

Simulating Spin Dynamics in NMR with a New Computer Program Intended for Education: *Insensitive*

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ABSTRACT: The NMR experiment is usually described by a choice of three models that operate on different levels of abstraction: the vector model, the product operator formalism and the density matrix approach. The transition between these models poses a didactic challenge for teacher and student alike. A new computer program is presented, which simulates a spin system on the textbook level and compares the three approaches, with the possibility to manipulate the system at every step. It closes a gap between NMR education and professional simulation tools. Some algorithms are explained, which are used in the simulation to extract information from the density matrix. © 2011 Wiley Periodicals, Inc. Concepts Magn Reson Part A 38A: 17–24, 2011.

KEY WORDS: simulation; software; spin dynamics; density matrix; product operators; vector model; magnetic resonance

INTRODUCTION

A new scholar of nuclear magnetic resonance spectroscopy has to familiarize himself with three models to

describe the physics behind the experiment he performs. Aside from the basic energy level diagram, these are the vector model, the product operator formalism (1–3), and the density matrix approach (3, 4) of statistical quantum mechanics. While the latter two models provide a much deeper insight into and a more complete description of the spin dynamics, they operate on a much higher level of abstraction. Especially with the density matrix approach, the visual interpretation of flipping spins is almost completely lost, a fact that poses a significant barrier of understanding for the typical NMR user, who is usually a trained experimental chemist or structural biochemist. From the author's own experiences, the difficulties lie not only in the formal understanding of the particular concepts of each

Received 14 November 2010; revised 13 January 2011; accepted 14 January 2011

Additional Supporting Information may be found in the online version of this article.

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Concepts in Magnetic Resonance Part A, Vol. 38A(2) 17–24 (2011)

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/cmr.a.20203

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model but also mainly the translation between different images of the same physical reality, or “letting loose” of the simpler, more intuitive vector model in favor of product operators and rotation matrices.

This article presents the new, free computer program “*Insensitive*” (*Incredible nuclear spin evolution simulation tool intended for visual education*). The program provides the three aforementioned models side by side and the means to manipulate the possible operations, which can be performed on a spin ensemble (Fig. 1). The approaches can be compared and pulse programs can be performed stepwise, to provide a thorough understanding. This is done on an educational level with a maximum of four distinct spins $\frac{1}{2}$ and two possible spin types (I and S), which simulate the gyromagnetic ratios of protons and carbon-13 nuclei. The program is accompanied by a tutorial that explains the basic concepts and includes a walkthrough of the most important pulse sequences.

Insensitive has been written in C and Objective-C, using the Cocoa frameworks of Mac OS X for the graphical interface. The code is free under the MIT license, and porting of the routines to other platforms is possible. The routines were intentionally written without using high-level languages such as MATLAB or Mathematica, so that no programming skills or third-party software packages are necessary for using *Insensitive*. Other software packages have been published to simulate real life spectrometers (5), and

as libraries of routines (6–9) for high-level languages to simulate larger and more realistic systems.

SIMULATING PRECESSION, COUPLING, AND RELAXATION

The spin system can be set up in *Insensitive* with a dialogue called the *Spin Network Editor*, which provides the possibility to set up the number of spins, spin type, Larmor frequencies, scalar coupling constants, and distances between spins, which are translated to dipolar coupling constants. The Larmor frequencies in *Insensitive* are all given relative to a reference frequency as $\Omega^0 = \omega^0 - \omega^{\text{ref}}$. The program simulates spins in an ideal, isotropic solution and, therefore, shows no splitting due to dipolar coupling. The dipolar-coupling constant is used to calculate the relaxation times if the *Dipolar relaxation* checkbox is checked.

On the level of elemental spin dynamics, the program simulates precession, scalar coupling, and relaxation. Each operation can be performed by itself or combined, in steps of a finite delay time τ , or as a continuous animation. To analyze the results *Insensitive* provides displays for the vector model, the density matrix, and the product operators for the current state.

Relaxation times (T_1 and T_2) are either directly specified by the user or calculated from the spatial separation of the nuclei (r), the gyromagnetic ratios (γ) and Larmor frequencies (ω) of the spins and the correlation time τ_c of the molecule (10–13). The latter method is necessary to simulate the nuclear Overhauser effect.

As with a normal sample, the spin system starts from a state of thermal equilibrium for which the density matrix is known. A *Matrix Composer* dialogue is available to set up a spin state from arbitrary, Cartesian product operators. This can be used to start the simulation from a nonequilibrium state. It also allows the observation of the temporal evolution of single product operators and the comparison of product operators and their matrix representation to learn to read the density matrix.

Radiofrequency pulses can be applied as infinitesimally short, strong pulses on all or a subset of spins. To simulate selective pulses more accurately, the *Pulse Shaper* module allows setting the pulse duration and frequency. Both the pulse shape and its power spectrum are displayed.

Scalar coupling can be applied in the weak or strong coupling limit. As the default, *Strong Coupling* effects are neglected, and the difference in Larmor frequencies between the coupled spins is assumed large compared to the coupling constant. If the strong coupling option is activated in the settings panel, homonuclear spins

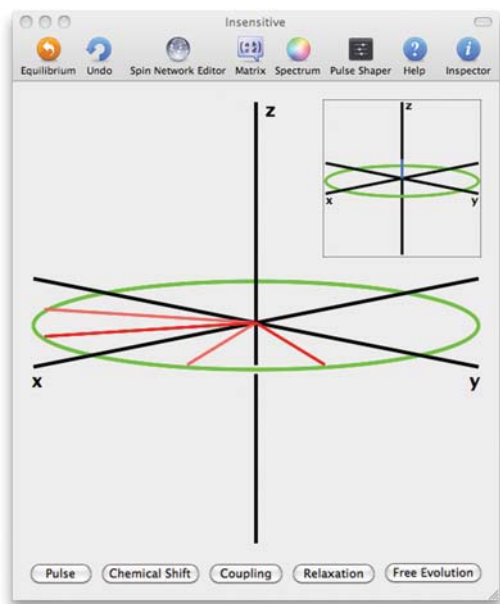


Figure 1 The main windows of *Insensitive* showing the vector model and the controls to manipulate the spin system. Spins of type I are shown in the main window, whereas the inset in the top right corner displays the S-spins.

are considered to be strongly coupled, which leads to the “roofing effect” in the simulated spectrum. Here, the coupling operator $2\pi J\tau \mathbf{I}_1 \cdot \mathbf{I}_2$ causes a flipflop exchange between the populations of the $\alpha\beta$ - and $\beta\alpha$ -state, which is proportional to the dot product of \mathbf{I}_1 and \mathbf{I}_2 . This in turn depends on the spin vectors’ angle after the delay time τ (3). The possibility of applying precession and coupling separately causes an artefact in the case of strong scalar coupling, which can be observed with *Insensitive*: Relative Larmor frequencies $\Omega_{\text{large}} > \tau^{-1}$ cannot be resolved. After the evolution time τ , spins that precess with Ω_{large} appear to be in the same state as spins with a frequency $\Omega_{\text{small}} = \Omega_{\text{large}} - n\tau^{-1}$ that is shifted to smaller frequencies by multiples τ^{-1} . The effect of strong coupling is, therefore, overestimated for large frequencies. During the acquisition of a simulated spectrum, the artefact can be neglected, because τ is chosen sufficiently small.

SIMULATING A SPECTRUM

On a higher level, *Insensitive* is able to generate simulated FIDs and perform the fast Fourier transfor-

mation (FFT) to a one-dimensional spectrum (Fig. 2). For the digital FFT, a range of parameters has to be considered, which have an effect on the spectral range and resolution and can be set in the program’s settings panel. The number of data points N and the sampling interval or dwell time τ_{sample} between data points limit the spectral resolution. Simple FFT algorithms such as Radix-2, which is used in *Insensitive*, require N to be a power of 2. The product $N\tau_{\text{sample}}$ gives the total time for the detection of the FID. This obviously sets the low-frequency limit of the resolution. The highest frequency that can be resolved is defined as $\tau_{\text{sample}}^{-1}$ (14). For an oscillation to be resolved, a minimum of three data points is necessary, with a sampling interval that is smaller than $1/(2\omega^0)$. Increasing the number of data points at a constant sampling interval will increase the spectral resolution (Fig. 3A), while increasing the sampling interval will decrease the spectral width, the interval of frequencies around ω^0 , which will be detected (Fig. 3B). Higher and lower frequencies will fold back into the spectrum and appear at incorrect chemical shifts.

Insensitive also simulates the effect of zero filling, a process in which the same number of zeros as data

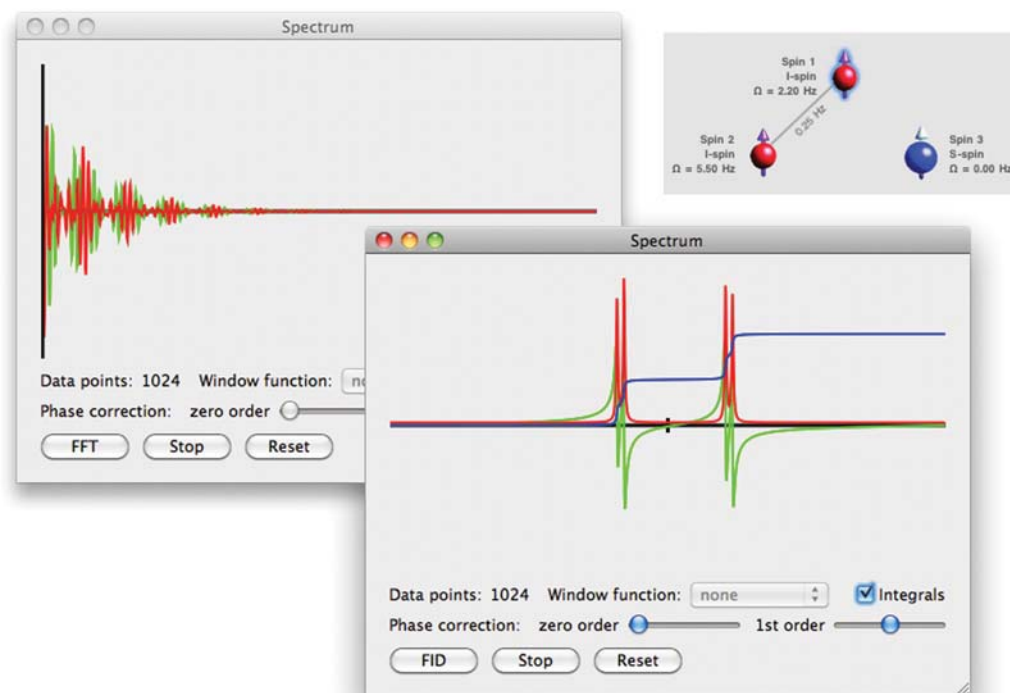


Figure 2 The spectrum window of *Insensitive* showing an FID and the 1D spectrum after Fourier transformation. The controls allow phase correction (zero and first order) and integration. The complete, complex spectrum is shown. Top right is the spin system that corresponds to the spectrum with a two coupled spins of type I (red) and one hetero nucleus of type S (blue), as it is displayed in the *Spin Network Editor*. The selected spin, marked in the editor by a blue glow, is drawn with a lighter color in the vector display (Fig. 1).

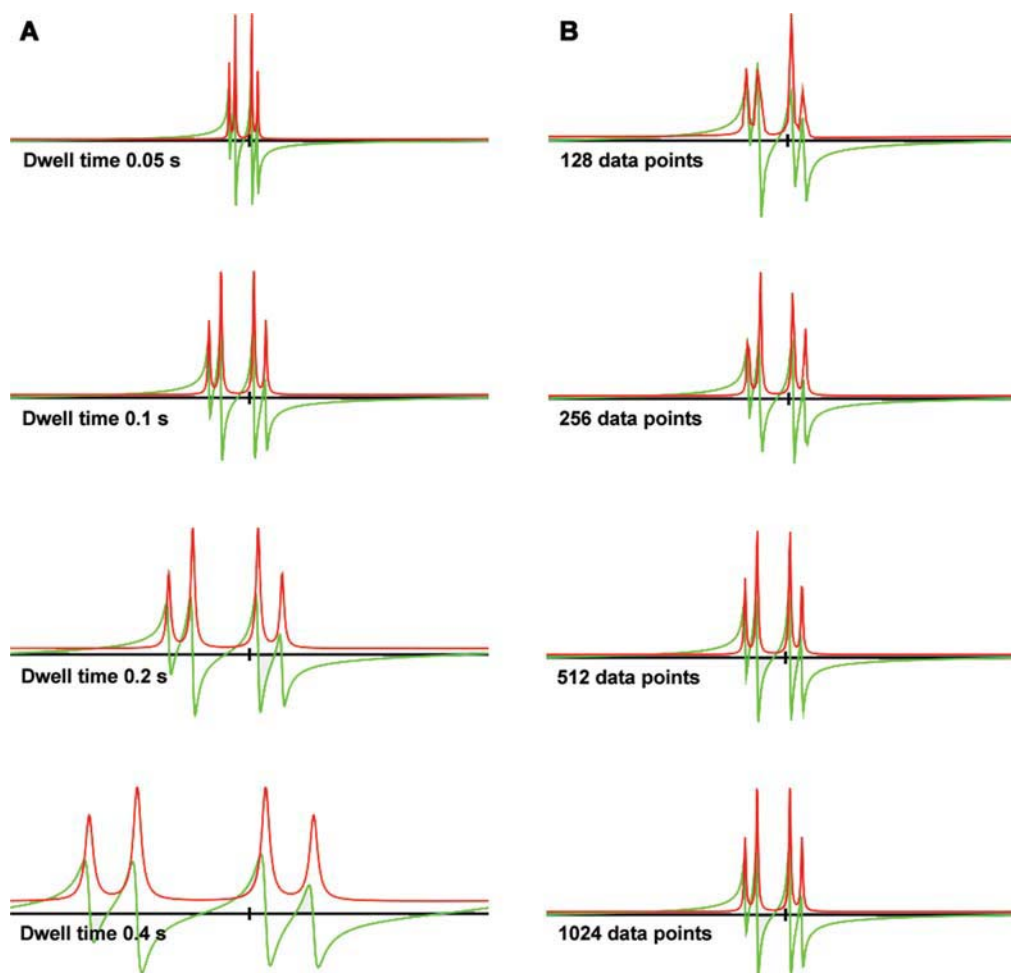


Figure 3 The effect of the number of data points and dwell time on the spectrum: (A) Spectra with 1,024 data points and an increasing dwell time have a decreasing spectral width. (B) Spectra with a constant dwell time of 0.1 s and an increasing number of data points show an increasingly higher resolution.

points in the original FID is appended to increase resolution. The program is able to calculate integrals of spectra and set the level of random noise to assess the effect of the signal-to-noise ratio. Spectra in the time and frequency domain can be manipulated with zero and first-order phase correction in real time.

THE DENSITY MATRIX

It is the conviction of the author that the key to understand the workings of all three aforementioned models for the spin dynamics of NMR lies in the density matrix approach, since the other models can be derived from it (15) but not vice versa. The density matrix is the only information about the spin system's state that is held in the memory in *Insensitive*.

Vectors and product operators are calculated from it when needed, as described in the following two paragraphs. Density matrices are, however, not practical for the day-to-day use due to their abstractness and complexity, which scales exponentially with the number of spins. Comprehensive descriptions are available elsewhere (4, 16–18); only a short treatment will be given here:

The description of the spin system in NMR needs to account for both the temporal evolution and the statistical nature of an ensemble of spin systems with the same behavior but not necessarily the same state at time t . When the spin system's Hamiltonian is represented as a matrix, each matrix element represents one particular aspect of the spin system ψ , either the population of a state (diagonal elements) or a coherence between two states (off-diagonal elements). The

corresponding matrix elements of the density matrix ρ are the statistical weight $P(\psi)$ of each of these aspects. To express the expectation value $\langle\omega\rangle$ for an operator $\hat{\Omega}$ of the spin system, one can take the trace of the matrix product of the density matrix with the operator's matrix representation.

$$\langle\omega\rangle = \text{Tr}(\hat{\rho}\hat{\Omega}) \quad [1]$$

The manipulation of the spin system can be expressed by solving the equation of motion or time-dependent Schrödinger equation for the density operator, called the Liouville-von Neumann equation (15, 18, 19).

The dimension of the density matrix is given by the number of states in the system, which is $(2I + 1)^n$ with the spin quantum number I and the number of spins in the system n . The size of the matrix sets the limits for both readability and computation. More sophisticated algorithms are needed for an efficient treatment of larger systems (6).

CALCULATION OF PRODUCT OPERATORS

The basis for the density matrix in a system on n spins comprises of 4^n orthonormal matrices. The product operators are symbols, which represent these basis matrices independent of their dimension. They can be constructed from single-spin basis matrices by taking the direct matrix product or Kronecker product of one single-spin matrix for every spin in the

system. Because matrix multiplication is not commutative, the matrices in the product have to be ordered by the spins' indices. To account for the correct dimension of the spin system, the identity matrix is used if a spin does not contribute to a specific state (3, 20). Several sets of basis matrices are possible, two useful ones are the cartesian and the spherical tensor basis (4), both of which are available in *Insensitive*. The Cartesian operators have the advantage of an intuitive, geometrical interpretation and translate easily into the vector model.

To calculate the coefficients for all product operators, their matrix representation must be computed with an internal order. By assigning an index k between 0 and 3 to each single-spin basis matrix, each product operator is given an unambiguous index p , which can be expressed as a number in the base-4 system.

$$p = \sum_{i=0}^n k \times 4^i \quad [2]$$

The presence of a specific component in a product operator can be tested with a simple bitwise operation on the operator index in the routine below. First, a base-4 number is computed from the spin number (starting from 0), which masks the given p except for the digit that identifies the requested spin (Fig. 4). The mask is then applied to the index with a bitwise AND operation, and the result shifted so that the result is a number between 0 and 3. This number k translates to one of the four possible basis operators.

```
int component_from_base4_coded_product_operator (int index, int spin)
{
    int mask, component;

    mask = 3 * pow(2, 2 * spin);
    component = index & mask;
    component = component >> (2 * spin);

    return component;
}
```

The algorithm is used in *Insensitive* as well as other simulation software (5) to display the product operators for the current spin state and compose a new density matrix from product operators. The operator's coefficient can be calculated from the density matrix by multiplication with the matrix representation of the product operator and taking the trace as show above.

THE VECTOR DISPLAY

Insensitive displays the vector model in three different ways, which can be chosen in the program's *Settings*

panel. The simplest display mode shows only one total magnetization vector. Its magnitude and phase in the x,y -plane is the data that is recorded as the free induction decay. Single spins of the system can be displayed by plotting the expectation values for their magnetization in all three spatial components. This does not, however, resolve coupling information. Consider the case of one spin, which is coupled to a second spin. Under free precession, it will evolve from $-I_{1y}$ to $2I_{1x}I_{2z}$ to I_{1y} to $-2I_{1x}I_{2z}$ back to $-I_{1y}$. The intermediate antiphase magnetization has no detectable magnetization, because it consists of two components that cancel

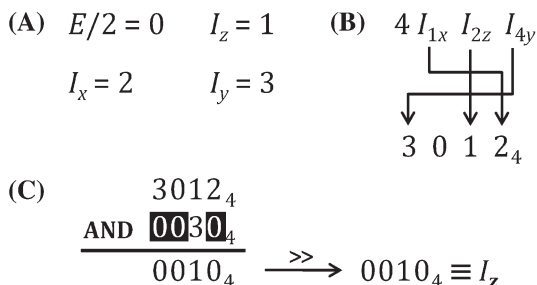


Figure 4 (A) The four basic spin operators for one spin are assigned to numbers between 0 and 3. (B) This way any product operator can be expressed by a base-4 index. If a spin does not contribute to a specific state, the identity operator is used. (C) The contribution of any spin can be extracted from the index by a bitwise AND-operation with a base-4 mask that is 3 at the position of the requested spin and otherwise zero.

each other out. Still antiphase magnetization holds valuable information that is the key to almost every two-dimensional NMR experiment. Instead of computing the additional antiphase operators from the density matrix by calculating more expectation values from the antiphase operators, there is a faster route by looking directly at the density matrix elements.

Each matrix element encodes one aspect of the total magnetization: The real, diagonal elements are the populations of energy eigenstates or elements of the magnetization parallel or antiparallel to the external magnetic field in z -direction. The off-diagonal matrix elements represent coherences between the energy states. Each two elements that are mirrored at the matrix diagonal are complex conjugates of each other, therefore, only half of the off-diagonal elements needs to be considered for a complete picture. The components of the x - and y -magnetization can be translated directly into coordinates if the x,y -plane is pictured as the complex plane. The real part of the coherences is the x -component, and the imaginary part is the y -component of the magnetization perpendicular to the external magnetic field.

Only a few of the off-diagonal matrix elements are directly observable, simple coherences. They are

```
int test_for_simple_coherence(int row, int column)
{
    if(log(row ^ column) / M_LN2 == (float) (int) (log(row ^ column) / M_LN2))
        return (row > column) ? row ^ column : -(row ^ column);
    else
        return 0;
}
```

Seeing the vector model fail, rather than being told that it fails helps appreciating the more abstract

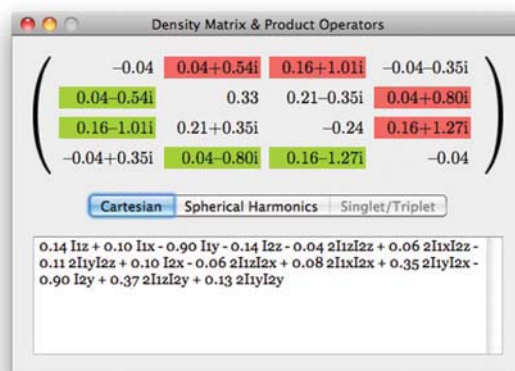


Figure 5 The density matrix for a system of two spins at an arbitrary state as it appears in *Insensitive*. The observable single-quantum coherences are color-coded depending on their sign. In the box below are the corresponding product operators. The operators are ordered by their base-4 index.

those elements, which comprise the product operators with only one component in the x,y -plane. They can be identified by the bitwise, exclusive disjunction XOR between the row and column index of the matrix element, starting from 0.

$$p_{\text{row}} \text{ xor } q_{\text{column}} = 2^{n-i-1} \quad [3]$$

n is the total number of spins and i the index of the spin in question. There are 2^n simple single-quantum coherences for each of the n spins in the system. Each pair of complex conjugate matrix elements represents one vector in the expanded vector model. The routine below tests matrix elements, identified by its row and column indices, for being a simple, single-quantum coherence and returns the number for the identified spin with the sign according to whether it is a positive or negative coherence. The result is 0 if the matrix element is no simple, first-order coherence. The routine is used in *Insensitive* to colour-code the observable matrix elements (Fig. 5).

concepts in NMR. The typical example, which shows the limits of the vector model, is the COSY

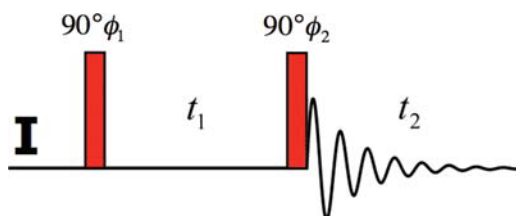


Figure 6 The pulse sequence of the COSY experiment. The second pulse turns the magnetization partly into unobservable double-quantum coherences, which are invisible in the vector model. Pulse sequences such as this can be performed stepwise in *Insensitive*.

experiment with the pulse sequence shown in Fig. 6. The coherence transfer due to the second pulse in the sequence turns antiphase magnetization (Fig. 7A) partially into double-quantum coherences, which remain unobservable (3).

$$2I_{1x}I_{2x} + 2I_{1y}I_{2z} \xrightarrow{\pi/2I_x} -2I_{1x}I_{2y} - 2I_{1z}I_{2y} \quad [4]$$

The term $-2I_{1x}I_{2y}$ cannot be displayed in any of the three possible vector models. This leads to a shorter magnetization vector (Fig. 7B), and in the case of a total conversion to no visible magnetization. Concepts to construct a vector image for higher order coherences have been devised (21) and are very instructional in a static picture. However, their application in a superposition of arbitrary product operators with more than one spin is confusing at best. Higher order coherences are intentionally not displayed in *Insensitive's* vector model to demonstrate its limits in adequately representing these states.

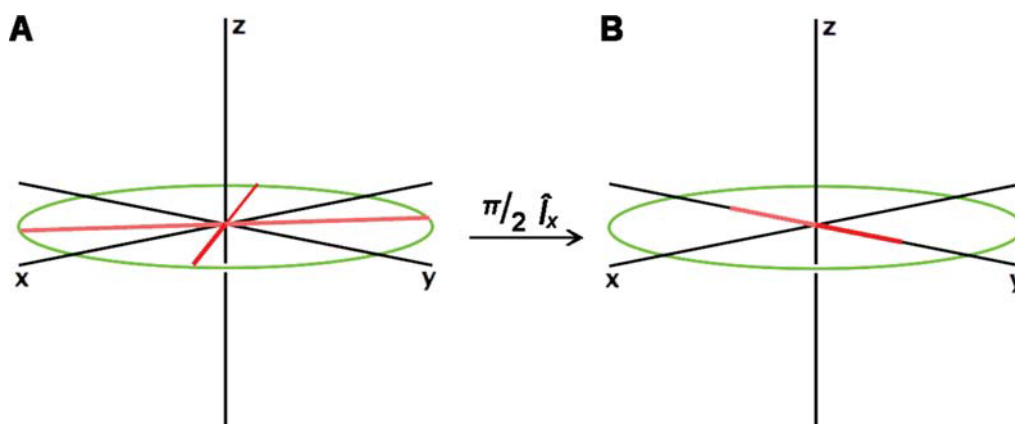


Figure 7 The second 90°_x pulse of the COSY experiment turns the antiphase magnetization in x -direction into unobservable multi-quantum coherences. The vectors in the vector model after the pulse (B) appear shorter than before the pulse (A). Vectors of different spins are indicated by light and dark vectors. The number of vectors after the pulse appears smaller, because the magnetization of both spins is oriented in parallel.

LIMITATIONS

The decision to base *Insensitive* on the density matrix brings a few limitations, which shall be discussed in this section. They are rooted in the description of the spin system on the level of the spin ensemble. The information about individual spins is, therefore, not accessible. If a spin echo sequence is applied to a real spin system, the transverse relaxation caused by inhomogeneities of the external magnetic field becomes refocused and signal strength is regained. In the simulation, this information is unavailable. A spin echo can be simulated with a set of spins with different Larmor frequencies, but *Insensitive* does not differentiate between T_2 and T_2^* relaxation, and magnetization lost to defocusing is not regained. The same reason prohibits the simulation of pulsed field gradients.

The only relaxation processes, which are available in *Insensitive* at the time of writing, are an empirical mechanism in which T_1 and T_2 relaxation is performed with simple, exponential terms, and a simulation of dipolar relaxation (18). Quadrupolar interactions and relaxation due to chemical shift anisotropy have not been taken into account.

Insensitive is available for Mac OS X. Versions for Windows and Linux are in preparation.

CONCLUSIONS

A new computer program, *Insensitive*, has been presented, which simulates the spin dynamics of a system of spins $1/2$ on the textbook level. It closes a gap between the education of NMR on an intermediate level and professional simulation tools, which require

a deeper knowledge of NMR and computer programming. Some algorithms are presented, which are used to extract information from the density matrix of a spin system and compute the data into more accessible pictures of the NMR experiment.

The software and source code are available free of charge at <http://www.chemie.uni-hamburg.de/nmr/insensitive>. A step-by-step introduction to the program is available online as supporting material, which illustrates the simulation of the COSY and INEPT experiments.

ACKNOWLEDGMENTS

The presentation of this work at the Worldwide Magnetic Resonance Conference 2010 in Florence, Italy, was financially supported by the University of Hamburg and the “Freundes- und Förderverein Chemie der Universität Hamburg e. V.” The author is grateful to Erhard Haupt, Thomas Hackl, and Volker Sinnwell for helpful discussions. Please cite this article if you use *Insensitive* or graphics from the program in publications or presentations.

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BIOGRAPHY



Klaus Boldt received his diploma in chemistry from the University of Hamburg in 2007 and is currently working to finish his dissertation on optical spectroscopy of semiconductor nanoparticles under the supervision of Prof. Dr. Horst Weller. His interest in nuclear magnetic resonance stems from his first contacts with chemistry. Being told in the early days of learning “the vector model fails to describe the more complex NMR experiments” without being offered a replacement model has strengthened his conviction that there must be an intuitive way of teaching NMR.