The intermolecular multiple quantum coherences (iMQCs) that are generated by intermolecular dipolar interactions between distant spins on different molecules, have recently gained considerable attention because their properties are intrinsically different from those of conventional single quantum coherences (SQC)s in solution NMR. This feature allows for a wider range of applications in NMR and MR imaging.  

Signal attenuation behaviors of the iMQCs induced by the translational diffusion of correlated molecules in the presence of pulsed field gradients should be different from those of SQCs. However, the diffusion effect on the iMQC signals resulting from intermolecular interactions is not yet well-understood. In the prototype CRAZED sequence, which differs from the conventional pulsed gradient spin echo (PGSE) experiment, the molecular diffusion affects the evolution of the iMQCs during both the evolution period and detection period of the iMQCs into detectable signals, while there is no diffusion effect in the conventional PGSE experiment.  

Hence, the diffusion effect on the signal attenuation with the multi-spins from different molecules should evolve sensitively with the relaxation processes, susceptibility variations, and translational diffusion. Additionally, during the evolution and detection periods, diffusion could attenuate the strength of the dipolar field (or dipolar demagnetizing field), which is created by the modulated z-magnetization, and can convert the iMQCs into detectable signals, while there is no diffusion effect in the conventional PGSE experiment. Hence, the diffusion effect on the signal attenuation with the dipolar field should be considered for both the evolution and detection periods in the CRAZED-type experiments.  

Previous studies have analytically revealed the diffusion effects on the iMQC signals for the limited condition. In this paper, we analytically show the evolution behavior of an iMQC signal in a CRAZED-type sequence with molecular diffusion effects, and a comparison with numerical simulations conducted using various diffusion coefficients. To distinguish the diffusion effects during the evolution and detection periods, the position of the first encoding gradient pulse was varied from the beginning to the end of the evolution period. It should be noted that the other dynamics, except for the distant dipolar field (DDF) and diffusion, were ignored in the analytical and numerical calculations to clearly understand the effects of diffusion on the iMQC evolution.

In principle, both the quantum and classical treatments yield the same predictions for the iMQCs signal generated by intermolecular dipolar couplings in solution NMR. The quantum picture retains the individual dipolar couplings for all evolution periods and averages them at the end, while the classical picture averages all dipolar couplings first and then makes evolution under that mean field. For evaluating the diffusion effects, the classical approach would be suitable since the modified Bloch equation can easily incorporate the diffusion effects as well as the distant dipolar field.  

The Bloch equation, which modified to include the distant dipolar field and molecular diffusion process, can be written as

$$\frac{d\mathbf{M}(r)}{dt} = \gamma \mathbf{M}(r) \times \{ \mathbf{B}(r) + \mathbf{B}_d(r) \} + D \nabla^2 \mathbf{M}(r), \quad (1)$$

where \(\mathbf{M}(r)\) is the magnetization, \(\mathbf{B}(r)\) is the applied magnetic field, \(\mathbf{B}_d(r)\) is the distant dipolar field, and \(D\) is the diffusion coefficient.  

When we apply the first gradient pulse at the beginning of the evolution period, we have to consider the diffusion effect on the modulated transverse magnetization during that period. After the second 90° pulse, which is followed by the evolution during \(t_1\), the longitudinal and transverse magnetizations in
the rotating frame are, respectively,

\[ M_i = -M_0 \cos(\Delta \omega t + \gamma G \delta) \exp\{-D(\gamma G \delta)^2 t_1\}, \]
\[ \dot{M}_i = M_i + iM_j, \]
\[ = iM_0 \sin(\Delta \omega t + \gamma G \delta) \exp\{-D(\gamma G \delta)^2 t_1\}, \]

where \( \Delta \omega \) is the resonance frequency in the rotating frame, \( \gamma \) is the gyromagnetic ratio, \( G \) is the gradient strength, and \( \delta \) is the gradient duration. For simplicity, we assume that \( t_1 \) and \( t_2 \) are much longer than \( \delta \).

The second decoding gradient might select a specific coherence depending on the ratio of two gradients, \( n \). For example, if \( n = 2 \), then only the SQCs, which were the intermolecular double quantum coherences (iDQCs) during the \( t_1 \) period, can pass through the gradient filter. If we consider the diffusion of the modulated longitudinal magnetization along \( z \)-axis and evolution of transverse magnetization under the distant dipolar field after the \( t_2 \) period, then

\[ M_i = -M_0 \cos(\Delta \omega t + \gamma G \delta) \]
\[ \times \exp\{-D(\gamma G \delta)^2 t_1\} \exp\{-D(\gamma G \delta)^2 t_2\}, \]
\[ \dot{M}_i = M_i + iM_j, \]
\[ = iM_0 \sin(\Delta \omega t + \gamma G \delta) \exp\{-D(\gamma G \delta)^2 t_1\} \]
\[ \times \exp\left\{ \frac{1}{\tau_d} \cos(\Delta \omega t + \gamma G \delta) \exp\{-D(\gamma G \delta)^2 t_1\} \right\} \]

where \( \int_0^t \exp\{-D(\gamma G \delta)^2 t_1\} dt = \frac{1}{D(\gamma G \delta)^2} \left( 1 - e^{-D(\gamma G \delta)^2 t_1} \right) \]

and the dipolar demagnetizing time \( \tau_d = (\gamma G M_0)^{-1} \).

For simplicity, let \( D^* = D(\gamma G \delta)^2 \). Using the Bessel function formalism,

\[ \exp(iz \cos x) = \sum_{m=-\infty}^{\infty} i^m J_m(z) \exp(imx), \]

\[ M_i = iM_0 \sin(\Delta \omega t + \gamma G \delta) \exp(-D^* t_1) \exp\{i(\Delta \omega t + \gamma G \delta)\} \]
\[ \times \sum_{m=-\infty}^{\infty} \left\{ J_m \left( \frac{1 - e^{-D^* t_1}}{\tau_d D^*} \right) \right\} \exp\{i(m \Delta \omega t + \gamma G \delta)\} \]
\[ = M_0^* \left( \frac{e^{i(\Delta \omega t + \gamma G \delta)}}{D^*} - e^{-i(\Delta \omega t + \gamma G \delta)} \right) \]
\[ \times \exp(-D^* t_1) \exp\{i(\Delta \omega t + \gamma G \delta)\} \]

\[ \frac{\Delta \omega t + \gamma G \delta}{\tau_d} \]

\[ \int_0^\infty \exp\{-D(\gamma G \delta)^2 t_1\} dt \]

\[ \frac{1}{D(\gamma G \delta)^2} \left( 1 - e^{-D(\gamma G \delta)^2 t_1} \right) \]

\[ \exp(iz \cos x) = \sum_{m=-\infty}^{\infty} i^m J_m(z) \exp(imx), \]

\[ M_i = iM_0 \sin(\Delta \omega t + \gamma G \delta) \exp(-D^* t_1) \exp\{i(\Delta \omega t + \gamma G \delta)\} \]
\[ \times \sum_{m=-\infty}^{\infty} \left\{ J_m \left( \frac{1 - e^{-D^* t_1}}{\tau_d D^*} \right) \right\} \exp\{i(m \Delta \omega t + \gamma G \delta)\} \]
\[ = M_0^* \left( \frac{e^{i(\Delta \omega t + \gamma G \delta)}}{D^*} - e^{-i(\Delta \omega t + \gamma G \delta)} \right) \]
\[ \times \exp(-D^* t_1) \exp\{i(\Delta \omega t + \gamma G \delta)\} \]

Figure 2. Calculated signal intensity profiles as a function of \( t_2 \) for diffusion coefficient variation samples based on the analytical solutions from (a) Eq. (10), and (b) Eq. (9). The gradient ratio, \( n \), indicates multiple quantum coherence order, which can pass through the gradient filter, during the \( t_1 \) period. Note that the values of the diffusion coefficient \( D \) in the legends are shown in units of \( \text{m}^2/\text{s}\).
water. Therefore, molecular diffusions could be an important
of many organic solvents are similar to or less than that of
water (altered by the diffusion effects with the actual value for pure
sample in a 600 MHz NMR spectrometer at 298 K were
depending on the diffusion coefficient values and the gradi-
ent ratio based on the analytical solutions, Eq. (9) and Eq.
(10), it can be deduced that the iMQCs during the \( t_1 \) period
are affected by molecular diffusion proportional to the quantum
order (i.e. \( n \)). In the other word, the iMQCs during
the \( t_1 \) period would decay exponentially at the rate of \( nD \) (if
\( t_1 \) is short enough). Additionally, diffusion has an effect on
the magnitude of the distant dipolar field during the acqui-
sition period \( t_2 \) by decreasing the amplitude of the modulated
\( z \)-magnetization exponentially. Evaluating this effect might
be complicated since the iMQCs signals grow with time \( t_2 \) in
a manner different from the case of the conventional SQCs
that decay with time. To make the iMQC signal sufficiently
large for detection, a longer time evolution under the distant
dipolar field is required depending on the coherence order,
as shown in Figure 2. In quantum treatment, it corresponds
to the time to strip up \( I_1 \) operators by dipolar couplings in
multi-spin single-quantum coherences (e.g. \( I_1d_1d_2 \)) to become
detectable single-spin single-quantum coherences (\( I_1 \)).
Consequently, the diffusion effect on the iMQCs should be
quite different from, and greater than, that on the conven-

\[
M = \tau^* \left\{ \frac{1 - e^{-D^* \tau_1}}{1 - e^{-D^* \tau_2}} \right\} \times \exp(\text{im} \Delta \omega t_1 + \text{m} \gamma G \delta z) \exp(\text{im} \Delta \omega t_1 + \text{m} \gamma G \delta z)
\]

To determine the effect of the spatial modulation of mag-
netization, we collect all the position dependent terms as,
\[
\left\{ \exp(i \gamma G \delta z) - \exp(-i \gamma G \delta z) \right\} \exp(\text{im} \Delta \omega t_1 + \text{m} \gamma G \delta z) \sum_{\text{m}=-\infty}^{\infty} \exp(\text{im} \Delta \omega t_1 + \text{m} \gamma G \delta z)
\]

For the magnetization to be nonzero after spatial averaging
over the sample, the position dependent term should be
constant with respect to position. This means that the
coefficient for the \( z \)-direction in Eq. (7) must be zero. There-
fore, the condition of \( m = -(n \pm 1) \) is required for a signal to
exist.

Using the Bessel function relations \( J_{-n}(x) = (-1)^n J_n(x) \) and
\( J_{-n}(x) + J_{+n}(x) = (2n+1)J_n(x) \), the observable magnetization
can be expressed, after spatial averaging, as follows:

\[
M = \tau^* \left\{ \frac{1 - e^{-D^* \tau_1}}{1 - e^{-D^* \tau_2}} \right\} \times \exp(\text{im} \Delta \omega t_1 + \text{m} \gamma G \delta z)
\]

If we apply the first gradient pulse at the end of the \( t_1 \) period (Fig. 1), then we can only consider the diffusion
effect during the acquisition period \( t_2 \). Therefore, Eq. (9)
could be simplified as

\[
M = \tau^* \left\{ \frac{1 - e^{-D^* \tau_1}}{1 - e^{-D^* \tau_2}} \right\} \times \exp(\text{im} \Delta \omega t_1 + \text{m} \gamma G \delta z)
\]

Figure 2 shows signal growth patterns along with \( t_2 \)
depending on the diffusion coefficient values and the gradient
ratio based on the analytical solutions, Eq. (9) and Eq.
(10). The following parameter values for the pure water
sample in a 600 MHz NMR spectrometer at 298 K were
used for the analytical calculations and numerical simulations:
\( G = 10 \text{ G/cm} \), \( \delta = 2 \text{ ms} \), \( t_1 = 50 \text{ ms} \), \( \tau_2 = 65.3 \text{ ms} \). When
diffusion is slow enough (e.g. \( D \sim 10^{-10} \text{ m}^2/\text{s} \)), it barely
affects the signal intensity of the iMQCs even at high orders.
While the signal growing profiles can be significantly
altered by the diffusion effects with the actual value for pure
water (\( D = 2.3 \times 10^{-9} \text{ m}^2/\text{s} \)), the self-diffusion coefficients
of many organic solvents are similar to or less than that of
water. Therefore, molecular diffusions could be an important
factor for determining signal intensities of the iMQCs.

From the expansion of the Bessel function in Eqs. (9) and

![Figure 3](image-url)

**Figure 3.** The comparison of the signal intensity profiles (for
\( n = 2 \)) using analytical calculations and numerical simulations that
depends on the diffusion coefficients (a) without and (b) with
diffusion effects during the \( t_1 \) period. The open circles indicate the
results of numerical simulations with the same conditions as those
of the corresponding analytical curves. Only a limited number of
circles are shown for clarity.
The signal profiles obtained through numerical simulation agree very well with those from the analytical calculations, as shown in Figure 3. This implies that the analytical calculation results, Eq. (9) and Eq. (10), could be appropriate solutions to explain diffusion effects on the iMQCs. In real experiments, the signal intensity behaviors of the iMQCs are influenced by other dynamics as well as diffusion. Hence, it would be difficult to evaluate the effects of diffusion separately. In this regard, the analytical solution could be meaningful when considering applications such as diffusion MRI. Note that the simulation was conducted by numerically integrating the modified Bloch equation (Eq. (1)) through the Cash-Karp Runge-Kutta method.19

In conclusion, we calculated the analytical solutions to evaluate the effects of diffusion on the iMQCs in CRAZED pulse sequences. The obtained solution has been verified using the results of numerical simulation. The diffusional behaviors of the iMQCs during both the evolution and detection time periods could be examined by the analytical solution, which was quite different from those of the conventional NMR experiments. Understanding the difference in diffusional behaviors could lead to useful applications such as diffusion MRI based on the detection of iMQCs.

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References

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