Multiple Quantum Coherences: New NMR Tools to Study Materials and Living Systems

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Abstract. Intermolecular multiple-quantum coherences have been proven in recent years to provide a novel contrast mechanism to study heterogeneity in liquid systems. This subject represents a source of remarkable interest in the fields of physics of matter and biomedicine. Recent results achieved on intermolecular double-quantum signal transverse relaxation decay in confined liquid systems (such as in vivo bone marrow in trabecular bone, and doped water in glass capillary pipes) are reported and discussed in this paper. Correlated two-dimensional spectroscopy revamped by asymmetric z-gradient echo detection-like sequences were implemented in order to perform intermolecular double-quantum transverse relaxation $T_{2D}$ and $T_{2I}$ measurements. Our experimental results indicated that the relationship $T_{2I} = T_{2}^n$ between $n$-quantum transverse relaxation time and the conventional single-quantum $T_{2}$ only applies for homogeneous systems and fails in the case of highly heterogeneous systems like porous systems.

1 Introduction

Intermolecular multiquantum coherences (iMQCs) [1] are generated by residual intermolecular dipolar couplings in liquids. This occurs when a magnetic field correlation gradient with amplitude $G_c$ breaks the sample magnetic isotropy, causing a signal refocusing by intrinsic long-range dipolar couplings.

In the conventional picture of nuclear magnetic resonance (NMR) in liquid-state systems, the effects of dipolar interaction are generally neglected because the short-range dipolar interactions between spins are averaged out due to Brownian motions. Long-range (intemolecular) dipolar interactions, on the other hand, are geometrically averaged to zero by symmetry over the sample scale, as long as the magnetization is spatially isotropic. When magnetization is a function of position, in fact, the long-range dipolar interactions give rise to an observable signal.

In the quantum mechanical approach to describe the signal from iMQCs, the high-temperature approximation [2] no longer applies and the iMQCs signal origi-
nates from the density operator expansion of higher orders. The basic pulse sequence for observing iMQCs is the correlated two-dimensional (2-D) revamped by asymmetric z-gradient echo detection (CRAZED) proposed by Warren and co-workers [3, 4]. According to the CRAZED sequence, iMQCs terms generated after the first 90° radio-frequency (RF) pulse are transferred into observable single-quantum coherences (SQCs) terms both during a mixing period under the effect of magnetic field gradient pulses which select a specific order of iMQC and during the following dipole-dipole Hamiltonian evolution period.

In the past few years, the iMQCs phenomena have attracted great attention especially for their potential application in diagnostic [5–8] and functional magnetic resonance imaging (MRI) [9] because of a new contrast mechanism based on the intermolecular dipolar interaction between spins at a macroscopic correlation distance. In particular, the amplitude of the iMQCs relies on sample heterogeneity over a correlation distance \( d_c = \pi / (\gamma G t) \), where the parameters \( G_c \) and \( t \) (the pulse gradient duration) can be varied as occasion may require. Despite of a lower signal-to-noise ratio (SNR) with respect to the single-quantum signal images, the iMQCs images revealed features [5, 8–10] undetectable with conventional MRI. The iMQCs signal intensity is in fact determined by the dipolar correlation distance, the magnetic field inhomogeneity, the susceptibility effects, the molecular multiquantum diffusion [11] and the radiation damping [12].

Despite a deep knowledge and a satisfactory description of the iMQCs signal behavior in homogeneous liquid systems achieved in the past years, scarce literature is available concerning the behavior of the iMQCs signal originated by heterogeneous systems such as fluids in porous media. Because of its huge interest in the fields of physics of matter and biomedicine, we have been studying the intermolecular double-quantum signal intensity in heterogeneous systems, and attention was devoted to the double-quantum signal obtained by the 2-D CRAZED pulse sequence.

In this paper, experimental results obtained both on water in capillaries and on in vivo bone marrow in trabecular bone were reported. Double-quantum transverse relaxation time \( T_{2DQ} \) and \( T_{2DQ} \) measurements were performed by CRAZED-like sequences indicating that multiquantum transverse relaxation time values could be helpful tools for a close investigation of properties of heterogeneous systems and iMQCs mechanisms.

2 Materials and Methods

In order to calibrate double-quantum relaxation time measurements, a simple phantom was first assembled by setting three glass capillary pipes with an inner average diameter of 0.62 mm filled with 10 mM copper sulfate-doped water. The attenuation of the single-quantum magnetization intensity, conventionally described by \( T_1 \) and \( T_2 \) relaxation times, satisfied a biexponential behavior during the evolution period. Two components associated with values of 1 s and about 200 ms were found for the longitudinal relaxation time, while 60 and 130 ms were ob-

![Fig. 1. CRAZED-like pulse sequence for the signal decay. The 90\(^{\circ}\) RF pulse was magnitude twice the first one constituting the two different iMQCs signal transverse relaxation time sequences. The evolution time \( 180° \) relaxation effects are mainly reported in the long relaxation time.](image-url)
orders. The basic pulse sequence was a 2-dimensional (2-D) revamped version of one proposed by Warren and co-workers. The iMQCs terms generated after the initial excitation period under the effect of a specific order of iMQC and the evolution period.

These have attracted great attention in the literature [5–8] and functional magnetic resonance imaging (fMRI) contrast mechanisms, the design and implementation of iMQCs relies on sample acquisition that, where the parameters $G_z$, $G_2$, and $G_3$ are chosen to occur at the frequency of the radiation damping [12].

By the description of the iMQCs signal in the past years, scarce is the iMQCs signal originated from the literature. Because of its huge potential in medicine, we have been studying the effects of iMQCs signal originated from inhomogeneous systems, in particular that from the $2$-D spin dipole lattice in water in capillaries and other heterogeneous media. Double-quantum transfer can be performed by CRAZED-like pulse sequences and the relaxation time values can be deduced from the properties of heterogeneous media.

In the measurements, a simple capillary pipe filled with water sulfate-doped water. The relaxation behavior, conventionally described by exponential behavior during the evolution period up to $1$ s and about $200$ ms later, $T_{1}$ and $T_{2}$ relaxation times were obtained for the transverse relaxation time. Then in vivo experiments on bone marrow in trabecular bone at the level of the distal human femur were performed. In such a case, the conventional relaxation time measurements produced the values of $1.1$ s for $T_1$ and $80$ ms for $T_2$. Furthermore the $T_2$ relaxation time of bone marrow in trabecular bone was found to be about $7$ ms.

CRAZED-type sequences were implemented on a Siemens Vision MR scanner operating at $1.5$ T (Siemens Medical System, Erlangen, Germany) to perform in vivo experiments and on a $7$ T Bruker Biospec horizontal magnet to perform experiments on water in glass capillary pipes.

The first sequence implemented (Fig. 1a) consisted of two $90^\circ$ pulses spaced by a delay time $\tau$ combined with a pair of magnetic field gradient pulses, with an integral ratio (gradient amplitude multiplied by duration) of $1:2$ in order to select second-order iMQCs (intermolecular double quantum coherences, iDQCs). An additional $180^\circ$ RF pulse after a delay $TE/2 + r$ after the second RF pulse refocuses conventional magnetic field inhomoenogenuity $TE/2 − r$ later.

A second CRAZED-like sequence (Fig. 1b) was obtained by adding a $180^\circ$ RF pulse between the two initial $90^\circ$ RF pulses in order to refocus multiplet quantum inhomogeneities. As reported by Warren et al. [2], iDQCs are produced after the first $90^\circ$, while the second $90^\circ$ pulse transfers the second-order iMQCs, selected by the magnetic field correlation gradients, to observable SQCs. The $180^\circ$ RF pulses are

![Image of CRAZED-like pulse sequences](image)

**Fig. 1.** CRAZED-like pulse sequences implemented for studying the intermolecular double-quantum coherence. The $90^\circ$ RF pulse with two magnetic field gradient pulses, the second one with amplitude twice the first one constitutes the double-quantum filter. a and b The sequences give rise to different iDQCs signal transverse relaxation weighting. a $T_{200}$ effects are present during the double-quantum evolution time (before the second $90^\circ$ RF pulse). b Because of the first $180^\circ$ RF pulse, $T_{200}$ relaxation effects are mainly present during the iDQCs evolution period; the total interval duration $TE$ was reported, rather than the values $TE/2 + r$ before the $180^\circ$ pulse and $TE/2 − r$ between the last RF pulse and the echo refocusing.
pulse refocuses therefore single-quantum magnetic field inhomogeneities, thus generating an echo at the time \( TE \) after the second 90° pulse.

Since the signal intensity of the SQCs is also weighted by the iDQC \( T_2^q (T_{2\text{DQ}}) \), which is the double-quantum relaxation time during the evolution period \( r \), \( T_{2\text{DQ}} \) can be calculated collecting CRAVED signal intensities for different values of the evolution period \( r \). By following the same idea and collecting the signal of the sequence in Fig. 1b, in which the double-quantum inhomogeneities are refocused by the 180° pulse between the 90° pulses, also \( T_{2\text{DQ}} \) can be calculated [12].

In vitro experiments were performed by applying the correlation gradients perpendicular to the glass capillary pipes symmetry axis (which is parallel to the main magnetic field). CRAVED-type measurements (\( TR = 10000 \) ms, \( r \) variable, correlation gradient duration \( t = 3 \) ms, number of accumulations \( n_s = 64 \)) were repeated for different values of the correlation gradient intensity \( G_c = 16.8 - 0.02 \) mT/m in order to select the appropriate range of correlation distance values \( d_c = 233 - 2000 \) μm. Experimental data were fitted with a biexponential decay function to obtain an estimate of \( T_{2\text{DQ}} \) and with a monoexponential function for the \( T_{2\text{DQ}}^q \).

To perform in vivo experiments, CRAVED-type spectroscopic sequences with 2 by 2 by 2 cm PRESS (point-resolved spectroscopy) volume selection were implemented. Healthy young individuals (age, 25–35 years) volunteered to participate in the study. Turbo spin echo measurements (\( TR = 3800 \) ms, \( TE = 22 \) ms and 90 ms, resolution, 0.89 by 0.89 by 10 mm) were performed to position an 8 ml volume of interest in the trabecular bone marrow (epiphysis) region. CRAVED-type spectroscopic measurements (\( TR = 5000 \) ms, \( r \) variable, correlation gradient duration \( t = 6 \) ms, \( n_s = 32 \)) were performed for different values of the correlation gradient intensity \( G_c = 10 - 4 \) mT/m in order to select the range of correlation distance values \( d_c = 200 - 650 \) μm to match the expected trabecular pore sizes.

The data obtained in vivo were also fitted with a monoexponential decay function to obtain an estimate of \( T_{2\text{DQ}}^q \).

### 3 Results and Conclusions

In order to test the potentiality of the \( T_{2\text{DQ}} \) parameter analysis to achieve information on the microscopic structure in heterogeneous porous systems, \( T_{2\text{DQ}} \) and \( T_{2\text{DQ}}^q \) measurements were performed as function of the correlation distance \( d_c \). Double-quantum \( T_{2\text{DQ}} \) and \( T_{2\text{DQ}}^q \) were evaluated from the experimental data reported in Figs. 2 and 3, respectively, and the related results are shown in Table 1.

The results obtained in vitro show that the \( T_{2\text{DQ}} \) magnetization decay is characterized by a nonmonoeponential behavior, best fitted by biexponential functions. The fast and slow components of the double-quantum magnetization decay show different dependences on the correlation distance value \( d_c \). The fast-component \( T_{2\text{DQ}} \) values decrease when the correlation distance increases, while the opposite was observed for the slow-component \( T_{2\text{DQ}} \) value. On the other hand,
field inhomogeneities, thus suppressing the 90° pulse.

The signal is weighted by the iDQC $T_2$ during the evolution period and then the intensities for different values of the correlation distance are collected. The monoexponential inhomogeneities at various distances, also $T_{200}$, can be calculated.

Figures 2 and 3 show the correlation gradients in the 200 ms time axis (which is parallel to the evolution time axis). The $TR = 10000$ ms, $\tau$ variable, and $ns = 64$) were used with a point intensity $G_s = 16.8\pm0.02$. The correlation distance values were calculated with a biexponential decay model and a monoexponential function for the $T_{200}$.

Fig. 2. a Experimental signal intensity as a function of the correlation distance $d_c$ to evaluate the $T_{200}$. b Ratio of fast and slow $T_{200}$ components. Data were obtained from 10 mM copper sulfate-doped water in glass capillaries.

Fig. 3. Experimental signal intensity as a function of the correlation distance $d_c$ to evaluate the $T_{100}$. Data are obtained from 10 mM copper sulfate-doped water in glass capillaries.
Table 1. Double-quantum relaxation times $T_{2DQ}$ and $T_{2DQ}$ for doped water in glass capillary for different correlation distances $d_c$.

<table>
<thead>
<tr>
<th>Correlation distance $d_c$ (μm)</th>
<th>$T_{1DQ}$ (ms) slow component</th>
<th>$T_{2DQ}$ (ms) fast component</th>
<th>$T_{IDQ}$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>233</td>
<td>16.7±0.1</td>
<td>15.9±0.1</td>
<td>25.0±0.1</td>
</tr>
<tr>
<td>280</td>
<td>15.6±0.1</td>
<td>10.4±0.1</td>
<td>22.7±0.1</td>
</tr>
<tr>
<td>600</td>
<td>71.4±0.1</td>
<td>6.2±0.1</td>
<td>29.7±0.1</td>
</tr>
<tr>
<td>1200</td>
<td>50.0±0.1</td>
<td>5.9±0.1</td>
<td>30.3±0.1</td>
</tr>
</tbody>
</table>

the $T_{2DQ}$ magnetization decay is characterized by a monoexponential behavior which seems to be unaffected by the $d_c$ variation.

We interpreted the behavior of the fast-component $T_{2DQ}$ value as due to the spin rate close to the liquid-solid interface in pores, which suffer from the internal gradient dephasing effect. We supposed indeed that in particular conditions (e.g., strong susceptibility differences between the liquid and solid phase) when the correlation distance is about or greater than the pore diameter in a porous system, susceptibility effects near the liquid and porous matrix interface produce a more rapid dephasing of correlated spins.

This particular behavior of $T_{2DQ}$ relaxation as a function of $d_c$ is confirmed also by results obtained in in vivo measurements on trabecular bone. In fact, the $T_{2DQ}$ values of bone marrow decrease with the correlation distance increase, as shown in Table 2.

It is known from literature that in homogeneous systems, such as water and various solvents, the $n$-quantum transverse relaxation time $T_{2,n}$ and $n$-quantum diffusion processes $D_n$ satisfy the following relationships [11]

$$T_{2,n} = n^{-1}T_2 \quad \text{and} \quad D_n = nD \quad (\text{with} \quad n > 1),$$

(1)

showing a monoexponential behavior of the magnetization decay. The multiple-quantum diffusion process is still under investigation, and further theoretical analysis has to be performed.

Since diffusion processes decrease the CRAVED signal decreases with gradient intensity that corresponds to the relationships Eq. (1) represents systems too, like in human systems too, like in human experimental results from heterogeneous systems, at the same correlation distance, especially in comparison, therefore be helpful both to understand transverse relaxation and to investigate on microstructure properties.


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analysis has to be performed in order to adequately understand the phenomenon. Since diffusion processes during the correlation gradients always take place, the CRAZED signal decreases to a greater extent by increasing the correlation gradient intensity that corresponds to the correlation distance of lower values. The relationships Eq. (1) represent a valid approximation [11, 12] in heterogeneous systems too, like in human brain white and gray matter, although the experimental results from heterogeneous systems reported in literature are all obtained at the same correlation distance value of about 60 mm, and no data on intermolecular double-quantum relaxation times in porous systems are available. The study of $T_{1DQ}$ and $T_{1DQ}^*$ in heterogeneous systems by varying the correlation distance, especially in comparison with conventional SQCs $T_2$ and $T_2^*$, could therefore be helpful both to understand fundamental mechanisms of intermolecular transverse relaxation and to provide a new tool to indirectly detect information on microstructure properties.

References


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