

Generalized Analysis of Motion Using Magnetic Field Gradients

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I. Introduction

The use of magnetic field gradients to detect the translational displacement of molecules via precessional motion of their atomic nuclear spins is almost as old as nuclear magnetic resonance (NMR) itself. In his original paper on spin echoes, Hahn (1950) pointed out that the echo amplitude would be affected by the Brownian motion in the presence of local magnetic field inhomogeneity. In their article on the use of multiple pulse trains, Carr and Purcell (1954) pointed out that diffusional attenuation could be avoided provided that the pulse spacing was made sufficiently short. These authors also developed a nice formalism for relating the echo amplitude to the discrete hops of the spins, while in a later paper, Torrey (1956) developed a continuum approach based on the magnetization diffusion equation. Later in the 1950s, Hahn suggested the measurement of flow in the presence of magnetic field gradient (Hahn, 1950) via phase shift in the spin echo.

With the suggestion by McCall, Douglass, and Anderson (1963) that the use of pulsed magnetic field gradients could lead to significant advantages in measurement strategies, a new phase in the measurement of molecular motion began. Stejskal and Tanner (1965) were responsible for initiating the methodology and theory of the pulsed gradient spin-echo (PGSE) experiment as well as for its implementation to measure diffusion in systems for which restriction to motion caused a deviation from Fickian behavior. Since then the method has been extensively developed to measure motion in restricted systems, taking advantage of a diffraction analogy based on Fourier methods. This "*q*-space" approach (Callaghan, 1991) to PGSE NMR is complementary to the *k* space of NMR imaging (Lauterbur, 1973; Mansfield and Grannell, 1973; Mansfield and Morris, 1982). With the extensive application of NMR imaging and NMR microscopy to both biological and material systems over the past decade, the combination of position and motion encoding methods in NMR has permitted the spatial localization and mapping of velocity and diffusion.

The PGSE NMR method relies on the use of two sharp gradient pulses separated by a well-defined time interval and is therefore naturally suited to time-domain analysis of motion. However, it is important to realize that this particular form of two-pulse gradient modulation is not unique. In particular, a number of other time-modulation schemes are possible in which the molecular motion is detected in a different manner. However, as we shall see, whenever modulated gradients are used to encode the spin magnetization for motion rather than position, it is appropriate to refocus any phase shift due to absolute spin position by means of a spin echo. Consequently, we refer to this more general type of experiment as modu-

lated gradient spin-echo (MGSE) NMR. A particular theme of this chapter will be the relationship of the chosen measurement technique to the type of motion analysis sought. An important aspect of the discussion will be the characterization of motion in molecular ensembles and, in particular, the effects of deviation from simple Brownian motion or simple flow. We review the measurement strategies that may be adopted along with their associated signal techniques. These strategies will include time-domain, spatial frequency-domain, and temporal frequency-domain analyses, spatial localization of motion, two-dimensional correlation and exchange analyses, and diffraction and scattering analogies. Given the recent importance of stray field and Earth's field NMR methods, we will also consider the condition where the magnitude of the applied magnetic field gradient is comparable to the polarizing field.

II. Generalized Motion

A. THE CONDITIONAL PROBABILITY FUNCTION, SELF-DIFFUSION, AND FLOW

Nearly all NMR experiments are performed using large numbers of spins whose signals form a coherent superposition. It is the averaging contained in this superposition that lies at the heart of any theoretical treatment.

To begin, we assume that we can describe the general motion of a molecule i in terms of some time-dependent displacement $\mathbf{r}_i(t)$. One of the most useful ways of handling the ensemble-averaging over the i -spins is to introduce a density function giving the probability that a particle will have displacement between \mathbf{r}' and $\mathbf{r}' + d\mathbf{r}'$ at a time t . Usually, this probability function will depend not only on the time interval t , but also on the starting position. In particular we will be concerned with the self-correlation function (van Hove, 1954; Egelstaff, 1967), $P(\mathbf{r}', t | \mathbf{r}, 0)$, which gives the chance that a molecule initially at \mathbf{r} will have moved to \mathbf{r}' after a time t . It turns out that this is a particularly useful description for NMR since, as we shall see, this function can be determined directly using the two-pulse PGSE experiment. Interestingly, the only other experimental method able to gain direct access to this conditional probability density is incoherent inelastic neutron scattering (Bacon, 1975), a point that is discussed in more detail by Callaghan (1991).

Suppose we denote the total probability density of finding a particle at

position \mathbf{r}' at time t by $\phi(\mathbf{r}', t)$. Then

$$\phi(\mathbf{r}', t) = \int P(\mathbf{r}', t | \mathbf{r}, 0) \phi(\mathbf{r}, 0) d\mathbf{r} \quad (1)$$

In general, $\phi(\mathbf{r}, 0)$ will be given by the time-independent particle density $\rho(\mathbf{r})$. For Brownian motion, the function $\phi(\mathbf{r}', t)$ will obey Fick's law, where the spatial derivatives refer to the coordinate \mathbf{r}' . Consequently, we may write

$$\frac{\partial P}{\partial t} = D \Delta P \quad (2)$$

where D is the molecular self-diffusion coefficient, Δ is the Laplacian operator, and P obeys the initial condition

$$P(\mathbf{r}', 0 | \mathbf{r}, 0) = \delta(\mathbf{r}' - \mathbf{r}) \quad (3)$$

For the special case of unrestricted Brownian motion, the boundary conditions lead to the solution

$$P(\mathbf{r}', t | \mathbf{r}, 0) = (4\pi Dt)^{-3/2} \exp(-(\mathbf{r}' - \mathbf{r})^2/4Dt) \quad (4)$$

The Markov nature of Brownian motion statistics is reflected in the fact that P depends only on the net displacement $\mathbf{r}' - \mathbf{r}$ and not the initial position \mathbf{r} . We will refer to the vector $\mathbf{r}' - \mathbf{r}$ moved over a time t as the dynamic displacement \mathbf{R} .

Using the concept of the dynamic displacement, it is possible to rewrite Eq. (1) so as to define a very useful function, known as the *average propagator* (Karger and Heink, 1993) $\bar{P}(\mathbf{R}, t)$. This function gives the average probability for any particle to have a dynamic displacement \mathbf{R} over a time t and is given by

$$\bar{P}(\mathbf{R}, t) = \int P(\mathbf{r} + \mathbf{R}, t | \mathbf{r}, 0) \phi(\mathbf{r}, 0) d\mathbf{r} \quad (5)$$

For the case of unrestricted self-diffusion we can then write

$$\bar{P}(\mathbf{R}, t) = (4\pi Dt)^{-3/2} \exp(-\mathbf{R}^2/4Dt) \quad (6)$$

Note that for the example of simple unrestricted Brownian motion, all molecules experience an identical "average propagator," irrespective of starting position, reflecting the Markov nature of the statistics. This is just one case that will be encountered in the study of molecule translational motion using NMR methods. This case is easily extended to include simple flow with common velocity \mathbf{v} . The solution is

$$\bar{P}(\mathbf{R}, t) = (4\pi Dt)^{-3/2} \exp(-(\mathbf{R} - \mathbf{v}t)^2/4Dt) \quad (7)$$

Generally, we will use spin-echo NMR to study systems for which more

complex motions occur. These examples might include Brownian motion within a special set of confining boundaries, systems in which some local motion is superposed upon a longer range migration or systems in which the fluctuating or randomized flow occurs,

B. VELOCITY CORRELATION, SPECTRAL DENSITY, AND THE SELF-DIFFUSION TENSOR

A complete knowledge of the propagator $P(\mathbf{r}', t | \mathbf{r}, 0)$ for the ensemble of nuclear spins will, in principle, allow one to calculate the echo amplitude for any gradient modulation function. However, the propagator approach is particularly amenable to solution in the special gradient modulation case of the narrow pulse PGSE experiment. For more general modulation methods, an alternative approach, based on autocorrelation function, is helpful. The autocorrelation function of A is defined as $G(t) = \langle A(t)A(0) \rangle$, where the brackets represent the molecular ensemble average (Uhlenbeck and Ford, 1963; Berne and Pecora, 1976).

For translational motion, the velocity correlation function is particularly useful and, as we will show, can be utilized to provide a relationship between the echo amplitude and the molecular dynamics in the case of general modulation wave forms. Its Fourier spectrum is simply the self-diffusion tensor (Lenk, 1977; Stepišnik, 1981) $D_{\alpha\beta}(\omega)$, where α and β may take each of the Cartesian directions, x, y, z , that is,

$$D_{\alpha\beta}(\omega) = 1/2 \int_{-\infty}^{\infty} \langle v_{\alpha}(t)v_{\beta}(0) \rangle e^{i\omega t} dt \quad (8)$$

Using the even property of $G(t)$, we write the diagonal elements of this tensor as

$$D_{zz}(\omega) = \int_0^{\infty} \langle v_z(t)v_z(0) \rangle e^{i\omega t} dt \quad (9)$$

For simple Brownian motion the velocity autocorrelation function decays rapidly to zero over the correlation time τ_c , corresponding to the average collision time. Consequently, the diffusion spectrum is relatively constant with frequencies above zero, attenuating in the vicinity of $\omega \approx \tau_c^{-1}$. Clearly, the lower-frequency plateau of the spectrum has amplitude $D_{zz}(0) = \langle v_z^2 \rangle \tau_c$. It should be noted that the collisional frequency for small molecules, τ_c^{-1} , is exceedingly high compared with the frequency regime accessible to MGSE NMR, i.e., less than or on the order of 10^5 Hz. However, for motion in complex fluids there may exist a number of characteristic time scales, which correspond to frequencies in the accessible regime. These might include tube disengagement times in entangled

polymers or wall collision times in simple liquids contained within porous solids. Such times relate more to the organizational structure of liquids than to local particle motion.

We will show that this diffusion spectrum may be directly probed in MGSE NMR by appropriate choice of gradient modulation wave form. For example, in the case of complex motion referred to previously, the spectrum may not be flat below τ_c^{-1} , but instead contain structure that is directly related to these characteristic "organizational" frequencies. For example, where superposed slow and fast stochastic motion occurs, such structure may be apparent and the velocity correlation function will contain the essential information. By contrast, the behavior of systems for which the local motion is Brownian, but whose boundaries impose constraints over a much longer time scale than the correlation time for local stochastic motion, is very different. For these systems the velocity correlation function is zero beyond τ_c and the diffusion spectrum contains no features at low frequencies that can be related to the boundary collision. For such systems the propagator approach to describing stochastic motions provides the best means of describing the outcome of the MGSE NMR experiment.

III. Modulated Gradient Spin-Echo NMR

A. THEORETICAL STARTING POINT

In this section we derive an expression for the NMR signal amplitude for a molecular ensemble experiencing generalized magnetic fields that vary in time and space. This enables us to provide a sound theoretical starting point for different measurement techniques without the need for hidden assumptions. While the details of the theoretical analysis in this section are not essential to an understanding of the measurement and analysis methods to be described, we include a brief description of the reasoning employed so that the reader can appreciate the basis of this starting point. By deriving all our subsequent expressions for particular methods from a single equation, the inherent unity of the various techniques is emphasized. Readers wishing to skip this derivation should move directly to Eq. (41).

B. THE INFLUENCE OF MAGNETIC FIELDS

Consider the situation where the local magnetic field at position \mathbf{r} is the sum of a uniform field \mathbf{B}_o and a nonuniform field $\mathbf{B}_g(\mathbf{r}, t)$, that is,

$$\mathbf{B} = \mathbf{B}_o + \mathbf{B}_g(\mathbf{r}, t) \quad (10)$$

We will be principally concerned with the situation where the molecules move a sufficiently small distance that the field experienced by a particular spin i can be expressed in terms of the zeroth and first order term in a Taylor expansion, that is,

$$\mathbf{B}_i = \mathbf{B}_{i_0} + \mathcal{G}_i(t)\mathbf{r}_i \quad (11)$$

where \mathbf{r}_i is the displacement of spin i from its local origin. Note that the zeroth order term is added to \mathbf{B}_0 to give the local value, \mathbf{B}_{i_0} . \mathcal{G}_i is necessarily a tensor since Maxwell's equations dictate that the nonuniform magnetic field cannot change in a single direction. The need to label the gradient tensor by the subscript i arises because of its local character. However, we will deal with special cases where the linear gradient is uniform across the sample and the subscript may be dropped. This definition includes some special cases of wide importance. The first concerns a uniform gradient common to all parts of the sample. In this case Eq. (11) reduces to

$$\mathbf{B} = \mathbf{B}_0 + \mathcal{G}(t)\mathbf{r} \quad (12)$$

where \mathbf{r} is now the displacement from the gradient origin. Most commonly we will encounter the condition in which the inhomogeneous field is weak, that is, $|\mathcal{B}_g(\mathbf{r}_i, t)| \ll |\mathbf{B}_0|$. Here the magnetic field components perpendicular to the static magnetic field may be neglected and we may define the remaining column of $\mathcal{G}(t)$ as the vector $\mathbf{G}(t) = \nabla B_{gz}(\mathbf{r}, t)$, where B_{gz} is the component of \mathcal{B}_g parallel to the z axis defined by \mathbf{B}_0 . In this special case the total magnetic field magnitude is given by

$$B = B_0 + \mathbf{G}(t) \cdot \mathbf{r} \quad (13)$$

This use of Eq. (13) has no meaning whenever the applied nonuniform magnetic field is on the order of or larger than the main magnetic field. While the small inhomogeneous field approximation will be useful in a wide class of experiments, we will find it useful to retain the more general treatment represented by Eq. (11).

In the NMR experiment the radiofrequency (rf) magnetic field

$$\mathbf{B}_1(t) = \mathbf{B}_{1_0}(\mathbf{r}_i, t)\sin \omega t \quad (14)$$

is used to excite the magnetization from an initial thermodynamic equilibrium and to manipulate it in the due course of an experiment. The rf magnetic field may be applied as a rectangular (hard) pulse or can be modulated with the desired spectral distribution (soft rf pulse). Its spatial homogeneity is defined by the geometry of the transmitting rf coil. Generally, the amplitude of the rf pulse may be a function of time and the location of the magnetization-bearing particle, that is, $\mathbf{B}_{1_0}(\mathbf{r}_i, t)$.

Our general Hamiltonian will be written in terms of spin operators \mathcal{S}_i

$$\mathcal{H} = -\hbar\omega_o\mathcal{S}_z - \hbar\gamma \sum_i \mathbf{B}_g(\mathbf{r}_i, t) \cdot \mathcal{S}_i + \mathcal{H}_{\text{rf}} + \mathcal{H}_{sL} \quad (15)$$

with $\gamma B_o = \omega_o$ and with \mathcal{H}_{rf} describing the effect of the rf pulses and \mathcal{H}_{sL} including all spin interactions with the surroundings. We will find it convenient to divide \mathcal{H}_{sL} into two parts. The first concerns those terms, \mathcal{H}_{rL} , responsible for T_1 and T_2 relaxation processes unconnected with translational motion. In the present treatment we will generally neglect these. The second term \mathcal{H}_{iL} concerns those processes responsible for particle migration. In the following discussion we account for \mathcal{H}_{iL} by assuming that the particle location is a time-dependent variable $\mathbf{r}_i(t)$ and by performing the appropriate ensemble average, which we call "L-average."

Note that the sum over i represents a sum over individual spins. However, because the number of spins dealt with is usually immense ($> 10^6$), one may reasonably group the spins into separate subensembles for which the dynamical behavior may be different. For example, one might distinguish groups of spins that have differing starting points for their motion or that occupy compartments with differing diffusion coefficients. For such a grouping the averages within and between the subensembles may be separately handled. In this case we regard i as a subensemble label. In either case we may separately sum over the i spins before carrying out the "L-average" over the surroundings. This latter average will be important when dealing with restricted diffusion.

Following the usual practice, we use the density matrix $\rho(t)$ to describe the state of the system, where

$$\rho(t) = \mathcal{U}(t)\rho(0)\mathcal{U}(t)^{-1} \quad (16)$$

and the operator $\mathcal{U}(t)$ defines the evolution of the system from the initial state $\rho(0)$. Prior to the application of the first rf pulse, the initial state is determined by thermodynamic equilibrium. In this chapter we are concerned with the effect of nonuniform fields applied after preparation by a selective or nonselective rf pulse sequence. Following this preparation, we may presume (in the usual high temperature approximation) that the initial density matrix can be written very generally as

$$\rho(0) = \rho_L(0)\hbar\omega_o \sum_i (A_i\mathcal{S}_{xi} + B_i\mathcal{S}_{yi} + C_i\mathcal{S}_{zi}) = \rho_L(0) \sum_i \rho_{si}(0) \quad (17)$$

Here ρ_L denotes the density matrix of the spin surroundings, while A_i , B_i , and C_i are the constants that denote the state of i th subensemble after the preparation. This decomposition of the total spin density matrix into a sum

of notional density matrices for each spin or subensemble i is particularly helpful in dealing with an ensemble in which the spins have different motion subsequent to preparation. Strictly speaking, this requires that we can describe the density matrix in terms of single spin operators and, hence, that dipolar interactions are neglected.

Given the complexity of the Hamiltonian described in Eq. (15) it would appear that the time evolution operator will be exceedingly complex. However, by judicious use of the factor theorem (Evans, 1968) it is possible to express this operator as a product of simple rotation operators in spin space. The use of various spin transformations in rotating or tilted frames results in a more lucid treatment, as well as nicely accounting for the various stages of the experiment, for example, the preparation, mixing, and detecting periods. The formal relationship between the evolution operator and the Hamiltonian [Eq. (15)] is given by

$$\mathcal{U}(t) = \mathcal{T} \exp \left(-\frac{i}{\hbar} \int_0^t \mathcal{H}(t') dt' \right) \quad (18)$$

where the operator \mathcal{T} implies time ordering of the applied interaction. In the case of a spin echo, \mathcal{U} takes the form of a natural time-ordered succession of evolution operators given by \mathcal{U}_{m1} for the application of a nonuniform field, followed by \mathcal{U}_π for the π rf pulse, and then \mathcal{U}_{m2} for the second evolution under the nonuniform magnetic field. The total evolution is therefore

$$\mathcal{U}(t) = \mathcal{U}_{m2}(t) \mathcal{U}_\pi \mathcal{U}_{m1}(t) \quad (19)$$

This operator split neglects relaxation effects and assumes that the π rf pulse is short enough that all other terms in the Hamiltonian may be neglected during its application. In the following discussion we will consider the details of this basic sequence, but we must bear in mind that it may be just the "joint in the chain" of a more sophisticated sequence. The effect of the nonuniform magnetic field is given by

$$\mathcal{U}_{m1,2} = \mathcal{T} \exp \left(i \int_{t_1}^{t_2} \left\{ \omega_o \mathcal{J}_z + \gamma \sum_i \mathbf{B}_g[\mathbf{r}_i(t'), t'] \cdot \mathcal{J}_i \right\} dt' \right) \quad (20)$$

This operator can be simplified by transformation into a frame with z -axis along the total magnetic field at the site of the particular spin. By the use of the factoring theorem (Wilcox, 1967), the operator given in Eq. (20) breaks into the product of two parts,

$$\mathcal{U}_m(t) = \mathcal{T} \exp \left(i \sum_i \int_0^t \left\{ \dot{\varphi}[\mathbf{r}_i(t'), t'] \cdot \mathcal{J}_i + \omega_{\text{eff}}[\mathbf{r}_i(t), t'] \cdot \mathcal{J}_{zi} \right\} dt' \right) \mathcal{R}(t) \quad (21)$$

