EFFICIENT PEAK EXTRACTION OF PROTON NMR SPECTROSCOPY USING LINESHAPE ADAPTATION

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ABSTRACT

Nuclear magnetic resonance (NMR) spectroscopy signals are ideally modelled as a superimposition of damped exponentials in additive Gaussian noise. In order to extract the information from these signals, methods are needed to decompose the signal into its components and estimate their parameters. This task can become quite difficult due to factors such as large number of samples, unknown and possibly large number of components, and lineshape distortion. In this paper, we propose a computationally efficient method for peak extraction in proton NMR spectroscopy without any a priori information. This method combines a simple damped complex exponential parameter estimation strategy with lineshape adaptation in the frequency domain. We apply the proposed technique on real NMR data and show that it outperforms competing state of the art methods. It is shown that the new method is capable of extracting very small lines such as satellites.

Index Terms— Parameter estimation, least square filtering, peak extraction, lineshape adaptation, nuclear magnetic resonance spectroscopy.

1. INTRODUCTION

Nuclear magnetic resonance (NMR) spectroscopy [1] [2] is a principal technique for the study of molecular structures in chemical compounds. The time domain signal generated by the NMR spectroscopy instrument, commonly known as the free induction decay (FID), is ideally modelled as a sum of complex damped exponentials in noise:

$$x(n) = \sum_{p=1}^{P} A_p e^{j\phi_p} e^{(-\eta_p + j2\pi f_p)n} + o(n), \quad n = 0 \dots N-1, \quad (1)$$

where the noise terms $o(n)$ are assumed to be additive Gaussian noise with zero mean and variance σ^2. The magnitude spectrum of the signal shows a combination of peaks that may overlap with each other. The key parameters including the frequency f_p, damping factor η_p, phase ϕ_p and amplitude A_p of each individual signal component convey important information on the underlying chemical compounds. Therefore, our goal is to extract all P signal components in the spectrum and estimate their parameters. In practice, however, the number of signals P is usually unknown and the signal length N is quite large ($N \geq 2^{14}$). Also, magnetic field inhomogeneities and variations in the chemical environment that the molecules are exposed to lead to lineshape distortion, meaning that the components in the acquired signals are not ideal decaying exponentials, [3]. These problems make the extraction task much more complicated.

Parametric estimators for multiple damped exponentials, such as HSVD [4], HTLS [5] and matrix pencil [6] can be used on NMR signals to achieve extraction and accurate quantitation, but their drawbacks include that they rely on the lineshape being undistorted. They also require the number of signals P to be known a-priori. Furthermore, they are computationally expensive for large N as they use singular value decomposition (SVD). Improvements on these methods have been proposed to alleviate some of these problems. The frequency selective methods for example, [7], reduces the computational cost by limiting the region of interest in the spectrum, while the ITMPM [8] method determines the number of components using information theoretic criteria such as the minimum description length (MDL). Nonetheless, these techniques are only reliable if the data is composed of ideal damped exponential signals without lineshape distortion. The recently developed time-domain iterative fitting method AQSES, [9], minimises the sum of the squares of the difference between the acquired signal and a linear combination of templates. Although this method overcomes the lineshape distortion, the templates need to be pre-generated as a-priori information. Additionally, like other iterative model function fitting methods [3], it is impractical for long FIDs due to its computational load.

In summary, previous techniques suffer from one or more of the following limitations: heavy computational load, required a-priori knowledge of P, and inability to handle lineshape distortion. To overcome these limitations, we propose an efficient technique to automatically extract the signal components in proton (^{1}H) NMR data. The method requires no a-priori knowledge on the number of components and is robust

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to lineshape distortion. Although we focus here on proton data, the method is easily adaptable to other types of NMR data [1].

The structure of the paper is organised as follows. Section 2 describes the new method while section 3 presents experimental results. Finally, conclusions are drawn in section 4.

2. THE PROPOSED METHOD

The proposed method extracts the spectral peaks iteratively by estimating the paramters of the largest peak and removing it from the signal. For each peak, the algorithm determines the lineshape distortion before removing it and iterating.

Let $\hat{\lambda}$ denotes the estimated value of parameter λ. Also let $\mathbf{x}$ be the FID signal and $\tilde{\mathbf{x}} = FFT(\mathbf{x})$. LOOP:

1. Find the maximum bin of $|\tilde{\mathbf{x}}|^2$: $\hat{k} = \arg\max_k |\tilde{\mathbf{x}}|^2$ and estimate $\hat{f}$, $\hat{\eta}$, $\hat{A}$ and $\hat{\phi}$ of the peak corresponding to $\hat{k}$;
2. If $\hat{k}$ corresponds to a new component, do
   (a) Increment the number of extracted components;
   (b) Initialise the lineshape filter length of the peak;
   else $\hat{k}$ corresponds to residual signals; Do:
   (a) Add the closest lineshape adapted large peak back to the spectrum;
   (b) Update $\hat{k}$ to be the maximum bin of the added peak and re-estimate the parameters $\hat{f}$, $\hat{\eta}$, $\hat{A}$, $\hat{\phi}$ of the peak;
   (c) Increase the lineshape filter length of the added peak;
3. Reconstruct the ideal lineshape of the peak corresponding to $\hat{k}$:
$$\tilde{\mathbf{s}} = FFT\left(\hat{A}e^{j\hat{\phi}}e^{(-\hat{\eta}+j2\pi\hat{f})n}\right) \tag{2}$$
   and determine whether it is a large peak;
4. Calculate the frequency domain lineshape adaptation filter corresponding to $\tilde{\mathbf{s}}$ and obtain the lineshape adapted peak by convolving the filter with $\tilde{\mathbf{s}}$;
5. Subtract the lineshape adapted peak from the spectrum;
6. If the stopping criterion is satisfied, END.

2.1. The parameter estimator

In the proposed scheme, we apply the Iterative Windowed A&M (IWAN) estimator, [10, 11], to obtain the estimates of the frequency $\hat{f}$ and damping factor $\hat{\eta}$ of the largest peak in the spectrum. Then the amplitude and phase, A and ϕ respectively, of the peak can be estimated using the following maximum likelihood estimators:

$$\hat{A} = \frac{\left|\sum_n x(n)e^{(-\hat{\eta}-j2\pi\hat{f})n}\right|}{\sum_n e^{-2\hat{\eta}n}}, \tag{3}$$

and

$$\hat{\phi} = \angle\left(\sum_n x(n)e^{(-\hat{\eta}-j2\pi\hat{f})n}\right). \tag{4}$$

The estimated parameters are now used to get the ideal lineshape of the peak, which can then be subtracted from the spectrum. However, as the lineshape of the peak in the signal is distorted, direct subtraction will be ineffective, leaving behind a large residual that can obscure smaller peaks. Therefore, the lineshape distortion must be accounted for.

2.2. The lineshape adaptation filter

We model the lineshape distortion as an unknown window applied to the signal component of interest (that is we assume each signal component is distorted individually), which leads to the signal model in Eq. (1) being:

$$x(n) = \sum_{p=1}^{P} w_p(n)A_p e^{j\phi_p}e^{(-\eta_p+j2\pi f_p)n} + o(n), \tag{5}$$

and $w_p(n)$ is the distortion window corresponding to the p^{th} component. Therefore, we perform lineshape adaptation by finding a frequency domain filter that minimises the sum of the squares of the errors between the frequency bins on both sides of the maximum bin and the corresponding bins in the distorted data spectrum.

Let $\tilde{\mathbf{s}}$ be the FFT of a reconstructed peak as shown in Eq. (2) and $\hat{k}$ its corresponding maximum bin index. Given the N-DFT of the data spectrum $\tilde{\mathbf{x}}$ and a filter length l, we define the following least square problem of size m (typically $m = 2l$),

$$\begin{aligned}\bar{\tilde{\mathbf{w}}} &= \arg\min_{\tilde{\mathbf{w}}'} |\tilde{\mathbf{y}} - \tilde{\mathbf{S}}\tilde{\mathbf{w}}'|^2 \\ &= (\tilde{\mathbf{S}}^H\tilde{\mathbf{S}})^{-1}\tilde{\mathbf{S}}^H\tilde{\mathbf{y}},\end{aligned} \tag{6}$$

where

$$\tilde{\mathbf{y}} = \left[\tilde{x}(\hat{k}-m), \ldots, \tilde{x}(\hat{k}), \ldots, \tilde{x}(\hat{k}+m)\right]^T, \tag{7}$$

and

$$\tilde{\mathbf{S}} = \begin{bmatrix} \tilde{s}(\hat{k}-l-m) & \cdots & \tilde{s}(\hat{k}-l+m) \\ \vdots & \ddots & \vdots \\ \tilde{s}(\hat{k}-m) & \cdots & \tilde{s}(\hat{k}+m) \\ \vdots & \ddots & \vdots \\ \tilde{s}(\hat{k}+l-m) & \cdots & \tilde{s}(\hat{k}+l+m) \end{bmatrix}. \tag{8}$$

The frequency domain lineshape adaptation filter $\tilde{\mathbf{w}}$ is the time-reversed complex conjugate version of $\bar{\tilde{\mathbf{w}}}$. The convolution of the filter and the ideal spectral line produces a distorted lineshape that is close to the measured lineshape in the least squares sense. Therefore the residuals after subtraction are significantly reduced. Intuitively, a filter with larger length can achieve better adaptation. However, it cannot be set too large as it will overlap adjacent peaks to that being processed. On the other hand, a filter that is too short achieves poor lineshape adaptation. Therefore, we start the process with a reasonably short filter length, l_0. Then for every large peak that is added back to the spectrum, we gradually increase the filter length (by a step α up to a maximum

value L: $l^{(n+1)} = \min\{l^{(n)} + \alpha, L\}$ or until the residual becomes small enough). This is done alternately with the parameter estimation to refine the spectral line estimates. By subtracting large peaks with increasingly better adapted lineshapes, the residuals in the spectrum are gradually reduced. This allows the algorithm to resolve closely spaced peaks and extract very small peaks close to the baseline.

2.3. Algorithm implementation

In this subsection, we discuss the practical implementation of the algorithm. We firstly focus on the lineshape filter length. The initial filter length l_0 and the increment of the filter length α are selected according to the density of the spectrum as both parameters are proportional to the speed of residuals elimination and at the same time inversely proportional to the ability of discovering closely spaced peaks. We find that for proton NMR, $l_0 \leq 5$ and $\alpha \leq 50$ work well. For the maximum filter length, L, in the other hand, we set it to be proportional to the signal length N: $L = \lfloor N/100 \rfloor$, where $\lfloor \bullet \rfloor$ is the floor operation.

In step 2, the algorithm determines whether the current maximum bin $\hat{k}$ belongs to a new peak or residual signals. In our implementation we deem that we have a new peak if $\eta_{\mathrm{l}} < \hat{\eta} < \eta_{\mathrm{u}}$ and $\left|\hat{f}/N - \hat{k}\right| < 0.5$, where η_{l} and η_{u} are respectively the lower and upper bounds of the damping factor estimates. The bounds can be chosen based on the characteristics of the data. Typically for proton NMR, where the spectrum lines are usually not very broad, they can be set to 10^{-4} and 10^{-3} respectively.

For the stopping criterion of the algorithm, we end the loop when the same large peak is consecutively added back to the spectrum twice while its lineshape adaptation filter length has already reached L before the second addition.

Also note that the algorithm treats large peaks differently from small peaks that are close to the noise floor (e.g. satellites). In our implementation, we differentiate between a large peak and a small peak by comparing their amplitudes with a pre-set threshold that may depend on the noise.

Finally, it is worth pointing out that the method is computationally efficient. For large N, the computational complexity is of the same order as the N-point FFT operation (of order $O(N \log N)$) plus the psuedo-inverse of the Hankel matrices $\tilde{\mathbf{S}}$ of sizes $(2l+1)\times(2m+1)$ (of order $O((2l+1)^3)$) where $l << N$.

3. EXPERIMENTAL RESULTS

In this section, we present an evaluation of the proposed method using real-life proton NMR data. The signal is obtained from a Bruker® Avance 300 MHz instrument and the signal length is $N = 16294$ time points. The 16N-point magnitude DFT spectrum of the signal is shown in Fig. 1 using a logarithmic scale for clarity. We see that the spectrum contains a water peak around 4.7 ppm, a sodium acetate peak around 1.8 ppm and a potassium hydrogen maleate (KHM) peak around 6.2 ppm. The sodium acetate peak has a satellite on either side of it, whereas the KHM peak has two satellites on either side of it. There is also an impurity peak that is extremely close to the leftmost satellite.

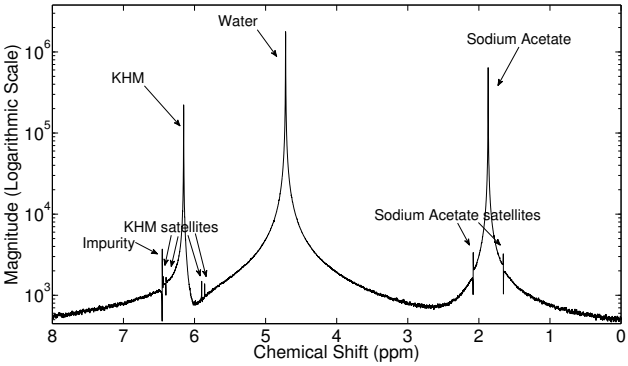

Fig. 1. Magnitude DFT spectrum of the experimental proton NMR signal consisted of a mixture of chemical components.

In our implementation we set $l_0 = 5$ and $\alpha = 30$. In Fig. 2 we show the 16N-point magnitude DFT of the adapted lineshape of the largest water peak using $l = l_0 = 5$ (the first adaptation) and $l = L = 162$ (the final adaptation) and the corresponding residuals after subtraction. As the algorithm gradually increases the filter length for the water peak during the iterative process, the reconstructed ideal lineshape is better adapted to the distorted lineshape and the residual which is seen to be large at the first iteration gradually reduces to an extremely small profile after the final adaptation and subtraction. This allows the method to eliminate the large peaks and uncover the small peaks and satellites. Fig. 3 shows the 16N-point magnitude DFT of the extracted peaks with ideal lineshape (the blue curves). The numbers on top of the curves indicate the order in which the method extracted them. Also plotted are the original signal spectrum in black, and in red is the sum of all the extracted peaks with lineshape adaptation. In order to benchmark our method, we applied ITMPM, [8], to the data and plotted the results in Figs. 4 and 5. The ITMPM requires the number of components P as a-priori information. If this is not given, then ITMPM uses information theoretic criteria to determine P. The result in Fig. 4 was obtained with ITMPM left to determine P, which is done here using the Akaike Information Criterion [8]. It is clear from the figure that the lineshape distortion causes ITMPM to perform very poorly, with the total number of peaks that are detected being 70. The large peaks in the spectrum are split into many peaks to account for the non-ideal lineshape. When P is given to ITMPM a-priori, no model order determination is needed and ITMPM reduces to the matrix pencil algorithm. This is the case for the results shown in Fig. 5 with $P = 10$. Even in this scenario, we see that the method ex-

tracts the large peaks multiple times and misses the satellites altogether. This clearly highlights the power of the proposed method as it uses lineshape adaptation to detect all 10 peaks correctly while at the same time not producing any spurious peaks. Finally we point out that, although one set of experimental data is reported here due to the lack of space, we have successfully applied the proposed method on a large number of other experimental proton NMR data sets.

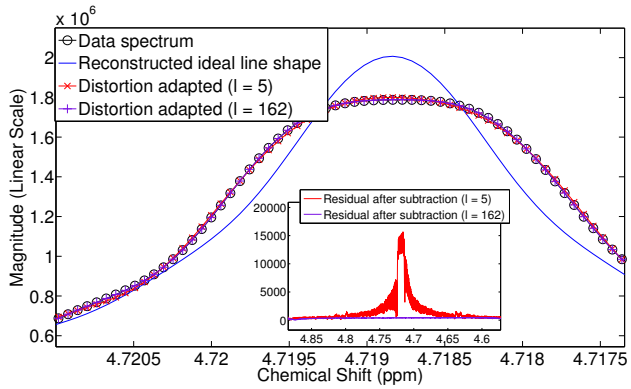

Fig. 2. Demonstration of lineshape adaptation and residuals after subtraction of the water peak using various filter lengths: $l = l_0 = 5$ and $l = L = 162$.

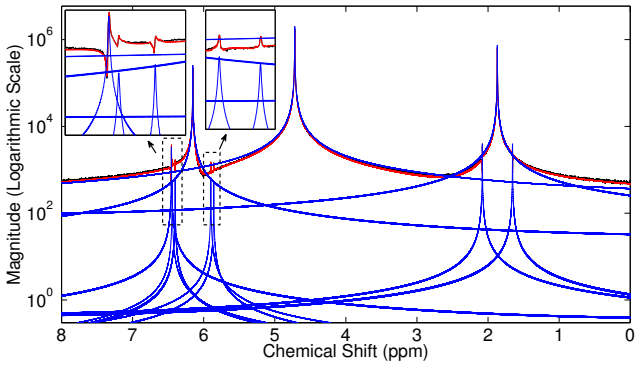

Fig. 3. Extraction of peaks in the experimental proton NMR data using the proposed method.

4. CONCLUSIONS

In this paper, we put forward a novel method for efficiently and automatically extracting signal components in proton NMR spectroscopy that is lineshape distortion adaptive and requires no a-priori information on the number of components. The method is an iterative process where the largest peak is estimated and removed from the spectrum which then uncovers the smaller peaks. This approach is enabled by a simple estimator of the parameters a damped exponential,

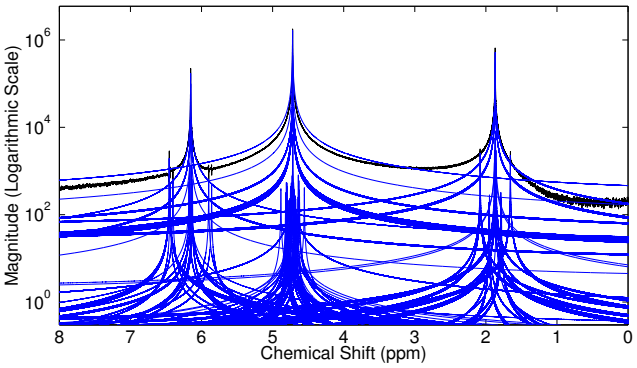

Fig. 4. Extraction of peaks in the experimental proton NMR data using ITMPM with the number of components not given. The detection scheme used is AIC [8] (as MDL shows similar performance).

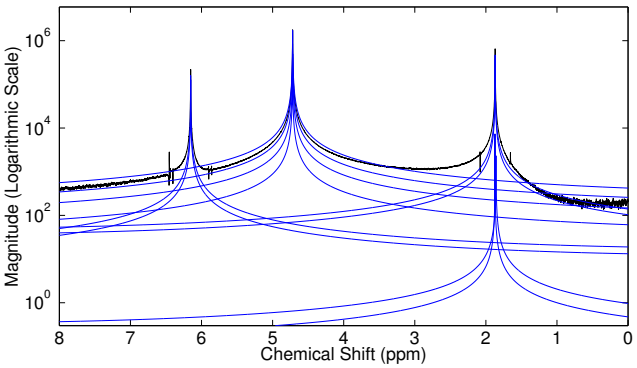

Fig. 5. Extraction of peaks in the experimental proton NMR data using ITMPM with the number of components given.

and by a lineshape adaptation step that accounts for lineshape distortion. Experimental results show that the method outperforms the Information Theoretic Matrix Pencil Method and is capable of extracting all the peaks including satellites in the spectrum without producing any spurious peaks.

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