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Signal Selection in High-Resolution NMR by Pulsed Field Gradients

I. Geometrical Analysis

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A geometrical description for the selection of coherence transfer pathways in high resolution NMR by the application of pulsed field gradients along three orthogonal directions in space is presented. The response of the spin system is one point of the three-dimensional Fourier transform of the sample volume affected by a sequence of field gradients. The property that a pathway is retained (or suppressed) when a sequence of field gradients is applied is expressed by the property of vectors, representing the pathway and the sequence, respectively, to be orthogonal (or not orthogonal). Ignoring imperfections of RF pulses, and with the exception of sensitivity enhanced experiments and experiments where the relevant coherence order is zero while field gradients are applied, it is shown that at most only half of the relevant pathways, as compared to a phase cycled experiment, are retained when field gradients are used for signal selection.

INTRODUCTION

The perturbation of a nuclear spin system by RF pulses allows the excitation of coherent superpositions of eigenstates, and their transformation into each other. A particular series of such coherence transfers forms a coherence transfer pathway (*1*). As RF pulses cause several coherence transfers to occur simultanously, a manifold of pathways are excited during the course of an experiment. Multidimensional NMR spectroscopy can be used to map coherence transfer pathways, and thereby provides detailed information about the structure and dynamics of molecular system in the liquid phase. However, the spectra would be hopelessly complicated if all the excited pathways were allowed to contribute, and the selection of particular coherence transfer pathways is a first-rank element of each NMR experiment.

The selection can either be performed by a phase cycling procedure (*2–4*), where different experiments recorded with different settings of the phases of the RF pulses are combined, or by the application of pulsed field gradients (*5–7*). The use of field gradients is often preferred over phase cycling, since the experiments are less susceptible to artifacts (no t_1 noise (*8*), inherent water suppression (*9*)), and spectra are, in general, of high quality (*10, 11*). The technique can be disadvantageous in comparison to phase cycling with respect to signal-to-noise. For some important RF sequences which are also basic building blocks of multidimensional experiments, such as homo- and heteronuclear correlation, and multiple quantum filters, signal selection by pulsed field gradients implies the loss of half of the pathways which encode for the relevant information of the experiment, whereas the maximal number is retained by phase cycling (*12*). It has been argued that such a loss is common to most experiments when pulsed field gradients are applied.

Recently, a geometric approach for the calculation of suitable sequences of pulsed field gradients for signal selection in any NMR experiment was presented (*13*). The method was derived for a case where field gradients are applied along a single direction in space, the direction of the Zeeman field.

In the present paper, the earlier work is extended to cope with the general situation where field gradients are applied along any direction in space. Such gradients can be generated with three mutually orthogonal coils. The action of an arbitrary combination of pulsed field gradients along any direction in space on a coherence transfer pathway is described by a geometric approach. The geometry is used to specify those experiments where signal selection by pulsed field gradients is inherently accompanied by a loss of signal-to-noise in comparison to phase cycling. The treatment focuses on basic aspects of signal selection by field gradients and is made for the case of idealized experiments. The influences of instrumental imperfections, relaxation, and exchange are not considered.

PULSED FIELD GRADIENTS ALONG ORTHOGONAL DIRECTIONS

A pulsed field gradient exposes a spin system for a well defined period to a spatially inhomogeneous magnetic field $\Delta\mathbf{B}(\mathbf{r}, \tau) = (0, 0, G_x f_x(\tau)x + G_y f_y(\tau)y + G_z f_z(\tau)z)$ which is aligned along the homogeneous Zeeman field. It is assumed that a spatially constant field gradient can be generated along each of three mutually orthogonal directions, the *x*-, *y*-, and

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z-axes, respectively. The amplitude G_A, for $A = x, y$, or z, of a field gradient may have the shape of a smooth function $f_A(\tau)$, where $-1 \le f_A(\tau) \le 1$ for $0 \le \tau \le \tau_{A0}$, and τ_{A0} is the overall duration of the pulse.

The coupling of a heteronuclear spin system of two species with gyromagnetic ratios γ_I and γ_S, and Cartesian spin operators $\mathbf{I}_i = (I_{ix}, I_{iy}, I_{iz})$ and $\mathbf{S}_k = (S_{kx}, S_{ky}, S_{kz})$, respectively, with the magnetic field $\Delta\mathbf{B}(\mathbf{r}, \tau)$ is described by the Hamiltonian

$$H_G = -\sum_i \gamma_I\{G_x f_x(\tau) x_i + G_y f_y(\tau) y_i + G_z f_z(\tau) z_i\} I_{iz} - \sum_k \gamma_S\{G_x f_x(\tau) x_k + G_y f_y(\tau) y_k + G_z f_z(\tau) z_k\} S_{kz}.$$

The loss of signal intensity by lateral diffusion in an inhomogeneous magnetic field (*14*), as well as the chemical shielding ($\sim 10^{-5}$), is neglected. The x_j, y_j, z_j are the coordinates of the nuclei. Since the applied field gradients are much too weak to resolve the different nuclear sites within a molecule ($G = 100$ gauss cm^{-1}), the same coordinates, x, y, and z, respectively, can be used for each site:

$$H_G = -\{G_x f_x(\tau) x + G_y f_y(\tau) y + G_z f_z(\tau) z\}\{\gamma_I I_z + \gamma_S S_z\}.$$

$I_z = \Sigma_i I_{iz}$ and $S_z = \Sigma_k S_{kz}$ are the z-components of the total spin angular momenta of each species.

H_G induces a precession of the spin system. A heteronuclear coherence, addressed by coherence orders p^I and p^S with respect to each species, experiences a phase shift of

$$\{\gamma_I p^I + \gamma_S p^S\}\{xG_x \int_0^{\tau_{x0}} f_x(\tau)d\tau + yG_y \int_0^{\tau_{y0}} f_y(\tau)d\tau + zG_z \int_0^{\tau_{z0}} f_z(\tau)d\tau\}. \quad [1]$$

In terms of quantities g^A, for $A = x, y, z$, called "strength" (*13*, *15*),

$$g^A := G_A \int_0^{\tau_{A0}} f_A(\tau)d\tau,$$

and the composite coherence order (*13*, *16*),

$$p := p^I + \left(\frac{\gamma_S}{\gamma_I}\right) p^S,$$

Eq. [1] reads $\gamma_I p\{xg^x + yg^y + zg^z\}$.

In the general case of an experiment which has a total of F periods of free precession, a number of pulsed field gradients of different amplitudes, time profiles, and durations may be used. Those pulses which are along the same axis can be represented by a vector of F real components,

$$\mathbf{g}^A := \begin{pmatrix} g_1^A \\ g_2^A \\ \cdot \\ \cdot \\ \cdot \\ g_F^A \end{pmatrix},$$

with $A = x, y, z$. g_i^A is the strength of a pulse applied in the ith period along the specified axis. $g_i^A = 0$ if no field gradient is applied. Analogously, a coherence transfer pathway is represented by a vector $\mathbf{p}$ of F real components,

$$\mathbf{p} := \begin{pmatrix} p_1 \\ p_2 \\ \cdot \\ \cdot \\ \cdot \\ p_F \end{pmatrix},$$

where p_i is the composite coherence order prevailing in the ith period of free precession.

For a particular pathway **p,** the phase shifts induced by the different field gradients accumulate during the course of the experiment. The overall phase shift can be expressed conveniently by extending the vector notation introduced above. The vectors $\mathbf{g}^A$, $\mathbf{p}$ are considered as elements of the Euclidean space $|R^F$, equipped with an inner product $(\mathbf{x}|\mathbf{y}) := \mathbf{x}^t\mathbf{y} = \Sigma_i^F x_i y_i$ between any two vectors $\mathbf{x}$ and $\mathbf{y}$**.** The transposed form of a vector $\mathbf{x}$ is $\mathbf{x}^t$, and $\mathbf{x}^t\mathbf{y}$ expresses the inner product as the matrix product of the row vector $\mathbf{x}^t$ and the column vector $\mathbf{y}$**.** The phase shift at the end of the experiment can be calculated as

$$\begin{aligned}\gamma_I\{(\sum_i^F p_i g_i^x)x + (\sum_i^F p_i g_i^y)y + (\sum_i^F p_i g_i^z)z\} \\ = \gamma_I\{(\mathbf{p}|\mathbf{g}^x)x + (\mathbf{p}|\mathbf{g}^y)y + (\mathbf{p}|\mathbf{g}^z)z\} \\ = \{k_x x + k_y y + k_z z\} = \mathbf{k}^t\mathbf{r},\end{aligned}$$

with

$$\mathbf{r} := \begin{pmatrix} x \\ y \\ z \end{pmatrix} \quad \text{and} \quad \mathbf{k} := \begin{pmatrix} k_x \\ k_y \\ k_z \end{pmatrix} = \begin{pmatrix} \gamma_I(\mathbf{p}|\mathbf{g}^x) \\ \gamma_I(\mathbf{p}|\mathbf{g}^y) \\ \gamma_I(\mathbf{p}|\mathbf{g}^z) \end{pmatrix}.$$

The phase shift is proportional to the coordinates, expressed by the inner product of the wave vector $\mathbf{k}$ and the position vector

r. The proportionality constants, the components of **k,** are determined by the inner product of vectors **p** and $\mathbf{g}^A$ of $|R^F$.

An individual pathway **p** gives rise to a macroscopic signal, denoted by $\sigma(\mathbf{k})$. $\sigma(\mathbf{k})$ comprises the contributions from all volume elements of the sample,

$$\sigma(\mathbf{k}) = \int \int_V \int \rho(\mathbf{r})\, M_0(\mathbf{r}) \exp\{i\mathbf{k}^t\mathbf{r}\} dv. \qquad [2]$$

$M_0(\mathbf{r})\exp\{i\mathbf{k}^t\mathbf{r}\}dv$ is the amplitude of the contribution from the volume element $dv = dx\, dy\, dz$ at position **r.** $\rho(\mathbf{r})$ is the spatial spin density. Equation [2] is a three-dimensional Fourier transformation from **r**-space to **k**-space which represents the basic relation of Fourier imaging (*17, 18*).

The excitation profile or, equivalently, according to the principle of reciprocity (*19*), the detection profile are assumed to be uniform. The sample volume affected by the field gradients may be a cylinder of radius R and length L whose symmetry axis is along the laboratory z-axis (common shape of NMR tubes). In this case, and for a homogeneous solution of molecules, $\rho(\mathbf{r}) = 1/(\pi R^2 L) =$ constant within the cylinder but vanishes outside, and Eq. [2] yields

$$\frac{\sigma(\mathbf{k})}{\sigma(\mathbf{k}=0)} = \frac{2J_1(k_r R)}{k_r R} \frac{\sin(k_z L)}{k_z L}, \quad \text{with } k_r = \sqrt{k_x^2 + k_y^2}. \qquad [3]$$

$J_1(x)$ is the Bessel function of the first kind of first order (*20*). Any possible combination of pulsed field gradients is represented by vectors $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$, and their action on a particular coherence transfer pathway **p** can be determined by the evaluation of expression [3].

A pathway **p** is fully retained, i.e., $\sigma(\mathbf{k}) = \sigma(\mathbf{k} = \mathbf{0})$, only if

$$\mathbf{k} = \mathbf{0} \Leftrightarrow (\mathbf{p}|\mathbf{g}^x) = (\mathbf{p}|\mathbf{g}^y) = (\mathbf{p}|\mathbf{g}^z) = 0, \qquad [4a]$$

i.e., the vectors $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$ must be orthogonal to **p.** In this case, the coherence transfer pathway may be called *rephased,* as the effects of the different pulsed field gradients cancel each other, and a coherence transfer echo is formed (*5*).

Otherwise, for $\mathbf{k} \neq \mathbf{0}$, i.e., if one or several of the vectors $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$ are not orthogonal to **p,** the pathway is attenuated to a certain extent and may be called *dephased.*

The attenuation of a pathway can be quantified by Eq. [3]. In practical applications the arguments, $k_z L$ and $k_r R$, have values of the order 10^2 and larger. The asymptotic behavior of the function $2J_1(k_r R)/(k_r R)$ is very accurately described by (*20*)

$$\frac{2J_1(k_r R)}{k_r R} \rightarrow \frac{2\sqrt{2}}{\sqrt{\pi}} \frac{\sin(k_r R - \pi/4)}{(k_r R)^{3/2}}.$$

$J_1(x)/x$ and $\sin(x)/x$ are oscillatory functions. However, expression [3] is an idealization, and its zero crossings are experimentally not feasible (inhomogeneous excitation, inhomogeneous Zeeman field). An estimate of the attenuation is the envelope function of expression [3] for large arguments

$$\frac{\sigma(\mathbf{k})}{\sigma(\mathbf{k}=0)} \approx \frac{2\sqrt{2}}{\sqrt{\pi}} \frac{1}{(k_r R)^{3/2} k_z L}, \quad \text{for } k_r R,\ k_z L \geq 1. \qquad [4b]$$

The attenuation is stronger for larger components of **k,** i.e., for larger projections of the applied gradient sequences onto the pathway (if the same strengths of the individual pulses are used).

SELECTION OF COHERENCE TRANSFER PATHWAYS

The Selective, Suppressive, and Free Subspaces

The evolution of a spin system during an NMR experiment is described by the set of all coherence transfer pathways, $\{{}^1\mathbf{p}, \ldots, {}^Q\mathbf{p}, {}^{Q+1}\mathbf{p}, \ldots, {}^J\mathbf{p}\}$, which are excited by the RF pulses. Each pathway is represented by a vector of $|R^F$, where F is the total number of periods of free precession. Let the first Q vectors, $\{{}^1\mathbf{p}, {}^2\mathbf{p}, \ldots, {}^Q\mathbf{p}\}$, be the wanted pathways, those which code for the relevant information of the experiment. The remaining $J - Q$ pathways, $\{{}^{Q+1}\mathbf{p}, {}^{Q+2}\mathbf{p}, \ldots, {}^J\mathbf{p}\}$, are the unwanted pathways. The purpose of applying pulsed field gradients is to block the unwanted coherence transfer pathways from contributing to the detected signal, whereas the wanted pathways should be detected without attenuation. According to Eqs. [4a] and [4b], sequences of pulsed field gradients, $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$, have to be found which are orthogonal to each wanted pathway but have possibly strong projections onto the different unwanted pathways.

Because of the linearity of the inner product, each of the vectors $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$ will be orthogonal not only to each wanted pathway, but also to any linear combination of these vectors. The set of all linear combinations of vectors $\{{}^1\mathbf{p}, {}^2\mathbf{p}, \ldots, {}^Q\mathbf{p}\}$ forms a subspace of $|R^F$, denoted by square brackets $[{}^1\mathbf{p}, {}^2\mathbf{p}, \ldots, {}^Q\mathbf{p}]$. It is called the *selective* subspace, as the vectors $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$ must not have a component along $[{}^1\mathbf{p}, {}^2\mathbf{p}, \ldots, {}^Q\mathbf{p}]$.

For the determination of the projections of the vectors $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$ onto an unwanted pathway, it is sufficient to take into account the component of the unwanted pathway which is orthogonal to the selective subspace. The orthogonal component, denoted by ${}^k\mathbf{q}$, can be calculated by

$${}^k\mathbf{q} = {}^k\mathbf{p} - \sum_i ({}^k\mathbf{p}|\mathbf{e}_i)\mathbf{e}_i, \quad \text{for } k = Q+1, \ldots, J.$$

The vectors $\{\mathbf{e}_i\}$ form an orthonormal basis of the selective subspace (the basis may be constructed from the set $\{{}^1\mathbf{p}, {}^2\mathbf{p}, \ldots, {}^Q\mathbf{p}\}$ by the Gram–Schmidt orthogonalization proce-

dure (*21*)). The components ${}^{k}\mathbf{q}$ of the unwanted pathways span again a subspace, denoted by $[{}^{Q+1}\mathbf{q}, {}^{Q+2}\mathbf{q}, \ldots, {}^{J}\mathbf{q}]$. It is called the *suppressive* subspace, since only pathways which have components along this subspace can be attenuated.

Field gradients are usually not applied in all periods of free precession (e.g., interference of field gradients with RF decoupling). In principle, the number of periods taken into account, N, can vary as $1 \leq N \leq F$. For $N < F$, it is sufficient to represent each pathway by a vector with F components as before, but the components, corresponding to periods of free precession not considered for an application of field gradients, are set to zero. Then, the pathways are effectively elements of $|R^N$. All coherence transfer pathways excited in the experiment, wanted and unwanted ones, are elements of the union of the selective subspace and the suppressive subspace. Because of possible linear dependencies, the union can be smaller than $|R^N$. Let M be the dimension of the union, and $M \leq N$. The vector space $|R^N$ can be decomposed into the direct sum (*21*)

$$|R^N = [{}^{1}\mathbf{p}, {}^{2}\mathbf{p}, \ldots, {}^{Q}\mathbf{p}] \oplus [{}^{Q+1}\mathbf{q}, {}^{Q+2}\mathbf{q}, \ldots, {}^{J}\mathbf{q}] \oplus |R^{(N-M)}. \quad [5]$$

The subspace $|R^{(N-M)}$ contains all vectors of $|R^N$ which are not elements of the other two subspaces. It is called the *free* subspace, since neither any wanted pathway nor any unwanted pathway has components along $|R^{(N-M)}$. It is shown in the Appendix that a free subspace is present whenever a perfectly refocusing π-pulse is applied in an experiment. As an example, the decomposition of $|R^3$, corresponding to a homonuclear multiple quantum experiment where gradients are applied in three periods of free precession, is illustrated in Fig. 1.

Decomposition [*5*] provides a framework for the description of signal selection by pulsed field gradients: To rephased wanted pathways, the sequences $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$ must be elements of the union of the suppressive subspace and the free subspace. A particular unwanted pathway can only be suppressed if it is not an element of the selective subspace, or, equivalently, if it has a component along the suppressive subspace. Otherwise, the unwanted pathway is invariably rephased by any sequence of field gradients which rephases the wanted pathways, and the pathway selection would be incomplete. Therefore, most of the unwanted pathways should have a component along the suppressive subspace, and, at the same time, as many wanted pathways as possible should be elements of the selective subspace. The number and distribution of pathways within the selective and suppressive subspaces depends crucially on the choice of periods of free precession where gradients are applied (Eq. [5]). The placement of gradient pulses is a particularly complex problem in multidimensional experiments with many periods of free precession.

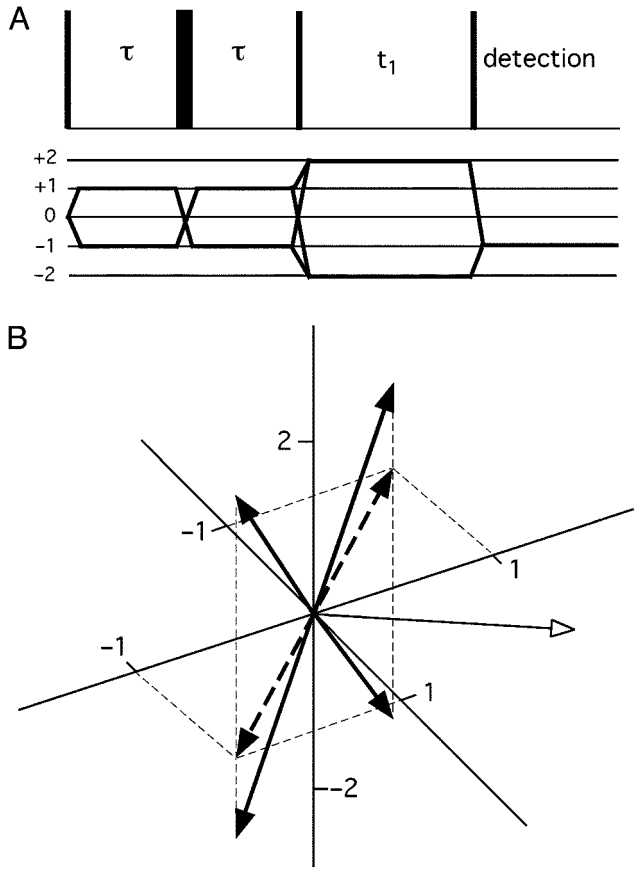

FIG. 1. (A) Basic pulse sequence for homonuclear double-quantum spectroscopy (*1*). The thin and thick bars represent $\pi/2$- and π-pulses, respectively. Only the wanted pathways are indicated on the pathway diagram. (B) In principle, field gradients can be applied in all four periods of free precession, and pathway vectors are elements of $|R^4$. If it is intended to apply gradients in all periods except the detection period, the fourth component of each pathway vector, representing the detection period, can be set to zero. Accordingly, the pathways are effectively elements of $|R^3$ and may be represented by vectors with three components. There are four wanted pathways, (1, −1, 2), (1, −1, −2), (−1, 1, 2), and (−1, 1, −2), which are shown as bold arrows in the figure. Since all wanted pathways lie in a plane, the selective subspace has dimensionality 2. For a perfectly refocusing π-pulse, the unwanted pathways are different form the wanted ones only with respect to the coherence order prevailing during the evolution time t_1 (unwanted multiple quantum order); an example are the dashed filled arrows in the figure, (1, −1, 0), and (−1, 1, 0). Any unwanted pathway lies in the plane spanned by the wanted ones; therefore, the suppressive subspace is empty, and a one-dimensional free subspace exists. Such a decomposition of the overall space ($|R^3$) is typical for experiments where refocusing π-pulses are applied (see text). Imperfections of the π-pulse can induce unwanted pathways which lie outside the plane (not shown). Any gradient sequence along the free subspace, e.g., (0, 1, 1) (open arrow), can dephase these artifacts while all four wanted pathways are rephased. However, the unwanted multiple quantum signals will also be rephased.

Comparison to Phase Cycling

For the majority of NMR experiments, it is a particular value of the magnitude of the coherence order in each period of free

precession which encodes for the relevant information, and wanted pathways with opposite sign of that value contribute equally to the desired signal. Phase cycling can be used to collect such complementary pathways (*2*), and thereby the maximal number of wanted pathways, while often the most significant unwanted pathways are suppressed. Optimum signal-to-noise is obtained in these experiments. When signal selection is performed by pulsed field gradients, the ultimate goal is to rephase the maximal number of wanted pathways, the same as in the phase cycled version, but to dephase the unwanted ones at the same time. This is not possible for most experiments. The suppressive subspace is empty whenever it is intended to rephase the maximal number of wanted pathways, and, consequently, no sequence of pulsed field gradients exists for such a task. To discriminate between wanted and unwanted pathways, it is neccessary to create a nonempty suppressive subspace. As a consequence, the number of wanted pathways which can be refocused will be halved.

The class of experiments for which the assertions are true is specified by induction with respect to the number of pulsed field gradients, N, which are applied during an experiment. For an experiment with a total of F periods of free precession, the different pathways are represented by vectors where the first N components are associated with the periods where gradients are applied, and the last $F - N$ components are zero (see Eq. [5]). It is no restriction when the ordering of the components of pathway vectors is different from the real succession of gradient pulses in an experiment. The following analysis is based on the specific structure of the pathway vectors, and some of their important properties are derived in the Appendix. To simplify the notation, only homonuclear experiments are considered.

The discussion is first restricted to experiments where the coherence order of the wanted pathways is different from zero in any period of free precession and where no refocusing π-pulses are applied. The ith component of each wanted pathway is $+n$ or $-n$, with some integer n, and the component representing the detection period equals -1 (quadrature detection (*22*)). When field gradients are applied in N periods of free precession, the pathway vectors are elements of $|R^N$ (N nonzero components). The total number of wanted pathways counts up to 2^N when the detection period is excluded from the N periods of free precession where field gradients are applied, and it equals $2^{(N-1)}$ when the detection period is included (see Appendix).

Let us assume the experimentalist decides to apply a single field gradient pulse ($N = 1$) in the detection period of the experiment (prior to detection). In our notation, the first component of each pathway vector is some integer (the coherence order prevailing in the detection period), and the remaining $F - 1$ components are equal to zero. Obviously, there is only one wanted pathway, ${}^1\mathbf{p}^t = (-1, 0, \ldots, 0)$, which already spans $|R^1$, and the suppressive subspace as well as the free subspace are empty (Eq. [5]).

Now, a further period of free precession may be anticipated for the application of a pulsed field gradient ($N = 2$). ${}^1\mathbf{p}$ splits into two wanted pathways:

$$ {}^1\mathbf{p} := \begin{pmatrix} -1 \\ 0 \\ 0 \\ . \\ . \\ 0 \end{pmatrix} \rightarrow {}^1\mathbf{p}_+ := \begin{pmatrix} -1 \\ +n \\ 0 \\ . \\ . \\ 0 \end{pmatrix}, \quad {}^1\mathbf{p}_- := \begin{pmatrix} -1 \\ -n \\ 0 \\ . \\ . \\ 0 \end{pmatrix}. \quad [6a] $$

The selective subspace spanned by the single wanted pathway for $N = 1$, $[{}^1\mathbf{p}]$, is a subspace of the selective subspace for $N = 2$, $[{}^1\mathbf{p}_+, {}^1\mathbf{p}_-]$. Specifically, the linear combination

$$ \frac{{}^1\mathbf{p}_+ + {}^1\mathbf{p}_-}{2} = \begin{pmatrix} -1 \\ 0 \\ 0 \\ . \\ . \\ 0 \end{pmatrix} \quad [6b] $$

spans $[{}^1\mathbf{p}]$, as it coincides with the vector ${}^1\mathbf{p}$. The linear combination

$$ \frac{{}^1\mathbf{p}_+ - {}^1\mathbf{p}_-}{2} = \begin{pmatrix} 0 \\ +n \\ 0 \\ . \\ . \\ 0 \end{pmatrix} \quad [6c] $$

generates a vector which is linearly independent of ${}^1\mathbf{p}$. It follows that the wanted coherence transfer pathways for the case $N = 2$ span a selective subspace of a dimension that is 1 larger than in the case $N = 1$. Since the addition of a single period of free precession can only increase the dimension of the overall space by 1 ($|R^2$), the suppressive and free subspaces remain empty. The former arguments can be repeated whenever a further period of free precession is included until the limit, $N = F$, is reached, and the suppressive and free subspaces are empty, whatever periods of free precession are considered for a possible application of gradient pulses. The same result is obtained in a similiar calculation (not shown) if one starts out from a period of free precession different than the detection period for the placement of a first gradient pulse (see also the Appendix).

The situation is different for experiments where the new included period of free precession is separated from one of the former periods by a π-pulse. For an ideal π-pulse, the component representing the newly added period, say the $(N + 1)$th component, is the negative of some other component, say the Nth. As the suppressive subspace is empty prior to the inclusion of a further period of free precession, each unwanted

pathway can be represented by a linear combination of the wanted pathways (linear dependence). For each component of a particular unwanted pathway, for example the Nth component, an equation of the form $p_N = \sum_i \alpha_i^i p_N$ holds, with the same expansion coefficients α_i. The summation runs over all wanted pathways ($2^{(N-1)}$ if the detection is considered for the application of a field gradient, or 2^N if it is not). Since $p_{N+1} = -p_N$, and ${}^ip_{N+1} = -{}^ip_N$, $p_{N+1} = \sum_i \alpha_i^i p_{N+1}$ is also valid, and the linear dependence of the unwanted pathway on the wanted pathways is preserved. Thus, the suppressive subspace remains empty. It is shown in the Appendix that the wanted pathways in the current case (one π-pulse, or echo) span a subspace of dimensionality N. Since the overall space is $|R^{N+1}$, a one-dimensional free subspace exists. It is straightforward to accomodate for more than a single π-pulse (see Appendix). The suppressive subspace will remain empty, but the dimensionality of the free subspace will increase by 1 whenever a new period of free precession is included which is separated by a former one by a π-pulse. If π-pulses are imperfect, additional unwanted pathways are excited which are not elements of the selective subspace. As is well known, these unwanted pathways, and only these, can be purged by a pair of gradient pulses surrounding the refocusing π-pulse (*23*).

In summary, for homonuclear experiments where the coherence order of the wanted pathways is always different from zero, and ignoring unwanted pathways induced by imperfect RF pulses, the suppressive subspace is empty whenever it is intended to rephase all wanted coherence transfer pathways, as might be done by phase cycling. The selective subspace has maximum dimension, and all unwanted pathways are elements of the selective subspace. No sequence of pulsed field gradients exists which rephases all wanted pathways and dephases any of the unwanted ones. To discriminate between wanted and unwanted signals, the dimension of the selective subspace has to be reduced by 1, say from L to $L - 1$. Some of the unwanted pathways may have a component orthogonal to the reduced selective subspace, i.e., a one-dimensional suppressive subspace may be formed, and those unwanted pathways can be dephased. There are infinitely many $(L - 1)$-dimensional subspaces of $|R^L$ but, as discussed in the Appendix, there are at most $2^{(L-1)}$ wanted pathways in $|R^{(L-1)}$ (or $2^{(L-1)-1}$ if the detection period is included), instead of 2^L in $|R^L$ (or $2^{(L-1)}$). Therefore, at most only half of the wanted pathways in comparison to a phase cycled experiment can be retained when signal selection is done by pulsed field gradients, and half of the maximum number of wanted pathways will be dephased together with some unwanted pathways. As an example, the pathway selection of the COSY experiment is geometrically analyzed in Fig. 2. In order to dephase all, or at least the most important, unwanted signals, it might be neccessary to increase the suppressive subspace by a further reduction of the selective subspace. Again, the number of wanted pathways which can be possibly rephased will be halved by each such step.

The preceding analysis excludes experiments where the coherence order of wanted pathways equals zero in one or several periods of free precession. A field gradient applied in such a period will have no effect on the wanted pathways (Eq. [1]), but may dephase any unwanted pathway with a nonzero coherence order prevailing in this period of free precession. The approach is often used to purge unwanted signals while a maximum number of wanted pathways are retained (*23*).

In principle, heteronuclear experiments can be carried out along similar lines as homonuclear ones. The composite coherence order, a real number, replaces the integer coherence order as components of the pathway vectors (the results of the

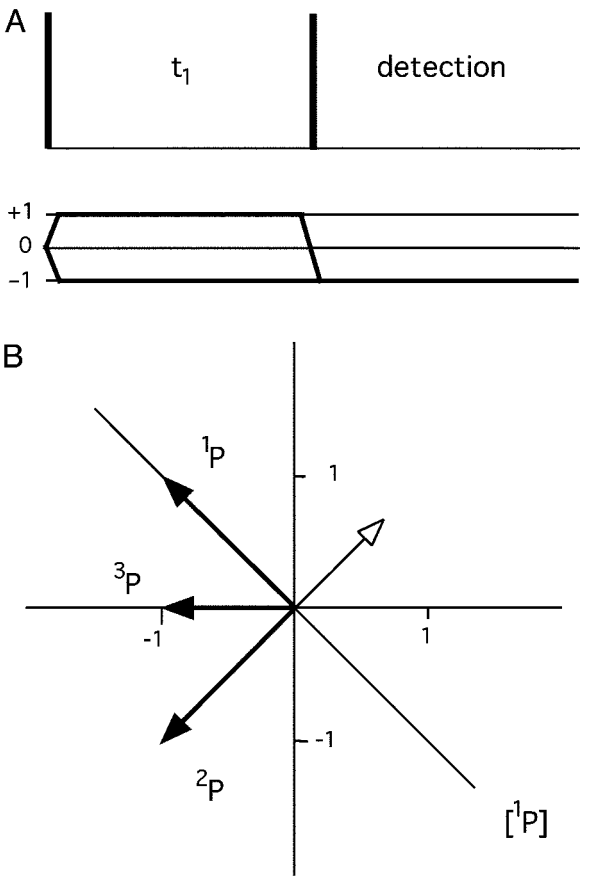

FIG. 2. (A) Pulse sequence of COSY experiment with pathway diagram (*1*). (B) The geometry of pathway selection in COSY is described in $|R^2$, as there are two periods of free precession. Phase cycling can be used to select the two wanted pathways, ${}^1\mathbf{p} = (-1, +1)$ and ${}^2\mathbf{p} = (-1, -1)$, where the first component is the coherence order during quadrature detection, and the second component represents transverse magnetization during t_1. The wanted pathways span $|R^2$ (selective subspace), and the suppressive as well as the free subspace are empty. Any sequence, $\mathbf{g}^x$, $\mathbf{g}^y$, and $\mathbf{g}^z$, is also represented by a vector in $|R^2$. It is not possible to rephase ${}^1\mathbf{p}$ and ${}^2\mathbf{p}$, as such a gradient sequence would correspond to a vector of $|R^2$ which is orthogonal to both pathways. However, if only one (half) of the two wanted pathways should be retained, e.g., ${}^1\mathbf{p}$, the selective subspace is one-dimensional, $[{}^1\mathbf{p}]$ (indicated by a line), and a rephasing gradient vector can be easily found (open arrow). Such a sequence dephases the other wanted pathway, as well as some unwanted pathways, e.g., ${}^3\mathbf{p} = (-1, 0)$ which can be induced by an imperfect preparation pulse.

Appendix are derived for real components). It is in the number of pathways into which a given wanted pathway can split, whenever a further period of free precession for the application of a field gradient is included in the analysis, that heteronuclear experiments can be different. The coherence orders of the different species can change simultanously (e.g., by RF pulses applied to two species at the same time), and a wanted pathway can split into more than two new pathways, say four. Conversely, the number of wanted pathways will be quartered when the dimensionality of the selective subspace is reduced by 1, as can be seen by a treatment analogous to the homonuclear case where only a duplication of wanted pathways occured. An example for pathway selection of a heteronuclear experiment is discussed in detail in Part II (*33*).

It is interesting to apply a geometric analysis to the special case of a two-dimensional experiment where field gradients are applied only during the evolution period and the detection period. The wanted pathways are readily described by Eqs. [6a] to [6c], with the second component representing the coherence order prevailing during the evolution period (e.g., $\pm n = \pm 1$ corresponds to frequency labeling of transverse magnetization; see also Fig. 2). If the two-dimensional data set is amplitude modulated with respect to the evolution period (*24*), both wanted pathways are selected by phase cycling. As shown earlier, one of the two wanted pathways has to be sacrificed when field gradients are applied, since otherwise a suppression of unwanted signals is impossible. Recently, schemes for phase modulated data acquisition were implemented in some experiments (*25, 26*). In comparison to amplitude modulation, a duplication of the amplitude of the two wanted pathways occurs. In these so-called sensitivity enhanced experiments, two data sets, where each of the two wanted pathways is selected at a time by phase cycling, are acquired separately but processed in a combined manner to obtain an improvement in signal-to-noise of up to $\sqrt{2}$. Clearly, a sequence of pulsed field gradients can be found which retains one of the wanted pathways and suppresses some unwanted pathways at the same time (Fig. 2). Indeed, field gradients can be applied in sensitivity enhanced experiments without a concomitant loss of signal-to-noise in comparison to phase cycling (*27, 28*).

CONCLUSION

Signal selection by field gradients implies in general the rephasing of several wanted pathways and the suppression of a manifold of unwanted pathways at the same time. These are competitive requirements, and the signal selection by field gradients is limited. The number of wanted pathways retained by field gradients can be increased only at the cost of reducing the number of unwanted pathways which are possible to suppress, and vice versa. In most widely employed experiments (ignoring imperfections of RF pulses, the exceptions are sensitivity enhanced experiments, and experiments where the coherence order of wanted pathways is zero while gradients are applied (purging)) at most only half of the number of wanted pathways can be selected by the application of field gradients in comparison to phase cycling, and a lower signal-to-noise is obtained.

The experimetalist is forced to find a compromise in applying a gradient sequence which rephases as many wanted pathways as possible while a few, but the most important, unwanted signals are suppressed. To obtain an optimum signal-to-noise, it is preferable to attenuate unwanted pathways confined to a one-dimensional suppressive subspace. The application of several gradient sequences along different directions in space is then not necessary, since signal selection can be done by a single sequence which spans the one-dimensional suppressive subspace. Field gradients along three orthogonal directions are necessary in some special cases where the unwanted pathways may span a high dimensional manifold. Their use is particularly valuable where gradient recalled echoes have to be avoided, as for example in the context of water suppression (*29, 30*), or where magic angle gradients are applied to suppress multiple quantum interference of bulk water (*31, 32*).

The geometrical approach provides insight into the problem of pathway selection, and simple NMR experiments may be analyzed completely. To find suitable gradient sequences in complex applications, in particular for multidimensional experiments, the geometrical approach has been implemented numerically. The program TRIPLE_GRADIENT, as described in Part II (*33*), enables the user to calculate optimal gradient sequences for signal selection in each individual NMR experiment.

APPENDIX

Some properties of vectors of $|R^N$, isomorphic to N-tuple of real numbers (coordinate vector), with particular restrictions on the choice of coordinates are derived.

The discussion is restricted to vectors with components different from zero. Consider a set of vectors with the property that the magnitude of each component is set to some pre-fixed nonzero value, say $\alpha_i > 0$ for the ith component, but the sign is undetermined. Such a set is denoted as a set of complementary vectors of $|R^N$. A member of the set is (using notation as row vectors)

$$\mathbf{x} = (\pm\alpha_1, \pm\alpha_2, \pm\alpha_3, \ldots, \pm\alpha_N),$$

with a definite choice of either the plus or the minus sign independently for each component. The number of members of the set is easily counted to be 2^N. There are strong linear dependencies within the set, e.g., for any member $\mathbf{x}$ the antiparallel vector $-\mathbf{x}$ is also a member. However, as can be verified by the Gram–Schmidt orthogonalization procedure (*21*), the set spans $|R^N$, i.e., a base of $|R^N$ can be constructed from complementary vectors of $|R^N$.

As a further requirement, assume that one of the N components is completely specified (magnitude *and* sign); say the kth component is identical to β_k in each vector,

$$\mathbf{x} = (\pm\alpha_1, \ldots, \beta_k, \ldots, \pm\alpha_N).$$

Clearly, there are only 2^{N-1} vectors of this form, and they may be called a reduced set of complementary vectors of $|R^N$. The notation for $\mathbf{x}$ can be rationalized by collecting the $N-1$ components with independent sign alternation in a vector $\alpha(N-1)$, so $\mathbf{x} = (\beta_k, \alpha(N-1))$. To any member of the reduced set, ${}^{+}\mathbf{x} = (\beta_k, \alpha(N-1))$, the vector which has components of opposite sign (except the kth), ${}^{-}\mathbf{x} = (\beta_k, -\alpha(N-1))$, is also a member of the reduced set. The set of linear combinations $({}^{+}\mathbf{x} - {}^{-}\mathbf{x})/2 = (0, \alpha(N-1))$, $({}^{-}\mathbf{x} - {}^{+}\mathbf{x})/2 = (0, -\alpha(N-1))$, for all realizations of $\alpha(N-1)$ within the reduced set, is isomorphic to the set of complementary vectors of $|R^{N-1}$, and, as discussed previously, $N-1$ base vectors can be constructed from these linear combinations which span a subspace of dimensionality $N-1$. The linear combination $({}^{+}\mathbf{x} + {}^{-}\mathbf{x})/2 = (\beta_k, \mathbf{0})$ is linearly independent of these $N-1$ base vectors (since it is independent of the combinations $({}^{+}\mathbf{x} - {}^{-}\mathbf{x})/2$ and $({}^{-}\mathbf{x} - {}^{+}\mathbf{x})/2$), and together they form a base of $|R^N$. Therefore, the reduced set of complementary vectors of $|R^N$ spans the total space $|R^N$.

Another restriction is to constrain a particular component to be the negative of another component within the set of complementary vectors of $|R^N$. For example, the jth component is $-\alpha_i$, when the ith component equals $+\alpha_i$ (with $\alpha_i > 0$), and it is $+\alpha_i$ when the ith component adopts the value $-\alpha_i$, while the sign of the other $N-2$ components is uncorrelated,

$$\mathbf{x} = (\pm\alpha_1, \ldots, +/-\alpha_i, \ldots, -/+\alpha_i, \ldots, \pm\alpha_N).$$

Such a case is denoted as an echo formed by the vectors. The number of complementary vectors of $|R^N$ forming one echo is easily counted to be 2^{N-1}. If ${}^{++}\mathbf{x} = (\alpha_i, -\alpha_i, \alpha(N-2))$ (using collective notation) is a member of the set, then the vectors ${}^{+-}\mathbf{x} = (\alpha_i, -\alpha_i, -\alpha(N-2))$, ${}^{-+}\mathbf{x} = (-\alpha_i, \alpha_i, \alpha(N-2))$, and ${}^{--}\mathbf{x} = (-\alpha_i, \alpha_i, -\alpha(N-2))$ are also members. The linear combinations $({}^{++}\mathbf{x} - {}^{+-}\mathbf{x})/2 = ({}^{-+}\mathbf{x} - {}^{--}\mathbf{x})/2 = (0, 0, \alpha(N-2))$, and $({}^{+-}\mathbf{x} - {}^{++}\mathbf{x})/2 = ({}^{--}\mathbf{x} - {}^{-+}\mathbf{x})/2 = (0, 0, -\alpha(N-2))$ are isomorphic to the set of complementary vectors of $|R^{N-2}$, and $N-2$ linearly independent base vectors may be constructed which span a subspace of dimensionality $N-2$. The combinations $({}^{++}\mathbf{x} + {}^{+-}\mathbf{x})/2 = ({}^{++}\mathbf{x} - {}^{-+}\mathbf{x})/2 = (\alpha_i, -\alpha_i, 0)$, and $({}^{--}\mathbf{x} + {}^{-+}\mathbf{x})/2 = ({}^{--}\mathbf{x} - {}^{+-}\mathbf{x})/2 = (-\alpha_i, \alpha_i, 0)$, are antiparallel vectors which span a one-dimensional subspace. A base vector of this subspace (e.g., $(\gamma_i, -\gamma_i, 0)$) is linearly independent from the previously constructed $N-2$ base vectors, and together they form a base for a subspace of dimensionality $N-1$. Since any member of the set of complementary vectors of $|R^N$ forming one echo can be decomposed into these $N-1$ base vectors, their span is a subspace of dimensionality $N-1$. The preceding calculations can be virtually repeated when one echo is formed by the vectors of a reduced set of complementary vectors of $|R^N$. One of the components of $\alpha(N-2)$ may simply represent the fixed component, β_k. In this case, the number of members is 2^{N-2}, and their span is of dimensionality $N-1$. It is straightforward to generalize the discussion when more than one echo is formed by the vectors. For each further echo, the number of complementary vectors of $|R^N$ is halved, and the dimensionality of the subspace spanned by these vectors is reduced by 1.

In summary, it has been shown that a (reduced) set of complementary vectors of $|R^N$ forming M echoes comprises 2^{N-M} (2^{N-M-1}) members, and the set spans a subspace of dimensionality $N-M$.

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