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YELLING OUT FOR THEORY - SPATIALLY SELECTIVE NMR AT THE LENGTH SCALE OF DIFFUSION

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Abstract. This contribution explores describes the effect of diffusion on the recovery of nuclear magnetization in small selectively excited volumes. Implications of these findings for microscale MRI experiments and mechanically detected NMR are discussed and the need for further developments on the theoretical side is pointed out.

1 INTRODUCTION

Presently, almost all spatially selective NMR takes place at length scales in the 100 µm range and above. Diffusion NMR, by contrast, is capable of mapping mean displacements even below the µm scale but most diffusion NMR experiments are carried out without spatial resolution. Diffusion mapping by MRI is also an old technique but encoding and spatial resolution are usually separated both by the implementation in the sequence and by different length scales. Some artifacts such as edge enhancement effects or diffusive echo attenuation due to the gradients responsible for spatial resolution have also been known for long time [1,2].

Only quite recently, the direct spatial resolution in MRI has been pushed down in all spatial directions to length scales well below the diffusion length scale of water which is about 50 µm in one second. As most of the early experiment in this field were carried out using liquid phases with a smaller self-diffusion coefficient [3], the effects were not systematically studied except for one paper describing the realization of DESIRE [4] in such a setup. With great advances in the technology for miniaturized MRI [5], subcellular MRI becomes now more and more accessible for a larger community of researchers. With this comes also a need for a systematic understanding of the interplay of spatially selective excitation techniques and diffusion phenomena at these length scales.

2 EXPERIMENTAL STUDIES ON LONGITUDINAL MAGNETIZATION RECOVERY IN THIN EXCITED SLICES

2.1 Magnetization recovery under non-periodic excitation conditions

A first set of experiments aiming at the interplay between diffusion and longitudinal magnetization recovery was conducted with a simple saturation-recovery-type experiment on thin selectively excited slices of water in a constant gradient magnet [6].

In these experiments, spatial selectivity was achieved by the use of "hard" 90° pulses of different length. Which results in a roughly sinc-shaped spatial excitation profile of the magnetization instead of a well-defined excitation volume. In order to avoid possible detrimental effects of the unwanted excitation outside the central maximum of the sinc-profile, the experiments were run in a way that the sample was allowed to fully relax after each excitation. The sequence consisted of a single 90° pulse for saturation followed by a variable waiting time and two 90° pulses in order to probe the magnetization recovery and detect it by means of a "figure-8" echo [7]. The use of pulses of the same length and shape ensured the same spatial profile for all pulses and like this the matching between saturation and probing. The experimental data showed an increasingly fast recovery of the magnetization with decreasing slice thickness *b* in the range of the saturation memory length

$$l_{sm} = \sqrt{2DT_1} \tag{1}$$

or shorter. For water, the saturation memory length is on the order of 140 µm.

A model was developed for the magnetization recovery behavior which can be analytically solved for the case of a Gaussian slice profile

$$< M(t) >_x = M_o \left(1 - Q \frac{\exp(-\,t/T_1)}{\sqrt{1 + Dt/b^2}} \right). \tag{2}$$

Eqn. (2) can be approximated for short time delays to a simple exponential decay with an effective longitudinal relaxation time T_{1Diff} given as

$$\frac{1}{T_{1Diff}} = \frac{1}{T_1} + \frac{D}{2b^2} \tag{3}$$

Equation (3) suggests a dramatical decrease of T_{1Diff} for thin slices: for a slice thickness of 1 µm (which was not accessible in the experiments reported in [6] both for signal/noise reasons and unrealistically long 90° pulse durations), an effective longitudinal relaxation time of less than 1 ms would be expected instead of 3 s for bulk water. Such an extreme reduction of the effective T_1 time would have a great impact on the applicability and results of many standard magnetic resonance imaging (MRI) methods.

However, it must be noted that the experiments reported here were conducted on fully relaxed samples. In MRI, by contrast, fully relaxed samples are rather uncommon as repetition times are often chosen considerably shorter both for speed reasons and for obtaining T_1 weighted images. Even faster cycling of saturation would be needed in saturation-recovery sequences suggested for mechanically detected magnetic resonance [8].

In contrast to the experiments on fully relaxed samples, there will be incompletely relaxed magnetization from earlier saturation cycles present outside the excited volume. This can be expected to lead to less efficient magnetization recovery as a result of diffusive exchange between the selected volume and its surroundings (see figure 1). These considerations provided the motivation for a further set of experiments.

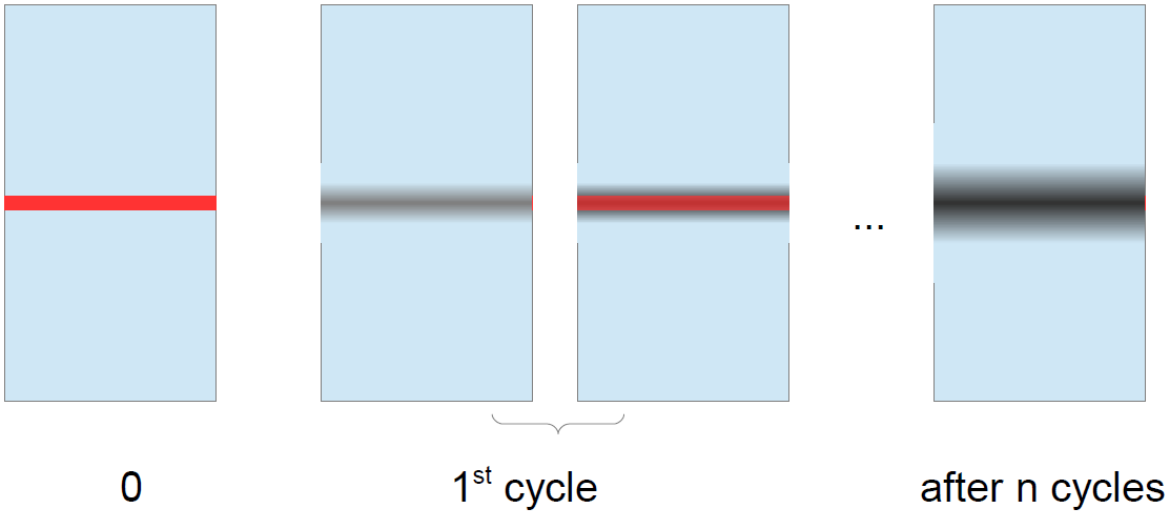

Figure 1: Excited slice profile (red) and remaining saturation of the magnetization (gray) in a cyclic excitation experiment

2.2 Magnetization recovery under periodic excitation conditions

Like the non-periodic study, there experiments [9, 10] were carried out in a constant-gradient magnet. After a series of first experiments using a train of "figure 8" echoes, the expected effect could indeed be observed [9], however it also turned out that a more sophisticated experimental setup would be needed for a systematic study of the effect: In order to improve the signal noise ratio of the NMR experiment by achieving a higher "signal filling factor", a flattened RF coil with a rectangular cross-section [11] was used instead of the simple solenoid used in the first study. Furthermore, a new spectrometer console allowing the use of shaped RF pulses was used in the new series of experiments. In order to allow experiments with a well-defined distance between diffusion barriers (such as the walls of the measurement cell) and the excited slice, a positioning stage was built.

Based on the results of first test experiments, the necessity of further modifications to the experimental setup become obvious, especially with respect to excitations at a well-defined distance to the wall: As a result of the Maxwell equations, the isofield lines in an anti-Helmholtz-type constant gradient magnet are substantially curved except for some really tiny regions with almost flat isofield lines. Moving the NMR excitation into this range was therefore

a crucial measure in order to be able to measure at a given distance to the wall. Furthermore, positioning these flatfield regions of the constant gradient magnet and the NMR probehead with respect to each other is also a considerable challenge as for example thermal expansion of the magnet and probe head materials may lead to relative position shifts in the range of several 10 µm for a change in the magnet temperature of just 1 K.

A further challenge is concerned with the slice-selective excitation itself: While sinc-like profiles were acceptable for the experiments on fully relaxed samples, any profile with considerable out-of-slice excitation may lead to serious experimental artifacts in the periodic excitation experiments where these effects will add up over many excitation cycles and will lead to additional modifications of the out-of-slice magnetization profile. Like this, highly selective excitation pulses were needed. Going to better slice profiles in a constant gradient magnet comes with yet another problem for the classical signal detection approach using a "figure 8"-echo: due to strongly increasing pulse durations, the diffusive signal attenuation during the echo time become more and more pronounced and further reduces the signal/noise ratio.

However, as described in [10], the narrow excitation bandwidth used in the slice-selective experiments allows the use of FID-like signals instead of the echo for detecting the NMR response of the selected slice. Good results for the FID-detection can be achieved when working with truncated sinc-pulses stopping after the main half-wave.

While the observation of FID-like signals seems qualitatively rather straightforward, the quantitative description of the signals is more complicated as the usual Fourier approximations are not valid any more under these conditions. The description of the effects was instead achieved on the basis of a full numerical integration of the Bloch-Torrey equations (with precession, relaxation and diffusion contributions calculated consecutively for each time step [12]). This analysis reveals a rather unexpected dependence of the FID signal on the excitation angle with maximum FID intensities occurring at a flip angle of 244° (see figure 2).

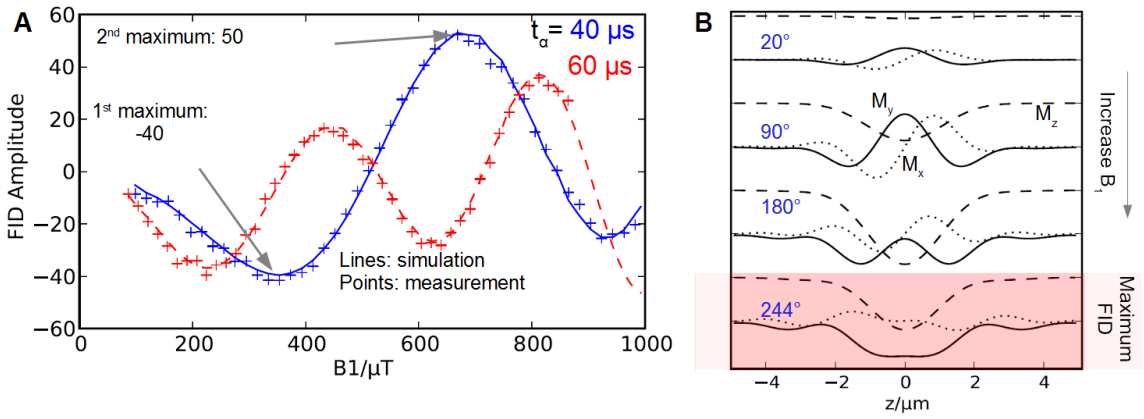

Figure 2: (A) FID amplitude for selective pulses with two different lengths as a function of the RF amplitude; both experimental results and simulations are shown (B) spatial magnetization profiles from the simulations. As one can see, the unusual flip angle leading to the first maximum is mainly the effect of side lobes with opposite signs. Only the y-component (full lines) contributes to the observed signal.

In figure 3, the amplitudes obtained in a train of FID-experiments with different repetition times are given for water with a slice thickness of 3.6 µm. As one can see from the figures on

the right hand side of the graph, the steady state signal intensity in all cases is more than an order of magnitude larger than the intensity that would be expected on the basis of the bulk T_1 value of water.

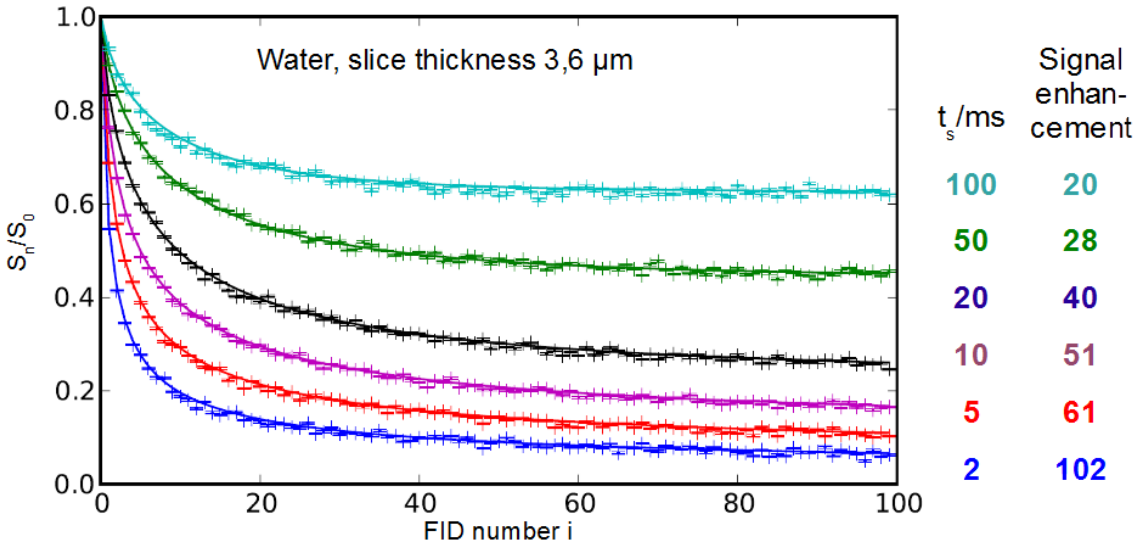

Figure 3: Measured and simulated FID amplitudes observed in a train of selective excitations on a thin slice of water for different time spacings t_s. On the right hand side, the signal enhancement over the expectations based on the bulk T_1 of water is given.

The experiments in figure 3 were carried out in a thin slice of free water far away from walls and in absence of relaxation sinks. Diffusion barriers located at distances shorter than the saturation memory length will lead to a further accumulation of partially saturated magnetization near the excited slice and thus to a reduced signal enhancement compared to a slice localized in free water [10]. By contrast, out-of-slice relaxation sinks located within the saturation memory length may lead to increased signal modulation inside the excited slice.

3 CONCLUSIONS AND NEED FOR FURTHER RESEARCH

As the results summarized here indicate, the impact of diffusion effects plays in spatially selective NMR experiments becomes even more dominating at length scales below the saturation memory length as also longitudinal magnetization recovery is increasingly affected by diffusion effects.

It should be noted that those effects are not just about dramatically different time constants for the magnetization recovery process but also lead to a fundamentally different nature of the contrast effects: While the contrast in conventional MRI is essentially determined by the NMR properties inside each voxel, the contrast on length scales below the saturation memory length is also sensitive to structures outside the actually excited volume.

This non-local behavior of the contrast creates a need for novel models to describe contrast phenomena for MRI at short length scales, e.g. subcellular MRI. While our present models are capable to describe the modulation effect in a 1D-experiment, a 3D description would be needed

to take into account the subcellular MRI scenario. However, the present approach to describe the effects via simulations is not really appropriate to be useful in a biophysical application context for subcellular MRI. In figure 4, a comparison between the present stage of description on the effects in classical MRI and in subcellular MRI is given: There is still an obvious gap in the field of rough quantitative interpretations which would be comparable with the kind of models used for the extraction of parameter maps from classical MRI data.

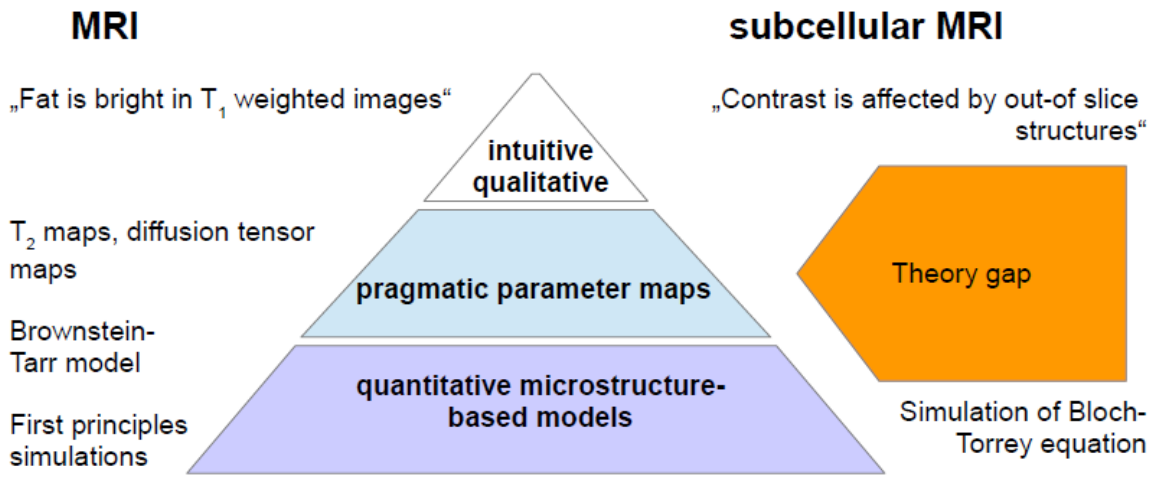

Figure 4: Different levels of quantitative understanding of effects in classical MRI and in subcellular MRI taking into account the diffusion effects on longitudinal magnetization described here. There is a clear theory gap with respect to simple quantitative models that allow an extraction of parameters and some correlation to microstructural features.

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