}$ and $K_{trans,5s+32s}$ resulting from simulations. The trend was compared to that observed with the real data in voxels where $9\% < v_e < 11\%$. It was found to be highly similar, which validated the reliability of the simulation.

The advantage of the simulation was that it also provided a measurement of the error between the true parameters and the estimates output by the final fit, the sources of error being in this case noise and the sampling rate. Detailed simulation inputs and outputs are collected in Table 4.3,
which presents the RMSE between theoretical inputs (\(K_{\text{trans},\text{th}}\) and \(v_{e,\text{th}}\)) and estimated outputs (\(K_{\text{trans},\text{est}}\) and \(v_{e,\text{est}}\)) as well as the quality of fits.

**Figure 4.9:** Absolute difference in \(K_{\text{trans}}\) estimates produced by the two examined sampling patterns in the segmented enhancing voxels and in simulations, for \(v_e \approx 10\%\). The errorbars are 2 SD long, indicating variability due to noise from 1000 iterations. The trend is similar in the experimental data and in the simulation.

The consistency of the simulation with experimental results allowed us to use the simulation for further exploration of the impacts of temporal resolution in different conditions. First of all, it was highlighted in Figure 4.6 that the 32 s resolution (compared to the 5 s + 32 s) might or might not provide a satisfactory sampling of the first pass peak, depending on the bolus arrival time and width. We explored, through simulations, the performance of these two types of acquisitions if an offset is added to the injection time (this offset is likely to occur during acquisitions because the exact time of injection with respect to acquisition start time may vary) or if the height and width of the first pass peak change. It was also of interest to evaluate the performance of the two patterns of temporal sampling over a wider range of \(K_{\text{trans}}\) and \(v_e\) values quoted in the MS literature [43].

**Impact of time offset on performance at various temporal resolutions**

The simulation inputs were: AIF1, \(K_{\text{trans},\text{th}}=0.01 \text{ min}^{-1}\), \(v_{e,\text{th}}=14\%\) and SNR values in Table 4.2. In our experiments, the measured delay between acquisition and injection start time was
<table>
<thead>
<tr>
<th>Sampling pattern</th>
<th>K_{trans,th} (min⁻¹)</th>
<th>K_{trans,est} (min⁻¹)</th>
<th>v_{e,th}</th>
<th>v_{e,est}</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>% Change</td>
<td>RMSE (%)</td>
<td>Mean</td>
</tr>
<tr>
<td>5s + 32s</td>
<td>0.030</td>
<td>0.0301</td>
<td>0.0017</td>
<td>6</td>
<td>10.0</td>
</tr>
<tr>
<td>32s</td>
<td>0.030</td>
<td>0.0301</td>
<td>0.0017</td>
<td>32</td>
<td>10.1</td>
</tr>
<tr>
<td>5s + 32s</td>
<td>0.025</td>
<td>0.0250</td>
<td>0.0015</td>
<td>6</td>
<td>10.0</td>
</tr>
<tr>
<td>32s</td>
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<td>0.0250</td>
<td>0.0015</td>
<td>27</td>
<td>10.1</td>
</tr>
<tr>
<td>5s + 32s</td>
<td>0.020</td>
<td>0.0200</td>
<td>0.0013</td>
<td>6</td>
<td>10.0</td>
</tr>
<tr>
<td>32s</td>
<td>0.020</td>
<td>0.0200</td>
<td>0.0013</td>
<td>23</td>
<td>10.0</td>
</tr>
<tr>
<td>5s + 32s</td>
<td>0.015</td>
<td>0.0150</td>
<td>0.0010</td>
<td>7</td>
<td>10.0</td>
</tr>
<tr>
<td>32s</td>
<td>0.015</td>
<td>0.0150</td>
<td>0.0010</td>
<td>20</td>
<td>10.0</td>
</tr>
<tr>
<td>5s + 32s</td>
<td>0.010</td>
<td>0.0100</td>
<td>0.0007</td>
<td>7</td>
<td>10.0</td>
</tr>
<tr>
<td>32s</td>
<td>0.010</td>
<td>0.0100</td>
<td>0.0007</td>
<td>19</td>
<td>10.0</td>
</tr>
<tr>
<td>5s + 32s</td>
<td>0.005</td>
<td>0.0050</td>
<td>0.0005</td>
<td>10</td>
<td>10.0</td>
</tr>
<tr>
<td>32s</td>
<td>0.005</td>
<td>0.0050</td>
<td>0.0005</td>
<td>19</td>
<td>10.0</td>
</tr>
<tr>
<td>5s + 32s</td>
<td>0.002</td>
<td>0.0021</td>
<td>0.0003</td>
<td>17</td>
<td>10.0</td>
</tr>
<tr>
<td>32s</td>
<td>0.002</td>
<td>0.0021</td>
<td>0.0003</td>
<td>28</td>
<td>10.0</td>
</tr>
</tbody>
</table>

**Table 4.3:** Simulated evolution of fit parameters with temporal sampling scheme, over a realistic range of K_{trans,th} values. The changes in K_{trans,est} and v_{e,est} for the 32 s resolution relative to the 5 s + 32 s (in grey) are indicated as a range that accounts for the associated uncertainties (using the SDs). The AIF used was fit on data from Subject #4. Means, SDs and RMSEs are calculated for 1000 iterations. The RMSE on K_{trans} is smaller with the dual temporal sampling, while the RMSE on v_e is mainly unaffected.

28.5 seconds, so we probed the 0 – 45 seconds range. Results for the RMSE on estimated K_{trans} and v_e as a function of the delay and for each of the two acquisition schemes are plotted in Figures 4.10 and 4.11 respectively.

The error in K_{trans} estimation with the 5 s + 32 s scheme is relatively low (7%) and fairly independent of the delay. On the contrary, the error in K_{trans} estimation with the 32 s scheme is always larger and very dependent on the delay, ranging from 7% to 16%. The reason for these large variations in the RMSE curve is that, depending on the timing of the acquisition data points (spaced every 32 seconds) with respect to that of the first pass peak, the sampling of the AIF does or does not render the peak. Missing the peak on this particular AIF (from Subject #1) can therefore lead to errors in K_{trans} up to 9% larger than with the 5 s + 32 s acquisition scheme. Although the RMSE curve for the 5 s + 32 s scheme is fairly flat, a slight positive slope is noticeable. Indeed, since the 5 s temporal resolution part lasts a limited amount of time (60 s in this case), the longer the delay, the less data are acquired at high temporal resolution and the poorer the sampling of the early part of the AIF.

The error in v_e estimation with the 5 s + 32 s scheme is reasonable (10%) and also fairly independent of the delay. The error in v_e with the 32 s scheme is very dependent on the delay, ranging from 9% to 16%. For very short or very long delays the error is larger than with the 5 s
4.1 Development of an accurate BBB permeability measurement protocol

**Figure 4.10:** RMSE on the estimation of $K_{\text{trans}}$, after 1000 iterations, as a function of the time delay between the acquisition start and the injection start. The error in $K_{\text{trans}}$ with the 5 s + 32 s scheme is low (7%) and fairly independent of the delay. On the contrary, the error in $K_{\text{trans}}$ with the 32 s scheme is always larger and very dependent on the delay, ranging from 7% to 16%.

+ 32 s scheme but for intermediate delays the error is smaller by 1.5%. However, an acquisition scheme that provides a parameter estimate with an error that is independent of the delay would still be favoured.

**Impact of the AIF shape on performance at various temporal resolutions**

The three AIFs available from subjects scanned with Magnevist cover a relatively large spectrum of possibilities for first pass peak amplitude and width: the peak in AIF2 is low and wide, while it is high and very narrow in AIF3 and intermediate in AIF1. Simulations were therefore also run with the same BBB parameters as before ($K_{\text{trans,th}}=0.01 \text{ min}^{-1}$ and $v_{e,th}=14\%$) using the two yet unused AIFs (AIF2 and AIF3). The injection time with respect to the acquisition start time (represented by the fit parameter $\alpha$) was set to 16 s (maximizing the difference in performance between the 5 s + 32 s and 32 s acquisition schemes in the previous section) in a first set of simulations, and then to 28 s (minimizing the difference in performance between the two schemes) in a second set of simulations. Results are collected in Table 4.4.

For all three input AIFs, the 5 s + 32 s acquisition scheme provides $K_{\text{trans}}$ and $v_e$ estimates that are stable with respect to the delay between acquisition and injection start times. Moreover, the variation in RMSE in the BBB permeability estimate for a given delay and across AIFs is relatively small (approximate range: 7–10.5%). The RMSE in the EES fraction varies by a greater amount (approximate range: 10–18%), but the 5 s + 32 s acquisition scheme was designed
Figure 4.11: RMSE on the estimation of $v_e$, after 1000 iterations, as a function of the time delay between the acquisition start and the injection start. The error in $v_e$ with the 5 s + 32 s scheme is reasonable (10%) and also fairly independent of the delay. The error in $v_e$ with the 32 s scheme is very dependent on the delay, ranging from 9% to 16%. For very short or very long delays the error is larger than with the 5 s + 32 s scheme but for intermediate delays the error is smaller by 1.5%.

primarily to improve the accuracy of BBB permeability measurements.

The 32 s acquisition scheme shows the same behaviour with AIF2 and AIF3 as it did with AIF1 (see previous section): the accuracy of the $K_{trans}$ and $v_e$ estimates varies greatly with the delay between acquisition and injection start times. The highest variability occurs with AIF3, which has the highest and narrowest first pass peak: RMSE($K_{trans}$) can be in this case 11% or 29% for a delay of 28 s and 16 s respectively. There is also non negligible variability in the accuracy of estimates across AIFs for the 16 s delay: the RMSE on $K_{trans}$ ranges from 14 to 29%. The RMSE’s in EES fraction estimation are very similar to those encountered with the 5 s + 32 s acquisition scheme.

Impact of the BBB permeability and EES space values on performance at various temporal resolutions

Two sets of simulations were run to assess whether the accuracy and precision of $K_{trans}$ and $v_e$ estimates varied with their actual values. AIF1 was used as an input, with a time delay of 16 seconds between acquisition start and injection start. This delay maximized the difference in performance between the 5 s + 32 s scheme and the 32 s scheme, with the set of input parameters ($K_{trans,th}=0.01\;\text{min}^{-1};\;v_{e,th}=14\%$), as shown in Section 4.1.2. SNR levels were the same as
Table 4.4: Performance of the 5 s + 32 s and 32 s acquisition schemes in terms of $K_{\text{trans},\text{est}}$ and $v_e$ estimation accuracy and precision, depending on the shape of the first pass bolus (as represented in AIF1, AIF2 and AIF3 – see Figures 4.8(a), 4.8(b) and 4.8(c)) and on the time delay between acquisition start and injection start. Simulation inputs were $K_{\text{trans},\text{th}}=0.01$ min$^{-1}$ and $v_{e,\text{th}}=14\%$. Mean values, SD and RMSE calculated from 1000 iterations.

<table>
<thead>
<tr>
<th>AIF</th>
<th>16 s delay</th>
<th>28 s delay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 s + 32 s</td>
<td>32 s</td>
</tr>
<tr>
<td>AIF1</td>
<td>Mean $K_{\text{trans},\text{est}}$ (min$^{-1}$)</td>
<td>0.0100</td>
</tr>
<tr>
<td></td>
<td>SD($K_{\text{trans},\text{est}}$) (min$^{-1}$)</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td>RMSE($K_{\text{trans}}$) (%)</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>Mean $v_{e,\text{est}}$ (%)</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>SD($v_{e,\text{est}}$) (%)</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>RMSE($v_e$) (%)</td>
<td>10.1</td>
</tr>
<tr>
<td>AIF2</td>
<td>Mean $K_{\text{trans},\text{est}}$ (min$^{-1}$)</td>
<td>0.0100</td>
</tr>
<tr>
<td></td>
<td>SD($K_{\text{trans},\text{est}}$) (min$^{-1}$)</td>
<td>0.0010</td>
</tr>
<tr>
<td></td>
<td>RMSE($K_{\text{trans}}$) (%)</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>Mean $v_{e,\text{est}}$ (%)</td>
<td>14.5</td>
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<td></td>
<td>SD($v_{e,\text{est}}$) (%)</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>RMSE($v_e$) (%)</td>
<td>15.6</td>
</tr>
<tr>
<td>AIF3</td>
<td>Mean $K_{\text{trans},\text{est}}$ (min$^{-1}$)</td>
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</tr>
<tr>
<td></td>
<td>SD($K_{\text{trans},\text{est}}$) (min$^{-1}$)</td>
<td>0.0010</td>
</tr>
<tr>
<td></td>
<td>RMSE($K_{\text{trans}}$) (%)</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>Mean $v_{e,\text{est}}$ (%)</td>
<td>14.5</td>
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<tr>
<td></td>
<td>SD($v_{e,\text{est}}$) (%)</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>RMSE($v_e$) (%)</td>
<td>15.1</td>
</tr>
</tbody>
</table>

In a first part, the EES fraction input value was kept to 14% while permeability input values were increased from 0.01 min$^{-1}$ to 0.07 min$^{-1}$ in steps of 0.02 min$^{-1}$. Figure 4.12 shows the evolution of $K_{\text{trans}}$ estimates with increasing $K_{\text{trans},\text{th}}$ for each of the two acquisition schemes.

These results show that the 5 s + 32 s acquisition scheme provides accurate and precise estimates of BBB permeability for a wide range of values encountered in MS enhancing lesions.

The 32 s scheme on the contrary leads to increasing overestimations of the BBB permeability and uncertainty of the measurement with increasing $K_{\text{trans},\text{th}}$. The relative error on $K_{\text{trans}}$ and the associated uncertainty increase from 13% to 39% and from 0.0008 min$^{-1}$ to 0.0087 min$^{-1}$ as $K_{\text{trans},\text{th}}$ increases from 0.01 min$^{-1}$ to 0.07 min$^{-1}$. Identical simulations run with a 28 s delay between acquisition and injection start times (which allowed the 32 s scheme to reasonably sample the first pass bolus, as explained in Section 4.1.2) show that the error in $K_{\text{trans}}$ estimation does not increase with $K_{\text{trans},\text{th}}$. This proves that the deterioration in estimation accuracy with the 16 s delay is due to the fact that the $K_{\text{trans},\text{th}}$ value acts as an enhancement of whatever error is
introduced in the sampling of the AIF, and not due to more rapid uptake in the lesion. In spite of increased BBB permeability, the CA uptake in the lesions is still slow enough to be well sampled with a 32 s resolution, which is consistent with our previous hypotheses.

![Graph showing K_trans estimates for increasing input K_trans,th values. Input EES fraction is 14% for all runs. The input AIF is AIF1, with a time delay between acquisition start and injection start of 16 s. Errorbars represent 2 SD from the mean value from 1000 iterations.](image)

**Figure 4.12:** $K_{\text{trans}}$ estimates for increasing input $K_{\text{trans,th}}$ values. Input EES fraction is 14% for all runs. The input AIF is AIF1, with a time delay between acquisition start and injection start of 16 s. Errorbars represent 2 SD from the mean value from 1000 iterations.

In a second set of simulations, the BBB permeability was kept to 0.01 min$^{-1}$ while the EES fraction was given the following input values: 14%, 25%, 35% and 45%. Figure 4.13 shows the evolution of $v_e$ estimates with increasing $v_{e,th}$ for each of the two acquisition schemes. The two perform in a similar fashion in terms of measurement accuracy and precision of $v_e$ for increasing $v_{e,th}$. The error in the estimate gradually increases by about 10 points in both cases when going from 14% EES to 45% EES. The difference lies in that the 5 s + 32 s scheme systematically overestimates, while the 32 s scheme systematically underestimates $v_e$. The uncertainty in the measurement also increases gradually by 10–14 points between a 14% EES and a 45% EES. This can be explained by looking at the two-compartment model of Equation (2.11) (p. 34) and tracing back the impact of an increase in $v_e$ on the uncertainty of its fit.
4.1 Development of an accurate BBB permeability measurement protocol

Figure 4.13: $v_e$ estimates for increasing input $v_{e,th}$ values. Input BBB permeability is 0.01 min$^{-1}$ for all runs. The input AIF is AIF1, with a time delay between acquisition start and injection start of 16 s. Errorbars represent 2 SD from the mean value from 1000 iterations.
4.2 Comparative study of enhancement between the “3T–triple dose“ and the “1.5T–single dose” protocols

Of the three subjects screened for the study to date, two showed enhancement upon their first 3T triple dose scan and were therefore enrolled. Both subjects underwent the complete four scanning sessions: two initially and two one month later.

The lesion counts and total volumes of enhancement with each protocol and at each timepoint are collected in Table 4.5.

The first patient initially showed 6 enhancing lesions with the 3T and 4 with the 1.5T protocol. At month 1 (M1), the count increased to 7 with the 3T vs 4 with the 1.5T protocol. As expected, the volume of enhancement is also much larger with the 3T protocol. As an illustration, Figure 4.15 shows post-Gd images of the largest lesion with the optimized and the standard protocols at month 0 (M0). Figure 4.14 also summarizes the evolution of enhancing volume on a per-lesion basis. In the case of Lesion #1 (shown in Figure 4.15), the decrease in volume after one month due to the transience of the inflammation process seems much more drastic with the 1.5T than with the 3T protocol (20-fold vs 2-fold), as expected. Results at M1 should however be interpreted with caution, as the two scans were one week apart (instead of 3–4 days) and some of the inflammation could have resolved during that week, making the enhancement volume erroneously low on the 1.5T scan.

In the second patient, both M0 and M1 sessions benefitted from good timing between the two scans (i.e. 3 days). At both timepoints, there was a 3:1 ratio of lesions visible with the optimized vs the standard protocol. This subject had a very large number of lesions, starting with 35 at M0 on the 3T scan. Within one month, the number of visible lesions was reduced to half on both protocols. But the total volume of enhancing WM decreased by 52% with the standard vs. only 13% with the optimized protocol. Individual evolution of each lesion between M0 and M1 was not evaluated due to the large number of lesions and their proximity to each other, which made it difficult to be sure that the same lesion was being compared between the two timepoints. Differences in enhancement volume evolution over time between the two protocols cannot therefore be attributed with certainty to the fact that enhancement lasts longer at 3T–triple dose, because some of the lesions might have been enlarging rather that shrinking during that one month.

The non-overlapping and overlapping pools of voxels produced by the three most reliable data sets (first patient at M0, and second patient at M0 and M1) were combined to form two larger pools. The data in the first patient at month 1 follow-up was not included because of the large time bias between the 3T and the 1.5T scans. Filtering the voxels based on goodness of fit
4.2 Comparative study of enhancement at “3T–triple dose” vs. “1.5T–single dose”

<table>
<thead>
<tr>
<th></th>
<th>First Patient</th>
<th>Second Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>3 T</td>
<td></td>
<td></td>
</tr>
<tr>
<td># lesions</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td># voxels</td>
<td>1136</td>
<td>943</td>
</tr>
<tr>
<td>1.5 T</td>
<td></td>
<td></td>
</tr>
<tr>
<td># lesions</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td># voxels</td>
<td>617</td>
<td>177</td>
</tr>
</tbody>
</table>

Table 4.5: Global evolution of enhancing lesion counts and volume, between timepoints M0 and M1, as seen with each protocol. Results at M1 in the first patient are to be considered with caution because one week had elapsed between the two scans. The ratio of lesion counts between the two protocols is between 3:1 and 3:2. The ratio of enhancement volume varies greatly, but is at least on the order of 2:1.

criteria ($R^2 > 0.5$ and $v_e < 60\%$) resized the pools of combined data as follows:

- Non-overlapping: 1078 voxels passed the criteria, 1210 were discarded;
- Overlapping: 1167 voxels passed the criteria, 178 were discarded.

The mean (median) of $R^2$ was 0.76 (0.77) in the non-overlapping and 0.89 (0.93) in the overlapping group. This shows that, even after filtering, voxels in the overlapping group benefit from higher quality of fit of $K_{trans}$ and $v_e$, which makes sense considering they are generally associated with higher signal increase post-Gd.

Figure 4.16 shows the histograms of $K_{trans}$ values in the overlapping and non-overlapping groups of combined data. The shape of the histograms was similar in all three separate data sets, hence presenting them combined makes them statistically more significant. Figure 4.17 is a useful representation of the same data in terms of percentiles. As predicted, voxels that enhanced on the 3T but not on the 1.5T protocol were generally associated with lower $K_{trans}$. The mean and median $K_{trans}$ were 57% lower in the non-overlapping pool with respect to their values in the overlapping pool. $K_{trans} = 0.005 \text{ min}^{-1}$ appears as a good candidate for the sensitivity threshold of the standard protocol, with 76% of non-overlapping voxels having a permeability below 0.005 $\text{min}^{-1}$ and 76% of overlapping voxels a permeability above that.

Figure 4.18 shows the histograms of $v_e$ values in the overlapping and non-overlapping groups of combined data. The shape of the histograms was also similar in all three separate data sets. Figure 4.19 provides a representation of the same data in terms of percentiles. As predicted, voxels that enhanced on the 3T but not on the 1.5T protocol were generally associated with lower $v_e$. The mean (median) $v_e$ was 45% (55%) lower in the non-overlapping pool with respect to its value in the overlapping pool. $v_e=8\%$ appears as a good candidate for the sensitivity threshold of the standard protocol, with 70% of non-overlapping voxels having an EES fraction below and 70% of overlapping voxels an EES fraction above 8%. 
Figure 4.14: Evolution of enhancing volumes between timepoints M0 and M1 on a per-lesion basis, in the first patient. At M0, six lesions were visible with the optimized protocol, and four of them were also seen with the standard protocol. At M1, one lesion had disappeared on the optimized protocol, but two new ones had appeared, taking the count to 7. The two new lesions were also visible with the standard protocol, but two of the four older lesions had disappeared. The volume of each segmented lesion is always larger with the optimized than with the standard protocol.
4.2 Comparative study of enhancement at “3T–triple dose” vs. “1.5T–single dose”

Figure 4.15: Same brain slice showing on the post-Gd images with the 3T–triple dose (a) and the 1.5T–single dose (b) protocols, at M0 in the first patient. The volume of enhancement is larger with the optimized protocol, and the enhancement is also more pronounced, with higher signal increase relative to surrounding normal WM. The normal tissue contrast is also different between the two because the 3T protocol uses an MT pulse prior to the $T_1$-weighted 3D-FLASH block to decrease the mean signal intensity, while the 1.5T protocol does not use an MT pulse.
Results

(a) $K_{\text{trans}}$ values in voxels enhancing on both protocols. Mean: $0.0089 \text{ min}^{-1}$. Median: $0.0077 \text{ min}^{-1}$.

(b) $K_{\text{trans}}$ values in voxels enhancing on the 3T-triple dose protocol only. Mean: $0.0039 \text{ min}^{-1}$. Median: $0.0033 \text{ min}^{-1}$.

**Figure 4.16: Histograms of BBB permeability values in the overlapping and non-overlapping voxels.** Some voxels were discarded on the basis of poor fit results. The mean and median values indicate that voxels that enhance only on the 3T protocol are generally associated with lower permeability than voxels that enhance on both.
Figure 4.17: Percentile representation of BBB permeability values distribution. Percentile = X. X% of non-overlapping voxels have a permeability below f(X) (red). X% of overlapping voxels have a permeability above f(X) (blue). The graph thus suggests that 76% of non-overlapping voxels have a permeability below $0.005 \, \text{min}^{-1}$ while 76% of overlapping voxels have a permeability above this same value. $K_{\text{trans}}=0.005 \, \text{min}^{-1}$ appears as a good candidate for the sensitivity threshold of the standard protocol.
Figure 4.18: Histograms of EES fraction values in the overlapping and non-overlapping voxels. Some voxels were discarded on the basis of poor fit results. The mean and median values indicate that voxels that enhance only on the 3T protocol are generally associated with lower EES fractions than voxels that enhance on both.
Figure 4.19: Percentile representation of EES fraction values distribution. Percentile = X. X% of non-overlapping voxels have an EES fraction below f(X) (red). X% of overlapping voxels have an EES fraction above f(X) (blue). The graph thus suggests that 70% of non-overlapping voxels have a $v_e$ below 8% while 70% of overlapping voxels have a $v_e$ above this same value. $v_e$=8% appears as a good candidate for the sensitivity threshold of the standard protocol.
Discussion

The previous chapter presented the performance of a new DCE-MRI protocol that improves the accuracy and precision of BBB permeability measurements in MS patients. This protocol was successfully tested on four MS patients during the validation step, and compared to a conventional protocol through simulations. Preliminary results from the study of differences in sensitivity of two enhancement protocols were also presented. The latter study makes use of the new DCE-MRI protocol to obtain quantitative permeability maps in the brain.

5.1 The dual-temporal resolution DCE-MRI protocol

The dual-temporal resolution data produced $K_{\text{trans}}$ and $v_e$ estimates that were consistent with the range of values previously reported in the MS literature [23]. The average $K_{\text{trans}}$ value in MS enhancing lesions was found to be $0.01 \ \text{min}^{-1}$, indeed lower than values reported in brain tumours ($0.03 \pm 0.05 \ \text{min}^{-1}$ [26]) and substantially lower than those in the body (e.g. $0.1$–$0.3 \ \text{min}^{-1}$ in muscle [31]). The permeability-limited regime approximation is therefore well justified in MS cases, and the addition of other parameters to the model (e.g. blood flow) unnecessary, unlike in brain tumour or body perfusion studies. The CA uptake curves in the enhancing lesions displayed no first-pass peak (characteristic of a significant vascular/plasma component in the voxel), which justifies neglecting the volumetric fraction of plasma $v_p$ in a WM voxel (see Equations (2.8) and (2.10), p. 33).

In spite of the slow kinetics of CA uptake in MS enhancing lesions, the DCE-MRI acquisition does nonetheless still require relatively high temporal resolution in the first minute following CA injection, because the AIF dynamics need to be sufficiently sampled.

The shape of the AIF, as acquired in the first minute post-injection, has a large impact on the $K_{\text{trans}}$ fit even if the CA uptake in the enhancing lesion is still negligible at that time, because
5.1 The dual-temporal resolution DCE-MRI protocol

the AIF is convolved with an exponential term to calculate the concentration in the enhancing lesion. The difference in $K_{\text{trans}}$ estimates produced by an AIF where the first-pass bolus was captured (using our 5 s + 32 s protocol) vs one where the first-pass bolus was undersampled (using the conventional protocol) was significant both in the experimental data and in simulations (see Figures 4.7 and 4.9).

The simulations also showed that, as expected, a correct sampling of the AIF with the dual-temporal resolution protocol ensures a more accurate and precise fit of $K_{\text{trans}}$ under many different circumstances:

- The suggested protocol is essentially insensitive to time offsets of up to 45 s between acquisition and injection start times, whereas a 32 s resolution acquisition displays peaks of error in $K_{\text{trans}}$ for delays that cause a complete miss of the first-pass peak. The dual-temporal resolution protocol therefore also removes any requirements for a power injector or any constraints on injection start time, provided the latter is not delayed excessively. Indeed, the high temporal resolution allows the detection of the exact time of arrival of the CA in the plasma, as well as the time of the peak;

- The dual-temporal resolution protocol is also relatively insensitive to differences in shape of the first-pass peak between patients and sessions, again in terms of permeability measurement performance. On the other hand, a 32 s resolution protocol leads to increased errors in $K_{\text{trans}}$ estimates for AIFs with higher and/or narrower peaks. Since the height and the width of the first-pass peak depend not only on the injection rate but also on the patient’s physiology at that time, it is essential to record this variability through the measurement of the AIF. Indeed, an accurate combination of input function and tissue uptake curve is necessary for proper $K_{\text{trans}}$ estimation. The various shapes of AIF that were measured during our experiments are also an argument in favour of the systematic measurement of the AIF upon each new scan, and against the use of a standard (either model-based or population-averaged) AIF;

- If the first-pass bolus is improperly sampled, the error that results in the permeability estimate increases with the permeability value itself. On the contrary, when the first-pass bolus is properly sampled (be it with a 5 s resolution or with a 32 s resolution and appropriate delay between acquisition and injection start times), the accuracy and precision of the $K_{\text{trans}}$ estimate remains relatively independent of the true $K_{\text{trans}}$ value, in the range encountered in MS enhancing lesions. The sustained good performance even on the higher end of $K_{\text{trans}}$ values (typically 0.03 min$^{-1}$ for MS lesions) also validates the assumption that the CA uptake is slow enough in the lesions to be negligible during the first minute. We stress that this assumption was important for the breakdown of the acquisition into two
parts: the first part at high temporal resolution and low spatial resolution (which we do not use to look at lesions) and the second part at lower temporal resolution and high spatial resolution (which we use to look at both uptake in the lesions and equilibration/washout in the plasma).

The performance of both the dual-temporal resolution and the 32 s acquisition schemes to accurately and precisely estimate BBB permeability, as assessed through our simulations, is realistic and unsurprising. However, the experimental results regarding the performance of the conventional scheme should be treated qualitatively rather than quantitatively. Indeed, no actual acquisition at a 32 s resolution in patients was performed: the data at 5 s temporal resolution was resampled to mimic a 32 s resolution. Although the resampling and averaging of data points was made around the time when the centre of k-space would have been acquired in a 32 s acquisition (which gives the main contribution to the signal level), a real experiment would have undoubtedly given slightly different values of signal. Neither does the simulation account for all the concentration levels reached during the acquisition of each time frame weighted by the various positions in k-space: it also only considers the concentration level at the time when the centre of k-space would be acquired, to calculate the signal magnitude. However, such an approximation introduces small distortions if the rate of concentration change is lower or comparable to the sampling rate. This is certainly the case after the first minute post-injection, and likely also during the first minute at a 5 s resolution. Therefore, the simulation results regarding the performance of the dual-temporal resolution protocol are quantitatively meaningful, whereas the ones of the conventional protocol are more likely only qualitatively meaningful. We note that a direct experimental comparison would be difficult since it would require scanning on two different days. Physiological changes with time would not be controlled for in this case.

All in all, the dual-temporal resolution protocol provides an estimate of BBB permeability in MS enhancing lesions with a -1% bias and a RMSE of about 7%. This accounts for two sources of error: noise and the sampling rate. Very importantly, the levels of inaccuracy and uncertainty remain independent of the delay between acquisition and injection start times, the shape of the first pass peak and the actual permeability value. This stability of performance is the major advantage with respect to the conventional protocol.

To further improve the overall accuracy of the permeability measurement, $B_1$ mapping should be included to correct for RF inhomogeneities and therefore improve the accuracy of the $M_0$ and $T_1$ maps. A rapid estimation of this error with our imaging parameters, magnet properties and tissue properties showed that the relative error introduced in $\Delta R_1$ (and therefore in CA concentration) could range from -30% to 60%. This experimental error is however not expected to impact the conclusions in this work, because the effect of temporal resolution was assessed through
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Simulations free of RF distortions. The other sources of error are expected to be comparatively negligible in our experimental conditions: exact relaxivity value in the tissues, non-linear relationship between relaxivity rate change and CA concentration and partial volume effects.

While studies of more rapid kinetics (such as brain tumour or muscle perfusion) made very good use of the evolving MR technology that allows ever higher temporal resolution for DCE-MRI data, the study of MS enhancing lesions with DCE-MRI has drawn very little attention since the work published by Tofts and Kermode in 1991 [23]. The dual-temporal resolution protocol improves permeability estimates from DCE-MRI data by making use of fast imaging methods (parallel imaging, fast gradient switching, spoiling methods...) to sample the first pass bolus in the AIF, without compromising on spatial resolution when it is needed to properly detect and segment the lesions. Accurate and reproducible permeability measurements could allow follow-ups on the severity of BBB disruption. They are also indispensable to studies on the sensitivity to BBB disruption of various enhancement protocols, such as the one that was started during this thesis. The proposed DCE-MRI protocol can be easily inserted into a standard contrast enhancement protocol, since the latter usually comes with a certain amount of ‘dead time’ during and after the injection, before the post-Gd image is acquired.

5.2 Comparative study of enhancement

The dual-temporal resolution DCE-MRI protocol was successfully incorporated into the comparative study of enhancement between the 3T–triple dose and 1.5T–single dose protocols. The post-Gd images obtained with one and the other protocol showed significantly different levels of enhancement, in terms of volume, number of lesions and intensity, proving the pertinence of the questions raised in this study. The preliminary results obtained support the main initial hypotheses:

- Voxels classified as enhancing only on the 3T protocol are generally associated with lower permeability values than voxels enhancing on both protocols. The optimized protocol is able to detect lower levels of BBB disruption than the standard protocol: each protocol has its own sensitivity threshold;

- In lesions that appear to be resolving between the M0 and the M1 scans, the decrease in volume is more pronounced with the standard than with the optimized protocol, the former sometimes even disappearing completely. Enhancing lesions do indeed appear to last longer on the optimized protocol. The hypothesized explanation was that permeability decreases below the level of detection of the 1.5T protocol, but not below that of the 3T scan.
The preliminary results are all the more encouraging as the distributions of permeability values between the overlapping and non-overlapping pools of voxels was very similar between patients and between timepoints. The permeability thresholds established upon each pair of scans were close in value, supporting the idea that the threshold is indeed intrinsic to the protocol. The hypothesis was further developed when analyzing histograms of EES fraction values. They showed the same trends and threshold effects as the permeability histograms. A more complete – and reasonable – statement would therefore be that each enhancement protocol is associated with a detection threshold defined by a combination of permeability and EES fraction levels. Indeed, given the same permeability level, a higher leakage space within a voxel allows more contrast to accumulate and therefore leads to larger signal increase. The interplay between permeability and EES fraction could actually be even more subtle: a protocol with a shorter delay between injection and post-Gd imaging is likely to have a detection threshold highly dependent on permeability and less so on the EES fraction, and vice versa for a protocol with an extended delay. The data collected so far is however insufficient to draw any definite conclusions on these matters.

The efforts put into beginning this study showed how challenging it is.

First of all, obtaining full data sets on patients is very difficult. As mentioned earlier, enhancement is not known a priori and in spite of rigorous screening, enhancing lesions are not systematically found. Moreover, the timings between the different scans (3–4 days between the 3T and the 1.5T and one month between M0 and M1 sessions) are very constraining in terms of scanner and patient availability. Also, any relapse or acceleration in disease progression between M0 and M1 would cause patients to be put either on steroids or on a more aggressive treatment, making scanning at M1 irrelevant. Patients must also have good kidney function because of the high doses of contrast injected. The initial plan of acquiring full data sets on 20 patients might be difficult to achieve and, based on our preliminary results, may not be necessary to test the hypotheses.

The screening method also introduces a bias. The first scan is always performed on the 3T because of the increased sensitivity of the optimized protocol: if no enhancing lesions are found, the patient is not enrolled in the study. An initial scan free of enhancing lesions with the standard protocol would not guarantee that the patient would show no lesions with the 3T protocol, requiring a second scanning session on the 3T anyway. For this reason, patients are always scanned on the 3T prior to the 1.5T, both at M0 and M1. Ideally, the order of the scans should be randomized, because they are 3–4 days apart and nonetheless associated to the same moment in time (M0 or M1). Any genuine changes in the WM inflammation within 3–4 days are for now systematically interpreted as differences in sensitivity of the standard protocol. Solutions to this issue for the remainder of the study are currently being considered.
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On the analysis part, image registration also constitutes a potential source of biases. Since most of the study is based on voxel-to-voxel analysis, care must be taken not to introduce any biases through the resampling of quantitative permeability maps or lesion label volumes. Resampling the former could result in an artificial decrease of permeability on the edges of an enhancing region by averaging with neighbouring zero-permeability voxels, and resampling the latter could alter their shape by nearest-neighbour interpolations. The current solution of registering every image from a given timepoint (M0 or M1) to the 3T post-Gd image at that timepoint is also not optimal. Indeed, the 1.5T post-Gd data gets somewhat blurred in the resampling process, while the 3T post-Gd data does not, which can potentially introduce a bias when determining enhancing or non-enhancing regions. This issue will be addressed in future analyses by registering every image from a given timepoint to a reference that is neither of these images. It is, however, unlikely to change the results in a dramatic way.

The analysis of the parametric maps raised another important issue. In the non-overlapping pool in particular, around half the segmented voxels were discarded on an “unreliable fit” basis ($R^2 < 0.5$ or $v_e > 60\%$). If the signal increase in a voxel was sufficient for it to be classified as enhancing, why is it that in half of these cases the fit to the pharmacokinetic model failed? The reason is very likely related to the fact that the classification as “enhancing” was done on a post-Gd image following a triple Gd dose and an extended 35 min total delay, while the BBB permeability and EES fraction maps were generated from dynamic data acquired during 20 min following a single dose injection. Since the non-overlapping pool contains voxels with low BBB permeability and/or EES fraction, the signal increase in those voxels was still too low after a single dose and within 20 min of uptake to allow the uptake curve to be reliably fit to the model, but signal increase was significant enough after a triple dose and an extended delay for uptake.

It would be extremely challenging to redesign the whole protocol to allow the quantitative maps to be calculated in the same sensitivity conditions as the more sensitive enhancement protocol. On the one hand, AIF and uptake curves are more difficult to model and fit in the case of multiple injections. On the other hand, injecting the triple dose as one bolus would cause signal saturation (the longitudinal relaxation would become too fast), making any $T_1$ measurement, and therefore CA concentration, impossible for some time following the injection.

For now, the selected approach still seems the most practical and reasonable. Its limitation in terms of sensitivity of the quantitative maps will likely have to be accepted. For the purpose of testing the proposed hypotheses, it should not prevent conclusions to be drawn. Indeed, the voxels discarded on poor quality of fit criteria likely have low $K_{trans}$ and $v_e$ values. The fact that they belong, for the most part, to the non-overlapping pool still brings a satisfactory conclusion.
Conclusion and future work

A new DCE-MRI protocol for MS was developed and tested. It is easy to implement and does not require a power injector. It is based on a split acquisition with a first part at high temporal and low spatial resolutions and a second part at low temporal and high spatial resolutions. The dual-temporal resolution protocol improves the accuracy and precision of BBB permeability estimates in enhancing lesions compared to the conventional protocol (low temporal and high spatial resolution throughout). Its performance is stable with respect to time offsets between the acquisition and the injection start times, differences in shape of the first-pass peak and permeability values. A major improvement that should and could be easily made to the protocol is the inclusion of a $B_1$ map acquisition to correct the $T_1$ and $M_0$ maps for RF inhomogeneities.

This BBB permeability mapping technique with improved accuracy can be used for the purpose of a comparative study of enhancement between an optimized and a standard non-dynamic protocol. Results on two patients were presented in this thesis and the study will continue with the total projected enrollment of up to 20 patients. Preliminary results are encouraging, with a noticeable permeability and EES fraction threshold effect between the two enhancement protocols. Further data analyses should incorporate optimized registration techniques. A larger pool of patients should give stronger statistical significance to our preliminary findings.
Bibliography


