Symbolic NMR Product Operator Calculations

PETER GÜNTERT

Tatsuo Miyazawa Memorial Program, RIKEN Genomic Sciences Center, 1-7-22 Suehiro-cho, Tsurumi, Yokohama 230-0045, Japan

Received 4 June 2005; accepted 8 June 2005

DOI 10.1002/qua.20754

ABSTRACT: Symbolic nuclear magnetic resonance (NMR) product operator calculations provide an analytic, intuitive, yet precise description of the time evolution of the density operator during an NMR experiment. NMR experiments are implemented as pulse sequences consisting of short radiofrequency pulses separated by delay periods during which the spin system evolves under the influence of the static external magnetic field and spin–spin interactions. The quantum mechanical calculations to follow the time evolution of the density operator can be decomposed into the repeated application of a set of simple rules, known as the product operator formalism, that naturally lend themselves to symbolic computation. This article describes a complete implementation of the NMR Product Operator formalism in MAthematica (POMA), which has greatly simplified the development of many NMR pulse sequences, and provided insight into their functioning. © 2005 Wiley Periodicals, Inc. Int J Quantum Chem 106: 344–350, 2006

Key words: nuclear magnetic resonance; NMR; product operator formalism; POMA; Mathematica

Introduction

Nuclear magnetic resonance (NMR) spectroscopy [1] has become a very important technique in structural molecular biology because of its unique ability to determine the three-dimensional structures of proteins and other biological macromolecules in solution [2]. Knowledge of the three-dimensional structures of proteins and nucleic acids has greatly improved our insight into biological processes and macromolecular structure–function relationships. Apart from structural data, NMR also provides information about the dynamics of proteins. The combined access to structure and dynamics renders NMR a powerful tool for the analysis of dynamic events, such as folding transitions in proteins, which are of major importance for biological function.

NMR experiments in solution are generally implemented as pulse sequences [1, 3]. The sample is placed in a strong, static magnetic field of up to ~22 tesla (T), produced by a superconducting magnet. Starting from thermal equilibrium, short "radiofrequency" pulses are applied that rotate the magnetization created by the nuclear spins. In the evolution periods between pulses, the spins precess under the influence of the static magnetic field and spin–spin (and other) interactions. Finally, the radiofrequency signal emitted by the spins (the "free induction decay") is detected as a function of time. Fourier transformation of the free induction decay yields the frequency domain NMR spectrum. Much of the power of the NMR technique results from the possibility to introduce additional time dimensions into the experiments. This is achieved by repeated application of the same pulse sequence in which only the duration of one or several evolution periods before the free induction decay are incremented systematically in order to obtain a signal as a function of several, in practice 2–4, time coordinates, from which a multidimensional NMR spectrum is computed by Fourier transformation. Multidimensional spectra can separate signals that would overlap in a one-dimensional spectrum, and therefore allow the simultaneous, individual interpretation of signals from a large number of spins in the macromolecule.

An essentially unlimited number of different pulse sequences that select specific interactions can be conceived in order to analyze particular aspects of the spin system and the underlying molecule. The design and optimization of pulse sequences are central to methodological NMR research [3–6]. Because of the weak magnetic moment of the nuclear spins, NMR is a relatively insensitive technique. The requirement to measure at least one free induction decay for each time increment of the preceding evolution period(s) results in long measurement times for multidimensional NMR experiments. This rules out pulse sequence development purely by trial and error and calls for simulation methods that can predict the outcome of an NMR experiment.

A variety of simulation methods have been proposed [7–21] that differ widely in their approach between analytic and numerical simulations, their scope with regard to the interactions and types of experiments covered, their implementation, and their presentation of the results. A rigorous theoretical approach that can provide proof of the optimality of a pulse sequence under given conditions has been presented [22] that has recently been extended in order to find constructively the optimal pulse sequence [23].

This study concentrates on a symbolic computing approach for the analytical calculation of the time evolution of the idealized density operator in a pulsed NMR experiment, neglecting relaxation and strong spin–spin coupling.

Product Operator Formalism

The time evolution of the density operator [24] ($\hbar \equiv 1$),

$$\sigma(t+\tau) = e^{-iH\tau}\sigma(t)e^{iH\tau}, \tag{1}$$

in a pulsed NMR experiment can be calculated analytically for weakly coupled spin systems by expressing the Hamiltonian H and the density operator σ in the basis of Cartesian product operators [1, 25]. The Hamilton operator H_f for the precession of the spins in the static magnetic field, parallel to the z-axis, under the influence of chemical shifts, ω_k, and weak scalar couplings, J_{kl}, is given by

$$H_f = \sum_k \omega_k I_{kz} + \sum_{k<l} 2\pi J_{kl} I_{kz} I_{lz}. \tag{2}$$

I_{kx}, I_{ky}, I_{kz} denote the x, y, z spin operators for spin $k = 1, 2, \ldots$. The Hamilton operator H_p for a short radiofrequency pulse of (infinitesimally short) duration τ, rotation angle β, and phase angle ϕ is given by

$$H_p = \frac{\beta}{\tau} \sum_k (I_{kx}\cos\phi + I_{ky}\sin\phi). \tag{3}$$

The individual terms of H_f commute with each other. The individual terms of H_p commute with each other, too, but not H_f with H_p. This observation reduces density operator calculations of Eq. (1) to the repeated application of simple rules that describe the time evolution of the density operator under the influence of individual terms of the Hamiltonians H_f and H_p. The rules of this product operator formalism [1, 25] are summarized in Figures 1 and 2 and can be derived in a straightforward way from Eq. (1) and the rules for spin-1/2 operators [24] if relaxation is neglected and infinitesimally short pulse lengths are assumed.

The product operator formalism combines a rigorous quantum mechanical treatment with an intuitive classical description, and was the basis for the development of a wide variety of NMR experi-

Product operator rules for Cartesian spin operators

Interaction: $H\tau$		
$\sigma(t) \to \sigma(t+\tau)$		
Chemical shift: $\omega_k I_{kz}\tau$	Scalar spin-spin coupling: $2\pi J_{kl} I_{kz} I_{lz}\tau$	
$I_{kx} \to I_{kx}\cos\omega_k\tau + I_{ky}\sin\omega_k\tau$ $I_{ky} \to I_{ky}\cos\omega_k\tau - I_{kx}\sin\omega_k\tau$	$2I_{k\mu}I_{l\nu} \to 2I_{k\mu}I_{l\nu} \qquad (\mu = x, y;\ \nu = x, y)$ $2I_{kx}I_{lz} \to 2I_{kx}I_{lz}\cos\pi J_{kl}\tau + I_{ky}\sin\pi J_{kl}\tau$ $2I_{ky}I_{lz} \to 2I_{ky}I_{lz}\cos\pi J_{kl}\tau - I_{kx}\sin\pi J_{kl}\tau$ $I_{kx} \to I_{kx}\cos\pi J_{kl}\tau + 2I_{ky}I_{lz}\sin\pi J_{kl}\tau$ $I_{ky} \to I_{ky}\cos\pi J_{kl}\tau - 2I_{kx}I_{lz}\sin\pi J_{kl}\tau$	
Pulse with rotation angle β and phase ϕ: $\beta(I_{kx}\cos\phi + I_{ky}\sin\phi)$		
$I_{kx} \to I_{kx}(\cos\beta\sin^2\phi + \cos^2\phi) + I_{ky}\sin^2(\beta/2)\sin 2\phi - I_{kz}\sin\beta\sin\phi$ $I_{ky} \to I_{ky}(\cos\beta\cos^2\phi + \sin^2\phi) + I_{kx}\sin^2(\beta/2)\sin 2\phi + I_{kz}\sin\beta\cos\phi$ $I_{kz} \to I_{kx}\sin\beta\sin\phi - I_{ky}\sin\beta\cos\phi + I_{kz}\cos\beta$		
x-pulse: βI_{kx}	y-pulse: βI_{ky}	z-pulse: βI_{kz}
$I_{ky} \to I_{ky}\cos\beta + I_{kz}\sin\beta$ $I_{kz} \to I_{kz}\cos\beta - I_{ky}\sin\beta$	$I_{kx} \to I_{kx}\cos\beta - I_{kz}\sin\beta$ $I_{kz} \to I_{kz}\cos\beta + I_{kx}\sin\beta$	$I_{kx} \to I_{kx}\cos\beta + I_{ky}\sin\beta$ $I_{ky} \to I_{ky}\cos\beta - I_{kx}\sin\beta$
$90°_x$-pulse: $(\pi/2)I_{kx}$	$90°_y$-pulse: $(\pi/2)I_{ky}$	$90°_z$-pulse: $(\pi/2)I_{kz}$
$I_{ky} \to I_{kz}$ $I_{kz} \to -I_{ky}$	$I_{kx} \to -I_{kz}$ $I_{kz} \to I_{kx}$	$I_{kx} \to I_{ky}$ $I_{ky} \to -I_{kx}$
$180°_x$-pulse: πI_{kx}	$180°_y$-pulse: πI_{ky}	$180°_z$-pulse: πI_{kz}
$I_{ky} \to -I_{ky}$ $I_{kz} \to -I_{kz}$	$I_{kx} \to -I_{kx}$ $I_{kz} \to -I_{kz}$	$I_{kx} \to -I_{kx}$ $I_{ky} \to -I_{ky}$

FIGURE 1. Product operator formalism rules for Cartesian spin-1/2 operators [1, 25]. Spin operators for which no rule is given are not affected by a given interaction. In the case of spin–spin couplings, the rules for products of two spins take precedence over those for one spin.

ments [3–6]. The time evolution of the density operator can, of course, be calculated numerically, but this obscures the intuitive analytical meaning of the result. Symbolic calculation, however, gives the analytical result that can provide a gifted spectroscopist with understanding and inspiration for the development of new experiments.

All calculations within the product operator formalism proceed by repeated application of the small number of rules of Figures 1 and 2, which describe the time evolution of individual product operators under chemical shifts, scalar couplings, and radiofrequency pulses. Although these calculations are straightforward, the large number of terms that arise can make them tedious, and computer support is highly desirable.

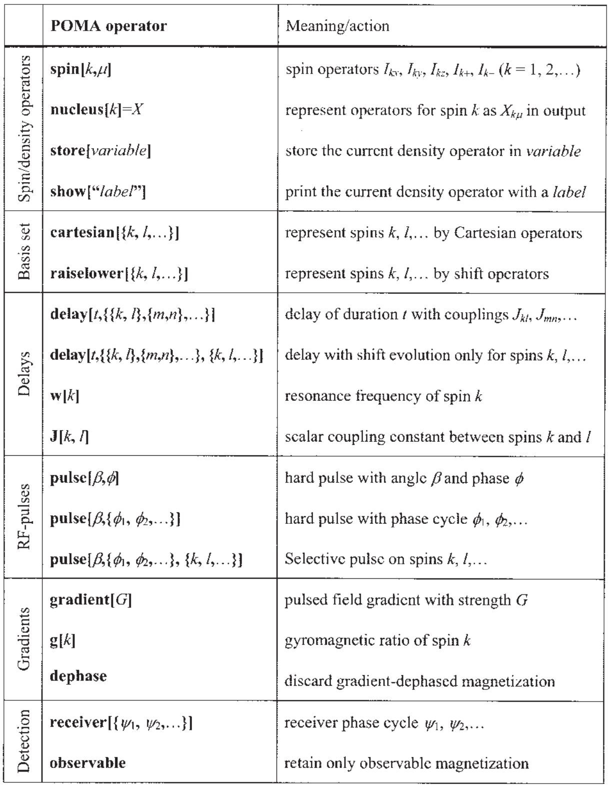
POMA

The Product Operator formalism in MAthematica (POMA) software is a complete, highly flexible Mathematica [26] implementation of the product operator formalism for spin-1/2 nuclei, which provides analytical results for the time evolution of weakly coupled spin systems under the influence of free precession, selective and nonselective pulses, phase cycling, and pulsed field gradients (Fig. 3). The complexity of the problems that can be treated is in practice only limited by the available computer time and memory. The complete Mathematica code of POMA is available from http://guentert.gsc.riken.jp/. It is apparent that Mathematica offers a particularly concise and elegant way to express the transformation rules of the product operator formalism. If desired, the results of the calculations can be further processed using

Product operator rules for raising/lowering operators

Interaction: $H\tau$		
$\sigma(t) \to \sigma(t+\tau)$		
Chemical shift: $\omega_k I_{kz}\tau$	Scalar spin-spin coupling: $2\pi J_{kl} I_{kz} I_{lz}\tau$	
$I_{k\pm} \to I_{k\pm}e^{\mp i\omega_k\tau}$	$2I_{k\mu}I_{l\nu} \to 2I_{k\mu}I_{l\nu} \qquad (\mu = +, -;\ \nu = +, -)$ $2I_{k\pm}I_{lz} \to 2I_{k\pm}I_{lz}\cos\pi J_{kl}\tau \mp I_{k\pm}i\sin\pi J_{kl}\tau$ $I_{k\pm} \to I_{k\pm}\cos\pi J_{kl}\tau \mp 2I_{k\mp}I_{lz}i\sin\pi J_{kl}\tau$	
Pulse with rotation angle β and phase ϕ: $\beta(I_{kx}\cos\phi + I_{ky}\sin\phi)$		
$I_{k\pm} \to I_{k\pm}\cos^2(\beta/2) + I_{k\mp}\sin^2(\beta/2)e^{\pm 2i\phi} \pm I_{kz}\sin\beta\, ie^{\pm i\phi}$ $I_{kz} \to I_{k+}\frac{i}{2}\sin\beta\, e^{-i\phi} - I_{k-}\frac{i}{2}\sin\beta\, e^{i\phi} + I_{kz}\cos\beta$		
$90°_x$-pulse: $(\pi/2)I_{kx}$	$90°_y$-pulse: $(\pi/2)I_{ky}$	z-pulse: βI_{kz}
$I_{k\pm} \to \frac{1}{2}I_{k+} + \frac{1}{2}I_{k-} \pm iI_{kz}$ $I_{kz} \to \frac{i}{2}I_{k+} - \frac{i}{2}I_{k-}$	$I_{k\pm} \to \pm\frac{1}{2}I_{k+} \mp \frac{1}{2}I_{k-} - I_{kz}$ $I_{kz} \to \frac{1}{2}I_{k+} + \frac{1}{2}I_{k-}$	$I_{k\pm} \to e^{\mp i\beta}I_{k\pm}$
$180°_x$-pulse: πI_{kx}	$180°_y$-pulse: πI_{ky}	$180°_z$-pulse: πI_{kz}
$I_{k\pm} \to I_{k\mp}$ $I_{kz} \to -I_{kz}$	$I_{k\pm} \to -I_{k\mp}$ $I_{kz} \to -I_{kz}$	$I_{k\pm} \to -I_{k\pm}$

FIGURE 2. Product operator formalism rules for spin-1/2 raising/lowering operators, $I_{\pm} = I_x \pm iI_y$ [1, 25]. Spin operators for which no rule is given are not affected by a given interaction. In the case of spin–spin couplings, the rules for two-spin operators have priority over the rules for single-spin operators.



	POMA operator	Meaning/action
Spin/density operators	**spin**[*k*,*μ*]	spin operators I_{kx}, I_{ky}, I_{kz}, I_{k+}, I_{k-} ($k = 1, 2, \ldots$)
	nucleus[*k*]=*X*	represent operators for spin *k* as $X_{k\mu}$ in output
	store[*variable*]	store the current density operator in *variable*
	show["*label*"]	print the current density operator with a *label*
Basis set	**cartesian**[{*k*, *l*,…}]	represent spins *k*, *l*,… by Cartesian operators
	raiselower[{*k*, *l*,…}]	represent spins *k*, *l*,… by shift operators
Delays	**delay**[*t*,{{*k*, *l*},{*m*,*n*},…}]	delay of duration *t* with couplings J_{kl}, J_{mn},…
	delay[*t*,{{*k*, *l*},{*m*,*n*},…}, {*k*, *l*,…}]	delay with shift evolution only for spins *k*, *l*,…
	w[*k*]	resonance frequency of spin *k*
	J[*k*, *l*]	scalar coupling constant between spins *k* and *l*
RF-pulses	**pulse**[*β*,*ϕ*]	hard pulse with angle *β* and phase *ϕ*
	pulse[*β*,{ϕ_1, ϕ_2,…}]	hard pulse with phase cycle ϕ_1, ϕ_2,…
	pulse[*β*,{ϕ_1, ϕ_2,…}, {*k*, *l*,…}]	Selective pulse on spins *k*, *l*,…
Gradients	**gradient**[*G*]	pulsed field gradient with strength *G*
	g[*k*]	gyromagnetic ratio of spin *k*
	dephase	discard gradient-dephased magnetization
Detection	**receiver**[{ψ_1, ψ_2,…}]	receiver phase cycle ψ_1, ψ_2,…
	observable	retain only observable magnetization

FIGURE 3. Product Operator formalism in MAthematica (POMA) operators.

the built-in capabilities of Mathematica to handle mathematical expressions.

SPIN OPERATORS

In the POMA implementation of the product operator formalism, a spin operator $I_{k\alpha}$ that corresponds to the α-component of spin k ($\alpha = x, y, z$; $k = 1, 2, \ldots$) is represented in the input by **spin[*k*, *α*]** and in the output by $X_{k\alpha}$, where the letter X can be set with the command **nucleus[*k*]** = *X*. The initial, thermal equilibrium state of the spin system before the application of the first radiofrequency pulse is normally specified as **spin[1, z]**.

Alternatively, some or all of the spins $k = 1, 2, \ldots$ can be represented in the basis of raising and lowering operators [24], $I_{k+} = I_{kx} + iI_{ky}$, $I_{k-} = I_{kx} - iI_{ky}$ (and I_{kz}), which are given in the input as **spin[*k*, plus]** and **spin[*k*, minus]** and in the output as X_{k+} and X_{k-}, respectively. The product operator rules that apply to raising/lowering operators are summarized in Figure 2 in analogy to those for Cartesian spin operators in Figure 1.

Two operators allow inspection of the density operator at intermediate points in a pulse sequence: **store**[*var*] stores the current density operator in the variable with name *var*, and **show**["*label*"] prints current density operator below the given label.

A basis change from Cartesian to raising/lowering operators for the spins in the set {*k*, *l*, . . .} is represented by

raiselower[{*k*,*l*, . . .}],

and the inverse basis change from raising/lowering operators to Cartesian spin operators by

cartesian[{*k*, *l*, . . . }].

These two commands can be used in a short form without parameters, **cartesian** or **raiselower**, in order to change to the corresponding basis for all spins in the present density operator.

DELAYS

A delay of time period t, during which the spins in the set {*k*, *l*, . . .} evolve under chemical shifts with frequencies ω_k, ω_l, . . . , and under scalar couplings J_{mn}, J_{pq}, . . . between the spin pairs in the set {*mn*, *pq*, . . .} is represented by

delay[*t*, {{*m*, *n*}, {*p*, *q*}, . . . }, {*k*, *l*, . . . }].

By default, all spins evolve under chemical shifts, and no scalar couplings are assumed. A new spin is normally introduced into the spin system simply through the presence of a spin–spin coupling with an existing spin during a delay. The time evolution during delays is most conveniently expressed by sine and cosine terms in the case of Cartesian spin operators (Fig. 1), or by complex exponentials if raising/lowering operators are used (Fig. 2). POMA applies the appropriate transformations of trigonometric factors in conjunction with basis changes.

RADIOFREQUENCY PULSES

A pulse of flip angle β that acts on the spins in the set {*k*, *l*, . . .} and is phase cycled according to {ϕ_1, ϕ_2, . . .} is represented by

pulse[*β*, {ϕ_1, ϕ_2, . . . }, {*k*, *l*, . . . }].

If a flip angle or a phase angle is given as a pure number, it is assumed to be given in degrees; the phases $\phi = x, y, -x, -y$ correspond to phase angles of 0, 90, 180, and 270°, respectively. If the expression for a rotation or phase angle is neither a pure number, as defined by the Mathematica function **NumberQ**, nor one of the symbols $x, y, -x, -y$, it is assumed to be given in radians. If the phase is identical in all steps of a phase cycle, $\{\phi, \phi, \ldots\}$, it can be represented by a single phase ϕ. By default, a nonselective pulse is assumed; i.e., all spins are affected by the pulse. Thus, for instance, a hard 90° x-pulse can be written in shorthand notation as

pulse[90, x].

PULSED FIELD GRADIENTS

Pulsed field gradients are an important feature of pulse sequences besides the radiofrequency pulses [6]. The effect of a pulsed field gradient on spin k is implemented in POMA as a rotation around the z-axis by an angle $\beta = \gamma_k Gz$ that is proportional to the gyromagnetic ratio, γ_k, of spin k, the (signed) gradient strength, G, and the z-coordinate. A gradient acting on all spins is represented in POMA by

gradient[G],

and the gyromagnetic ratio, γ_k, of spin k by **g[k]**. Thus, after the application of a pulsed field gradient, all transverse magnetization terms will be "dephased," i.e., have a dependence on the z-coordinate. Another gradient of appropriate strength, which is applied later in the pulse sequence, may refocus part or all of the originally dephased magnetization. Dephased magnetization can be discarded from the density operator with the command

dephase

that permanently removes any magnetization terms that have a dependence on the z-coordinate.

DETECTION

The receiver phase cycle $\{\psi_1, \psi_2, \ldots\}$ is specified as

receiver[$\{\psi_1, \psi_2, \ldots\}$].

A receiver phase ψ is implemented by applying a pulse of rotation angle $-\Delta\psi$ around the z-axis to the product operators present before signal detection, where $\Delta\psi$ is the phase difference with respect to the x-axis.

The program repeats the calculation for each individual step of the phase cycle, adds the results, and normalizes the terms by the length of the phase cycle. The final result may be screened for the observable terms, i.e., terms with a single transverse spin operator, using the command

observable[$\{k, l, \ldots\}$],

where $\{k, l, \ldots\}$ denotes the set of transverse spins that are of interest during the detection period; by default, this includes all spins.

In the simulation of a pulsed NMR experiment, the Mathematica commands are combined in the order of the pulse sequence by using the postfix operator "//" (in Mathematica, $x//f$ has the meaning: "apply the operator f to the expression x"; it is equivalent to $f[x]$). This form of expression in Mathematica has major benefits for symbolic calculation [27] and allows the expression of pulse sequences as Mathematica expressions in a straightforward, natural way. For example, a pulse sequence with n pulses, intervening delays, and acquisition,

$$\beta_1\text{—}t_1\text{—}\beta_2\text{—}\cdots\text{—}\beta_n\text{—acquisition},$$

has the POMA representation

pulse[$\beta_1, \ldots$]//**delay**[$t_1, \ldots$]//**pulse**[$\beta_2, \ldots$]
//…//**pulse**[$\beta_n, \ldots$]//**receiver**[…].

In general, a pulse sequence is applied to the thermal equilibrium state of the spin system, i.e. I_{kz}, or, in Mathematica input form, **spin**[k, z], and at the end one retains only the observable terms by using the aforementioned **observable** operator.

Examples

3QF-COSY EXPERIMENT

As a simple example, we have simulated the homonuclear 3QF-COSY (triple quantum-filtered correlation spectroscopy) experiment [3, 28]:

$$90°_{\phi}—t_1—90°_{\phi}—90°_{x}—\text{acquisition}_{\psi}$$

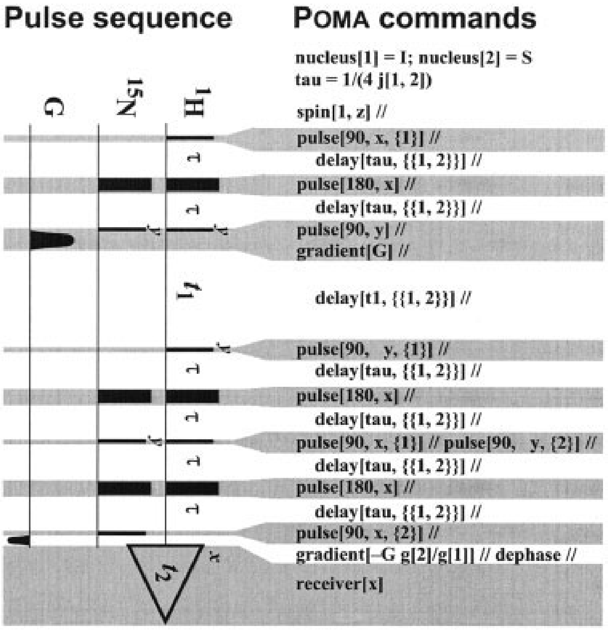
with the phase cycle $\phi = 0, \pi/3, 2\pi/3, \pi, 4\pi/3, 5\pi/3$; $\psi = 3(x, -x)$. In POMA, this experiment is represented by the following sequence of commands:

```
spin[1, z]//
  pulse [90, {0, Pi/3, 2Pi/3, Pi, 4Pi/3, 5Pi/3}]//
  delay [t1, {{1, 2}, {1, 3}}]//
  pulse [90, {0, Pi/3, 2Pi/3, 3Pi/3, 4Pi/3, 5Pi/3}]//
  pulse [90, {x, x, x, x, x, x}]//
  receiver [{x, −x, x, −x, x, −x}]//
  observable//Simplify
```

The experiment starts from thermal equilibrium, all pulses are nonselective 90° pulses, and during the delay t_1 the spin 1 is scalar coupled to the spins 2 and 3, but the spins 2 and 3 are not mutually scalar coupled. **Simplify** is a built-in Mathematica command for algebraic simplifications [26]. The POMA result for this pulse sequence is

$$-\sin(\omega_1 t_1)\sin(\pi J_{12} t_1)\sin(\pi J_{13} t_1) \times (I_{1z}I_{2z}I_{3x} + I_{1z}I_{2x}I_{3z} + I_{1x}I_{2z}I_{3z}).$$

ω_1 is the resonance frequency of the spin 1. Although the final result is simple, 124 terms had to be handled after the second pulse, which would make a manual derivation of this result rather cumbersome.



```
nucleus[1] = I; nucleus[2] = S
tau = 1/(4 j[1, 2])
spin[1, z] //
pulse[90, x, {1}] //
  delay[tau, {{1, 2}}] //
pulse[180, x] //
  delay[tau, {{1, 2}}] //
pulse[90, y] //
gradient[G] //
  delay[t1, {{1, 2}}] //
pulse[90,   y, {1}] //
  delay[tau, {{1, 2}}] //
pulse[180, x] //
  delay[tau, {{1, 2}}] //
pulse[90, x, {1}] // pulse[90,   y, {2}] //
  delay[tau, {{1, 2}}] //
pulse[180, x] //
  delay[tau, {{1, 2}}] //
pulse[90, x, {2}] //
gradient[–G g[2]/g[1]] // dephase //
receiver[x]
```

FIGURE 4. Product Operator formalism in MAthematica (POMA) simulation of the [^{15}N, ^{1}H]-TROSY NMR experiment [29]. The conventional schematic representation of the pulse sequence is shown on the left, the corresponding sequence of POMA operators on the right.

TROSY-HSQC EXPERIMENT

The pulse sequence of the [^{15}N, ^{1}H]-TROSY-HSQC (transverse relaxation optimized spectroscopy–heteronuclear single quantum coherence) experiment [29] in Figure 4 shows the straightforward correspondence between the conventional graphical representation of a pulse sequence and the equivalent sequence of POMA commands. This [^{15}N, ^{1}H]-TROSY pulse sequence includes two gradients with relative strengths G and $-G\gamma_N/\gamma_H$, respectively, that are chosen such that the magnetization of interest is refocused while other, undesired terms are dephased. The POMA result for the simulation of this pulse sequence is

$$-\tfrac{1}{2}\sin(\omega_2 t_1 + \pi J_{12} t_1)I_{1x} + \tfrac{1}{2}\cos(\omega_2 t_1 + \pi J_{12} t_1)I_{1y} + \sin(\omega_2 t_1 + \pi J_{12} t_1)I_{1x}S_{2z} - \cos(\omega_2 t_1 + \pi J_{12} t_1)I_{1y}S_{2z}$$

when expressed with Cartesian spin operators, and

$$-\frac{i}{4}e^{-i(\omega_2 t_1 + \pi J_{12} t_1)}I_{1+} + \frac{i}{4}e^{i(\omega_2 t_1 + \pi J_{12} t_1)}I_{1-} + \frac{i}{2}e^{-i(\omega_2 t_1 + \pi J_{12} t_1)}I_{1+}S_{2z} - \frac{i}{2}e^{i(\omega_2 t_1 + \pi J_{12} t_1)}I_{1-}S_{2z}$$

when raising/lowering operators are used. ω_1 and ω_2 are the resonance frequency of the spins 1 (I) and 2 (S), respectively.

ACKNOWLEDGMENTS

The author thanks Nikolaus Schaefer, who implemented an initial version of POMA, and Gottfried Otting, Gerhard Wider, and Kurt Wüthrich for helpful discussions.

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