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Fast and accurate algorithm for the simulation of NMR spectra of large spin systems

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ABSTRACT

The computational cost for the simulation of NMR spectra grows exponentially with the number of nuclei. Today, the memory available to store the Hamiltonian limits the size of the system that can be studied. Modern computers enable to tackle systems containing up to 13 spins [1], which obviously does not allow to study most molecules of interest in research. This issue can be addressed by identifying groups of spins or fragments that are not or only weakly interacting together, i.e., that only share weakly coupled spin pairs. Such a fragmentation is only permitted in the weak coupling regime, i.e., when the coupling interaction is weak compared to the difference in chemical shift of the coupled spins. Here, we propose a procedure that removes weak coupling interactions in order to split the spin system efficiently and to correct *a posteriori* for the effect of the neglected couplings. This approach yields accurate spectra when the adequate interactions are removed, i.e., between spins only involved in weak coupling interactions, but fails otherwise. As a result, the computational time for the simulation of 1D spectra grows linearly with the size of the spin system.

1. Introduction

Nuclear Magnetic Resonance (NMR) is an exquisite tool for the study of molecular structures and therefore its use is in constant increase. However, the analysis of the spectra of large molecules is often a tedious and time consuming task, since each signal of the spectra has to be assigned to a nucleus of the molecule. Thus, procedures are sought to assist spectroscopists with this task. Several approaches have been proposed recently [2,3], but the efforts to reach this dream begun long ago and are best summarized in the recent work of Elyashberg et al. [4]. The simplest approach consists in simulating the spectra of a guess structure from its predicted chemical shifts and scalar coupling constants. The assignment of the resulting spectra can be used as a starting point to assign the experimental one. This approach relies on the accuracy of the prediction of the NMR parameters and on the accuracy of the simulation of the spectrum. Several algorithms available for the prediction of chemical shifts and scalar coupling constants are fast and reliable [5–13]. Unfortunately, the simulation of the spectrum using spin dynamics scales exponentially with the number of atoms, and thereby making the available algorithms unsuitable for large systems [14–24].

Recently, algorithms have been proposed to reduce the computational cost of quantum spin dynamic simulations [1,25,26]. The authors recognized that only a small fraction of the available spin states are populated and therefore proposed to neglect the less populated high order states, thereby reducing the size of the problem. Ignoring high order spin states, typically higher than four, allows to approximate the complete Hamiltonian by computing and summing a large number of smaller Hamiltonians [26]. The number of such cluster Hamiltonians that have to be computed represents a potential bottleneck, since it grows exponentially with respect to the size of the spin system. Additionally, they proposed to find the adequate Krylov subspaces, i.e., the minimal basis that spans the trajectories of the spin system and to perform a zero track elimination to further compress the resulting Hamiltonian [1]. This can be seen as finding the principal states of the spin system in analogy to principal component analysis. The combination of these three methods is attractive, since the exact Hamiltonian is never computed and the approximated Hamiltonian is very compact. This approach enables to evaluate the evolution of the large spin systems, since the CPU time grows almost linearly with the number of nuclei. The main drawback is that restricting the state order to four, as proposed by the authors, prevents the faithful simulation of the spectra of molecules containing more than four coupled nuclei.

To improve the accuracy of the simulated spectra we propose to split the spin system according to its nature, i.e., to split the system in a manner that less affects the accuracy of the resulting spectrum. Intuitively, many structures can safely be regarded as containing independent sub-systems that can be solved separately.

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In this paper we show that if couplings are removed adequately to fragment the spin system efficient calculations can be performed without affecting the quality of the results. Furthermore, if chosen correctly, the effects of these neglected couplings can be accounted for *a posteriori*. We present an algorithm that performs this clustering task efficiently, simulates the spectrum of each fragment, corrects these spectra to account for the removed couplings and reconstructs the complete spectrum. We demonstrate with some examples the quality of the results. Later, we discuss the robustness of the clustering procedure and its limitations. Finally we show how the calculation time scales with respect to the size of the spin system.

2. Results and discussion

2.1. Clustering procedure

Our algorithm performs the simulation of NMR spectra in the four steps described in Fig. 1. First it checks for independent fragments. This step is important although usually not implemented in simulation packages, since it allows a large reduction of the problem size without making any approximation. This reduction should be performed always, except when dipolar relaxation mechanisms are taken into account, thereby connecting spins otherwise coupled. Then, it drops weak couplings in order to further fragment the spin system into independent clusters until reaching a desired dimension. Second, it propagates, in the Hilbert space, a trajectory for each fragment. Third, it applies a correction to the trajectories of the spin pairs involved in the scalar couplings that were disregarded in the first step. Several approaches can be used to perform this correction that will be discussed later. Finally, it reconstructs the trajectory of the whole system by adding all the contributions. A more detailed description for each step follows:

Clustering (step 1). The property of a system made of several non-interacting sub-systems is the sum of the properties of each of them. The task thus narrows to find independent clusters of coupled spins prior to the creation of the Hamiltonian. Using the predicted NMR parameters, the chemical shifts and coupling constants, for a molecule, a correlation matrix C can be built whose matrix elements C_{ij} represent the magnitude of the couplings between each nucleus. Dividing its element C_{ij} by the difference in chemical shift $\Delta\Omega_{ij}$ between the ith and jth nuclei provides a symmetric matrix β, whose elements $\beta_{ij} = -J_{ij}/\Delta\Omega_{ij}$ indicates the regime of the coupling. Values of β_{ij} lower than 0.01 signify weak couplings, while values greater than 0.1 represent strong couplings. Clustering consists in finding independent clusters and in iteratively removing elements of β, starting with the smallest ones, until the resulting matrix may be written in block diagonal form. This procedure stops when the largest block is smaller or equal to a threshold value defined by the user. This approach provides an acceptable clustering without needing to exhaustively compute all the solutions, but might fail if strong interactions are removed or if one partner spin is itself involved in another strong interaction. Additional tests are thus required to ensure that, ideally, couplings are removed only between spins that are not involved in any strong coupling interactions. This issue will be illustrated and discussed later in more details.

As an example of the reduction that can be achieved, more than 67 millions ($2^{13} \times 2^{13}$) matrix elements are necessary to fully describe the Hamiltonian of a 13 spins system ($N = 13$). If this spin system can be regarded as two independent fragments of 2 and 11 spins, only a little more than 1 million matrix elements are necessary to describe the Hamiltonians of each fragment ($2^2 \times 2^2 + 2^{11} \times 2^{11}$) and thereby 93.7% of the spin states are dropped. If the same spin system ($N = 13$) is regarded now as two fragments of 6 and 7 spins each, 99.97% of the spin states are dropped. In other words, in the latter case, a good approximation of the Hamiltonian of the whole system (13 spins) can be achieved with as few as 20,480 matrix elements, instead of the initial 67 millions.

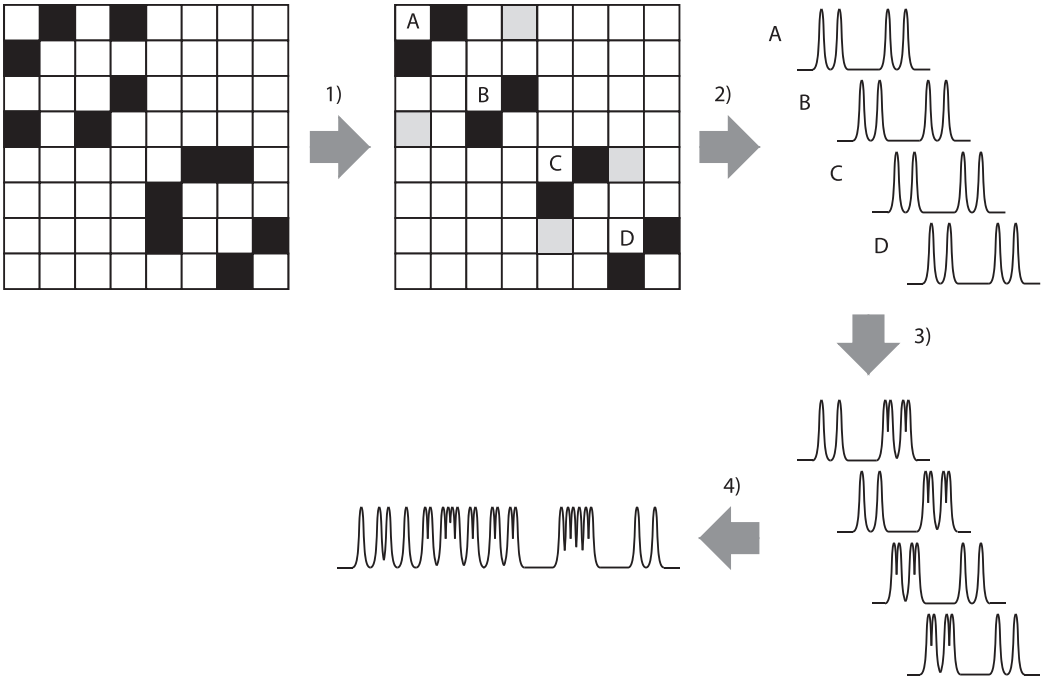


Fig. 1. Schematic description of the proposed procedure for simulating NMR spectra: (1) removes couplings to obtain fragments of no more than 2 spins, in this example, (2) simulates the trajectories for each cluster, (3) applies a correction to reintroduce the effect of the dropped couplings and (4) superimposes the trajectories to obtain the full approximated spectrum. For the sake of simplicity, trajectories are displayed in the frequency domain.

Propagation (step 2). After the spin system has been reduced into sub-systems of acceptable size, individual Hamiltonians and density matrices are created in the Hilbert space for each of them. The evolution is evaluated for each cluster using the equation of motion [27]. Working in the Hilbert space yields more compact Hamiltonians, in a factor of 4^N, than the ones in the Liouville space used by Kuprov and coworkers. In the Liouville space the operators are written in a manner that is more convenient to simulate relaxation phenomena. However, this work only focuses on simulating spectra to extract information about chemical shifts and scalar couplings constants. Since the relaxation parameters cannot be easily obtained from such spectra, the relaxation parameters only represent additional unknowns in our simulation and therefore the Hilbert space is preferred.

Accounting for the effect of neglected couplings (step 3 and 4). At this point, the detectable signals, i.e., the expectation value of the transverse component I^- for each spin, are known and yield an oscillating function of time $s_i(t)$. However, the signals $s_i(t)$ and $s_j(t)$ for the spin pair for which the coupling constant J_{ij} has been dropped during clustering will not faithfully reproduce the experimental signals. This can be corrected simply by multiplying the oscillating trajectories of these spins by $\cos(\pi J_{ij} t)$.

This simple procedure provides faithful results only if the removed couplings are indeed weak and if both partners aren't involved in another strong coupling interaction. Only in this case, the spectrum of this spin pair is of first order and the two signals can be considered as a superimposition of doublet. Such signals are always symmetric and can easily be simulated, assuming a linear response regime [27], using products of cosine functions. Multiplying the trajectory $s_i(t)$ of a single spin (a singlet) by $\cos(\pi J t)$ will produce a doublet with a separation equal to the coupling constant J. Thus, the accuracy of the resulting spectrum relies on our ability to fragment the spin system by only removing adequate couplings. Once this correction has been performed, the sum of the individual trajectories reproduces a simulated FID that can be Fourier transformed to obtain a spectrum.

Another approach consists in simulating a new trajectory for the spin pair with its closest neighbors. This approach was evaluated and abandoned, since it yields similar results compared to the simpler approach.

2.2. Examples

The spectrum of the 4-methyl-2-pentanol (Fig. 2a) was chosen to illustrate the procedure explained before. Ignoring the alcoholic proton, this molecule contains 13 protons and represents the maximum size for which we are able to simulate the exact solution for the sake of comparison. The chemical shifts and the scalar coupling constants were obtained directly from the experimental spectra; this to avoid errors arising from the prediction procedure.

Fig. 2 shows spectra simulated using the exact (Fig. 2b) and an approximated Hamiltonian (Fig. 2c). As expected, the simulation using the exact Hamiltonian reproduced with great accuracy the experimental spectrum, but required more than two minutes using the package spinevolution [14]. In contrast, clustering allowed performing the simulation (Fig. 2c) in 636 ms, more than 2 orders of magnitude faster than the exact solution. Comparison with the

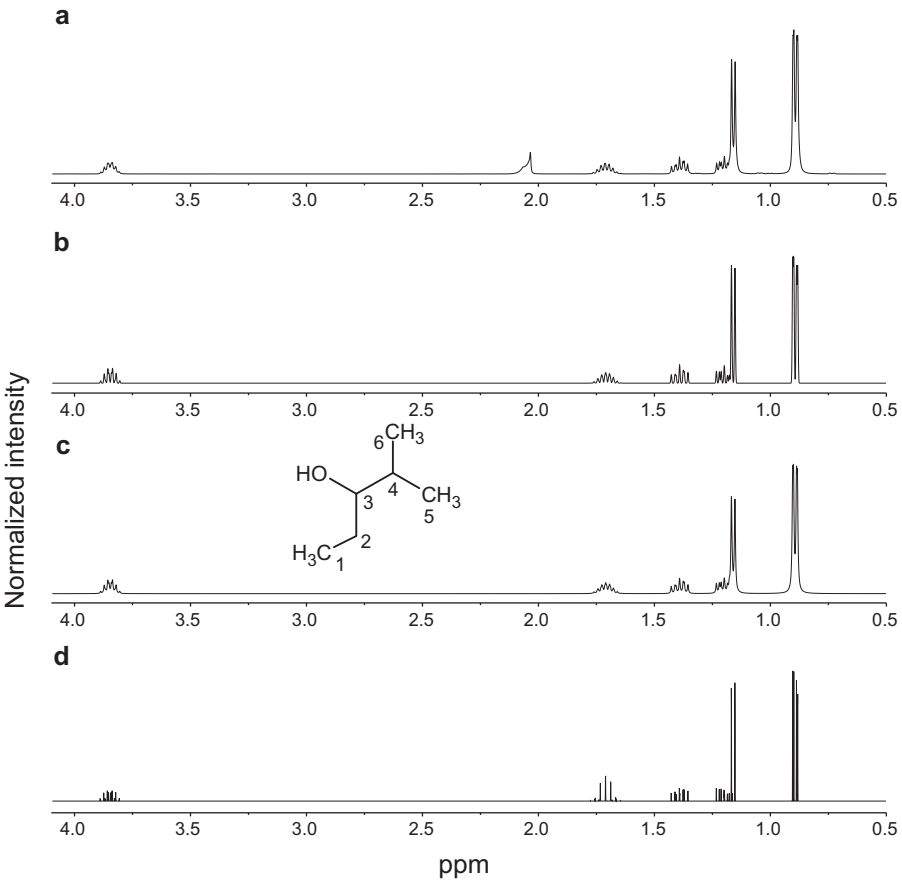


Fig. 2. Spectra of 4-methyl-2-pentanol: (a) experimental spectrum, (b) spectrum simulated with the exact Hamiltonian in 2 min using spinevolution [14], (c) with an approximated Hamiltonian in 636 ms using clusters of 5 spins and (d) using Spinach [33] (during the revision of this work, Kuprov and coworkers published a new algorithm [33], that is more accurate than the former version [1]).

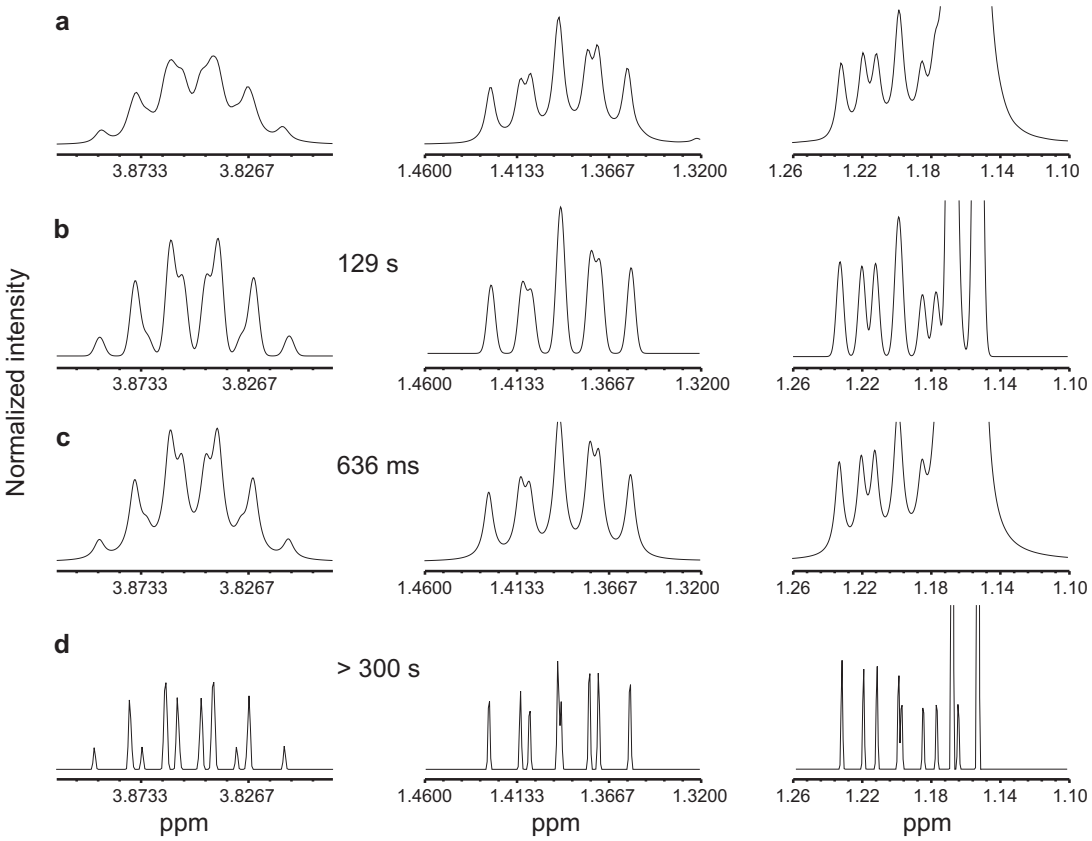
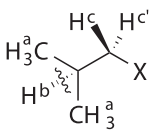


Fig. 3. Regions of the spectra shown in Fig. 2: (a) experimental spectrum, (b) spectrum simulated (2 min) using the exact Hamiltonian, (c) in 636 ms using an approximated Hamiltonian of maximum allowed cluster size of 5 and (d) spectrum obtained in several minutes as described elsewhere [33] (during the revision of this work, Kuprov and coworkers published a new algorithm [33], that is more accurate than the former version [1]). The line-width of the simulated spectra was intentionally kept inferior to the experimental one to better delineate the feature of the multiplets.

experimental spectrum agreed well, although the multiplet at 3.85 ppm was found completely symmetric (Fig. 3c), meaning that our approximated Hamiltonian did not properly reproduce second order effects. This should not be a surprise, since the coupling between the protons bound to carbons 1 and 2 are the first being dropped by our algorithm.

For the sake of comparison, a spectrum was simulated using the algorithm proposed by Kuprov [1] that restricts the highest state order to four. The resulting spectrum, shown in Fig. 2d, was computed in more than 300 s. Some care has to be taken when comparing those computational times; the script developed by Kuprov was written for matlab [28], whereas the scripts proposed in this paper were written either in java (for the online applications) or for Scilab [29]. Although a systematic comparison of the performances of both procedures is beyond the scope of this work, our algorithm clearly outperforms Kuprov's algorithm both in speed and accuracy. At this point, important differences between both approaches must be highlighted. Kuprov's approach is fully general and can be used to simulate virtually any pulse sequence or experiment, whereas our only allows to simulate the dynamic of the spins in the absence of rf fields, i.e., our algorithm cannot be used to simulate TOCSY spectra. This is because the approximation done with respect to the regime of the coupling doesn't hold under the perturbation of an rf field. In turn our procedure represents an important alternative for applications where a high accuracy is required, in particular for automatic retrieval of NMR parameters from experimental spectra and further work will be done in that direction.

δ_a	β_{ab}	β_{bc}	$\beta_{bc'}$
1.5	0.01	0.2	0.3
2.5	0.02	0.2	0.3
3.0	0.04	0.2	0.3
3.3	0.1	0.2	0.3



$^2J_{aa}$ = 16 Hz (intra)
$^3J_{ab}$ = 8 Hz (inter)
$^3J_{bc}$ = 4 Hz (intra)
$^3J_{bc'}$ = 6 Hz (intra)
$^2J_{cc'}$ = 16 Hz (inter)

Fig. 4. Spin system used to determine the limit of the clustering approximation. The chemical shift of the protons **a** were shifted from 1.5 to 3.3 ppm in order to increase the beta values β_{inter} from 0.01 to 0.1. The other parameters were kept constant, the coupling constants not mentioned in the figure were all assumed to be zero and the Larmor frequency was set to 400 MHz.

2.3. Accuracy of the approximation

The accuracy of the simulation depends on the network environment at the spin pair where the system is being cut, i.e., the number and the regime of the scalar interactions existing between the pair of spins and external spins and the regime of the coupling within the pair. The former are referred to as coupling intra cluster (J_{intra}), while the latter are referred to as coupling inter cluster (J_{inter}). To estimate the sensitivity of our approach with respect to β_{intra} and β_{inter} four spin systems were constructed as described in Fig. 4. The chemical shifts of the protons attached to the carbon **a** were shifted from 1.0 to 3.3 ppm, which corresponds to sweeping the beta (β_{inter}) values of the coupling constants $^3J_{ab}$ from 0.01 to 0.1, assuming a Larmor frequency of 400 MHz.

Fig. 5 shows the resulting spectra for proton **b** when 3 (solid black line) and 6 (gray solid line) couplings J_{ab} between protons **a** and **b** were removed during clustering. As expected, the procedure failed to faithfully reproduce the exact solution (dashed line) when the coupling constants associated with the larger values of beta

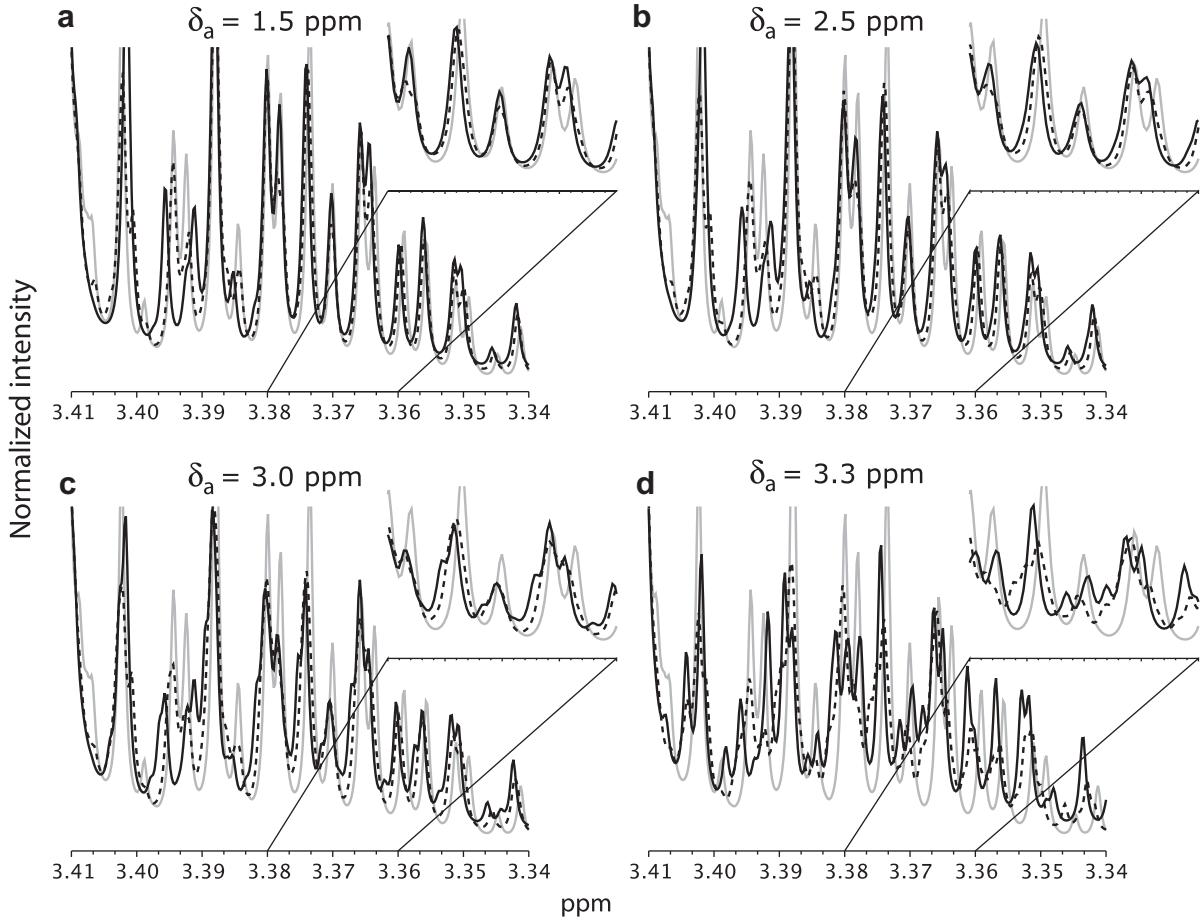


Fig. 5. Region of the simulated spectra for the system described in Fig. 4 corresponding to proton **b**. The dashed lines represent the exact solutions, while the solid black and gray lines represent the approximated spectra after the spin systems have been fragmented into clusters of maximum 6 and 3 spins (3 and 6 J_{ab} coupling removed), respectively. The chemical shifts of the protons **a** were shifted from 1.5 to 3.3 ppm in order to simulate for couplings J_{ab} with beta β_{inter} values of (a) 0.01, (b) 0.02, (c) 0.04 and (d) 0.1. The Larmor frequency was set to 400 MHz.

were dropped, since the correction to the trajectories only accounts for weak coupling effects. Surprisingly, many features of the multiplet of proton **b** are still delineated when 3 couplings with beta values of 0.1 are removed during clustering (Fig. 5d). However, when this threshold is increased J_{ab} is not anymore a good candidate for clustering and the accuracy of the simulation drops rapidly, because **b** is involved in several strong couplings. Clearly, the chemical shifts and the coupling constants for the protons b, c and c' were chosen to show the limits of the approximation, i.e., what happens if a coupling is removed inadequately.

We then investigated in more detailed the values of beta (inter and intra) that yields faithful simulations for this simple example. 100 simulations (Fig. 6a) were performed by sweeping simultaneously the chemical shifts of protons **a** from 1.5 to 3.3 ppm and the chemical shifts of protons **c** and **c**′ from 4.5 to 3.6 ppm. Thus, β_{ab}, β_{bc} and $\beta_{bc'}$ were swept from 0.01 to 0.1. A careful peak-picking of each spectrum allowed to report the positions of each line corresponding to the signal of proton b as a function of beta values. The same exercise was repeated (Fig. 6b) by sweeping only proton **a** from 1.5 to 3.3, leaving protons **c** and **c**′ at 4.5 ppm. The resulting trajectories (Fig. 6a) clearly show that accurate simulations can be performed provided that interactions are not removed between spins involved in couplings with beta larger than 0.07. The superimposed vertical lines indicate that similar results are obtained using either the full Hamiltonian or the approximated ones and that removing interactions with values of beta ($\beta_{inter} = \beta_{intra}$) smaller than 0.7 has almost no effect on the predicted multiplet. In addition, the errors in the predicted intensities are negligible in this area, since transfers of magnetization are only possible in presence of strong interactions. This example demonstrates that under certain circumstances methyl groups can indeed be simulated independently without affecting the accuracy of the final spectrum. Although this value should be extrapolated with great care to other systems, it still provides a reference and will be used in the remaining of the paper as an indication.

2.4. Range of application

Cholesterol was chosen to demonstrate the potential of our approach to reduce the dimension of the problem. This molecule contains a large cluster of coupled protons (46) and nearly all of them are aliphatic. We can therefore expect that this is the worst-case scenario for the simulation of NMR spectra. Based on the experimental results [30] we show in Fig. 7 that clusters of maximum 11 spins can be obtained by removing 15 couplings with values of β_{inter} inferior or equal to 0.05 and β_{intra} inferior or equal to 0.1 (at 400 MHz). These conditions are comparable to that illustrate by the horizontal line in Fig. 6b, and thereby a spectrum of high accuracy can reasonably be expected.

In order to evaluate the applicability of the clustering procedure in a more systematic manner, the algorithm was tested with a set of 42,632 molecules [31] using several threshold values for β_{inter} and β_{intra}. The analysis was performed in two dimensions: increasing those threshold values and varying the maximum cluster size

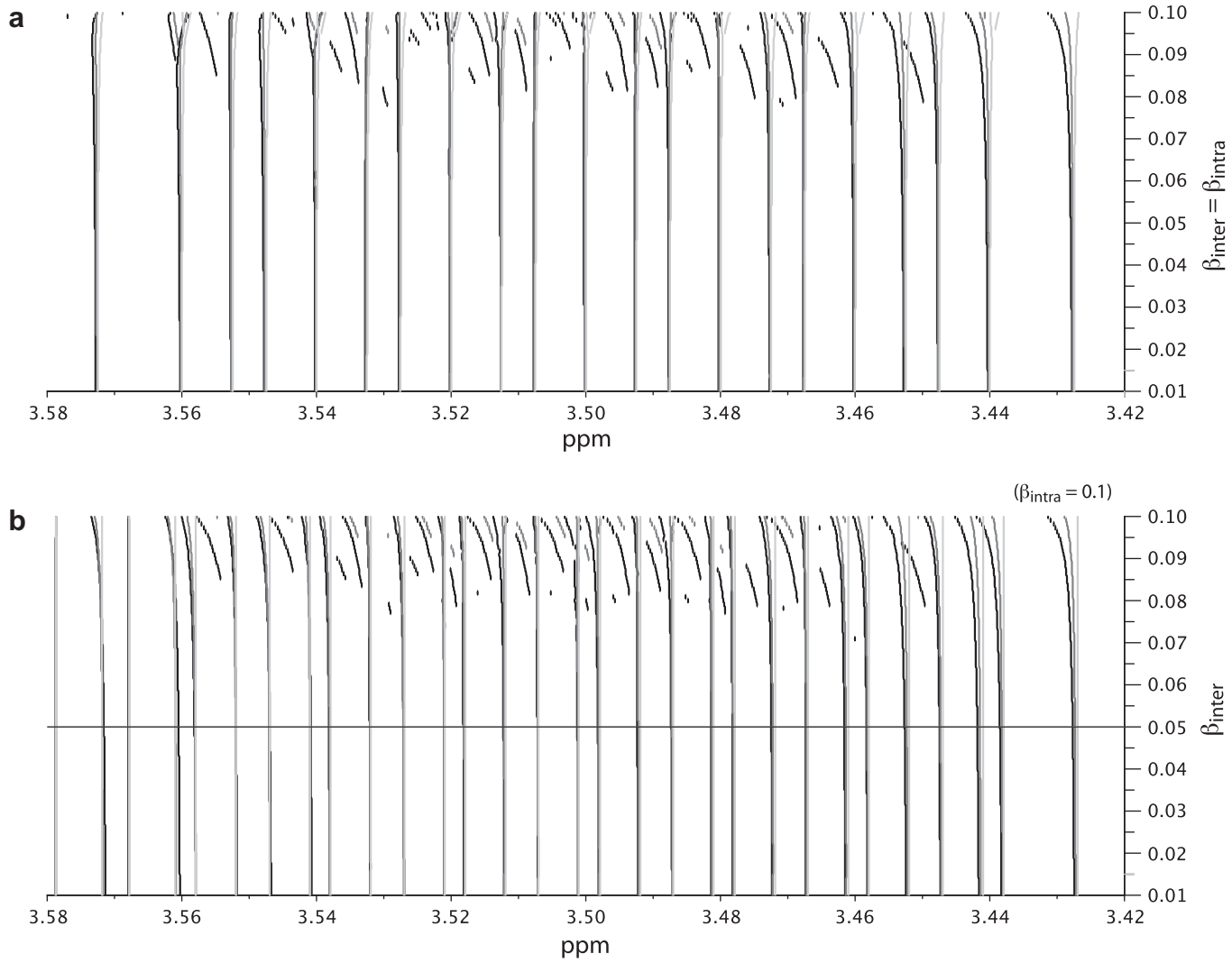


Fig. 6. (a) 100 simulations of the spin system of Fig. 4 were performed sweeping the chemical shifts of protons **a** from 1.5 to 3.3 ppm and the chemical shifts of protons **c** and **c′** from 4.5 to 3.6 ppm. The lines represent the trajectories of the transitions corresponding to proton **b** when the values of beta are sweeped. The black lines represent the trajectories obtained using the exact solution, while the lines in light and dark gray represent the ones obtained with a maximum cluster size of 3 and 6, respectively. (b) These simulations were repeated, but the chemical shifts of proton **c** and **c′** were set to 3.6 and 3.65 ppm, respectively, that correspond to a $\beta_{intra} = 0.1$ for the J_{bc} and $J_{bc'}$ couplings.

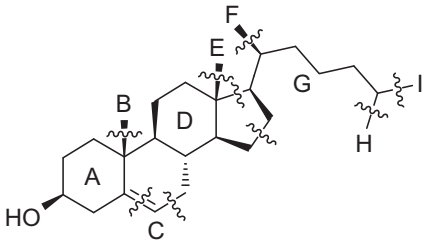


Fig. 7. Cholesterol ($C_{27}H_{46}O$). Clusters obtained after removing 15 couplings with values of β_{inter} inferior or equal to 0.05 and β_{intra} inferior or equal to 0.1. Clusters A, B, C, D, E, F, G, H and I contain 8, 3, 1, 11, 3, 3, 11, 3 and 3 protons.

allowed. For simplicity the thresholds were chosen equal for β_{inter} and β_{intra}. This allowed to determine the number of molecules for which the spectrum could be simulated within a certain degree of accuracy. Only the molecules larger than the maximum cluster size were considered for analysis. These numbers were plotted against the maximum cluster size and are shown in Fig. 8 (top) while the size distribution of the database is shown in Fig. 8 (bottom).

Interestingly, 74% of the molecules containing nine protons of more ($N \geqslant 9$), i.e., 74% of 24,541 molecules, could be split into fragments of no more than eight ($N - 1$) spins without removing any couplings. This proportion increases to 87% for $N \geqslant 13$ (87% of 12,804 molecules contains 13 or more protons). When couplings with $\beta < 0.02$ are dropped, 90.7% and 84% of the molecules (larger than 13 and 9, respectively) could be reduced into smaller clusters. Since fragments of nine spins represent the upper limit acceptable for online applications, for which the available memory is limited, our procedure can simulate spectra for 91.7% of the molecule presented here with a high accuracy ($\beta_{inter} = \beta_{intra} < 0.06$).

2.5. Linearity

Once the maximum cluster size has been defined, the computational time required by our algorithm becomes linear with respect to the number of nuclei. This enables the simulation of spectra for molecules that contain hundreds of spins within minutes. This linear behavior is illustrated in Fig. 8 for random spin systems. Nine

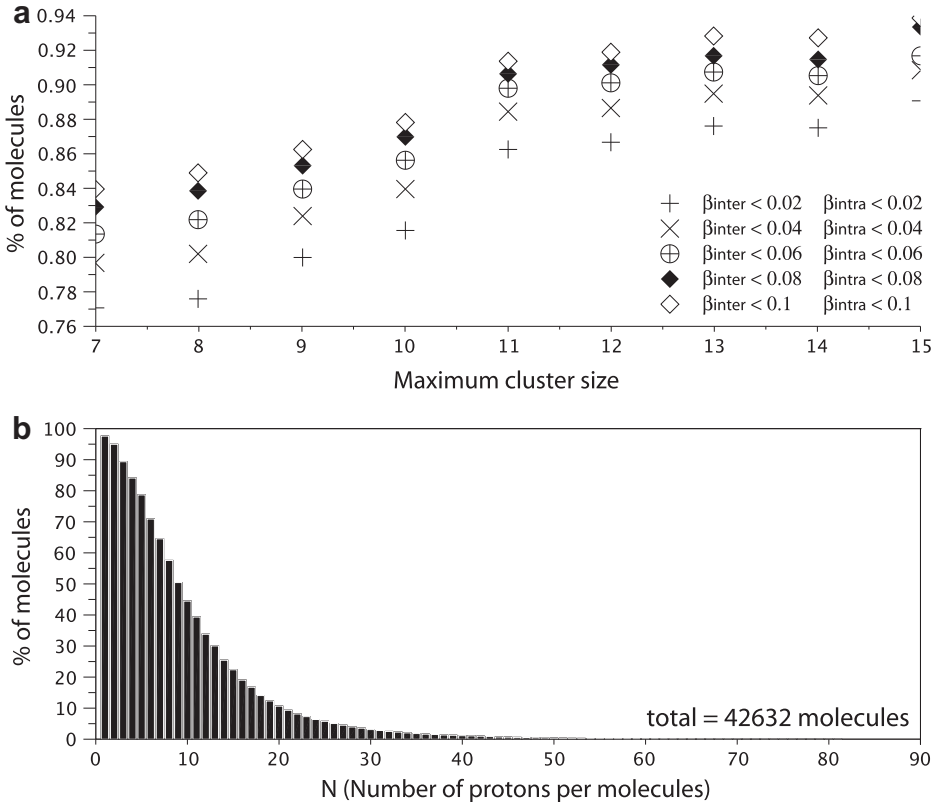


Fig. 8. Top: Number of molecules that can be successfully fragmented vs. the maximum cluster size allowed. The analysis was repeated allowing to remove couplings with values of $\beta_{inter} = \beta_{intra}$ ranging from 0.01 (weak coupling) to 0.1 (strong coupling). Only the molecules larger than the maximum cluster size were considered. Bottom: Number of molecules with N protons. A total of 42,632 molecules were considered.

spin systems of N nuclei were randomly generated, where N ranged from 12 to 126. Thus, 1026 systems were prepared. For each of them, a spectrum was simulated while increasing the maximum cluster size from four to nine. The computational times required for the simulation of the nine spectra corresponding to systems of identical size were averaged and are shown in Fig. 9. Despite the oscillations observed for large spin systems and large cluster size, the computational time was found to increase rather linearly with the number of spins. As shown earlier, the degree of reduction of the Hamiltonian, and thereby of the problem size, depends on the size of the fragments. This explains the oscillations observed in Fig. 9.

As a conclusion, the algorithm presented here provides a very fast and accurate tool for the simulation of 1D NMR spectra of large spin systems. The accuracy of the simulated spectra depends on the interactions that are removed; only spins involved in weak interactions may be considered independent. Accurate spectra were obtained for methylpentanol in less than a second. This represents a considerable acceleration, two orders of magnitudes, with respect to the exact solution. Our algorithm works in the

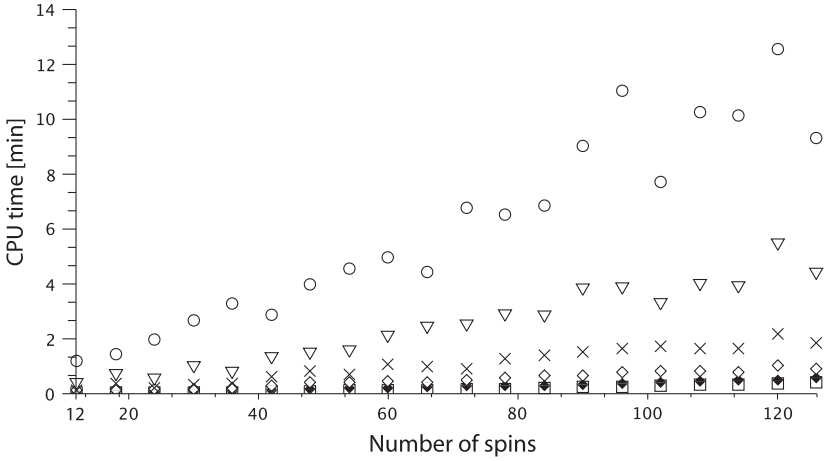


Fig. 9. CPU time required to simulate spectra. Each point represents the average time necessary to simulate the spectra of nine randomly generated fully coupled spin systems. Open circles, open triangle, crosses, open diamonds, black diamonds and open squares represent the time required by the simulation when the maximum cluster size was decreased from nine to four.

Hilbert space that is more compact than the Liouville space and relaxation, if needed, is simply handled by attenuating the individual spin trajectories differentially, i.e., in a phenomenological manner. In addition, this algorithm can only be used for the generation of 1D spectra. The computational time was shown to grow linearly with respect to the size of the spin system, once the maximum size of the cluster has been defined. Since the problem is divided into several sub-systems that can be solved separately, this approach is a good candidate for parallel computing. Finally, a java implementation of this algorithm is available (http://www.nmrdb.org/simulator) as part of the online NMR processing and assignment tool NMRdb.org [32].

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