

Applications of the Whittaker smoother in NMR spectroscopy

Carlos Cobas 

Mestrelab Research S.L., Santiago de Compostela, A Coruña 15706, Spain

Correspondence

Carlos Cobas, Mestrelab Research S.L., Santiago de Compostela, A Coruña 15706, Spain.
Email: carlos@mestrelab.com

Abstract

The Whittaker smoother, a special case of penalized least square, is a multipurpose algorithm that has proven to be very useful in many scientific fields, including image processing, chromatography, and optical spectroscopy. It shares many similarities with the Savitzky–Golay algorithm, but it is significantly faster and easier to automate. Its use in nuclear magnetic resonance, however, is not widespread although several applications have recently been published. In this review, the mathematical background of the method and its main applications in nuclear magnetic resonance spectroscopy will be discussed.

1 | INTRODUCTION

In 1991, Richard Ernst wrote that “Without computers - no modern NMR.”^[1] This quote can be extended to include *signal processing* methods, which have been key players in bringing nuclear magnetic resonance (NMR) to the level of sophistication it is at today. Indeed, NMR is a discipline strongly linked to signal processing techniques. Typically, these techniques are initially developed in different disciplines, which are then incorporated into the realm of NMR. A well-known example is the maximum entropy method, which was first developed within the context of statistical mechanics and information theory. Later, it found applications in many other fields such as image processing^[2a] and NMR.^[2b] Likewise, nonuniform sampling became standard practice in the world of radioastronomy in the early 1970s and used in NMR in the late 1980s.^[3,4] Nonuniform sampling was further developed into what is now known as compressed sensing.^[5] These are just two examples, but can equally apply to the vast majority of NMR processing algorithms, which have their roots in other fields.

This is also the case of the so-called Whittaker–Henderson smoother, an algorithm whose origins can be traced back to the 19th century when actuaries began to develop smoothing methods to graduate (i.e., smooth)

raw mortality data to set life insurance premia.^[6] After some initial attempts, most of them based on moving weighted average filters, Bohlmann proposed solving a regularized least squares problem, in which a scalar parameter determines the trade-off between fidelity to the data and smoothness of the filtered sequence.^[7] This concept of fidelity versus smoothness served as a basis for further development and will be discussed in more detail throughout this paper. However, Bohlmann's work did not receive much attention at that time. It was not until two decades later when Whittaker, unaware of Bohlmann's work, came up with the same idea,^[8] which was further elaborated by Henderson^[9,10] and Aitken,^[11] among others. The method is conventionally credited to Whittaker and Henderson, although from a historical point of view, it may be argued that it should be called the Bohlmann–Whittaker–Henderson–Aitken algorithm. A very similar procedure is known as the Hodrick–Prescott filter in econometrics.

These ideas were revived by Eilers in a seminal paper published in 2003,^[12] which opened the way to other new applications in different fields and, in particular, in chromatography, optical spectroscopy, and NMR. He derived a close-form solution of the penalized least squares problem and introduced the concept of weights, giving the method greater flexibility and broadening the range of

applications, including the possibility to handle missing data (useful, e.g., for interpolation purposes).

In this work, we will refer to the algorithm proposed by Eilers as Whittaker smoother (WS), which seems to be the terminology he uses although credit should also be given to the other pioneers of the method (*vide supra*). The applications of this technique are numerous in the area of signal processing, but this review focuses on those applied in NMR spectroscopy only.

2 | THEORY

The explanations of the principles and developments of WS are taken mostly from Eilers^[12] and Garcia.^[13] A brief introduction to this method is presented here for completeness.

2.1 | Penalized least squares

Let a series of m points y_i be sampled at equal intervals, a condition that will hold in many applications. Handling of arbitrarily spaced samples is discussed in Eilers^[12] (supplementary information).

The goal of the penalized least squares algorithm is to determine a smooth series z that balances two competing goals: (a) fidelity to the raw data and (b) smoothness of the reconstruction.

The *fidelity* F of the two series can be expressed as the sum of squares of differences:

$$F = \sum_{i=1}^m (y_i - z_i)^2, \quad (1)$$

and the *smoothness* S of z can be expressed in terms of the d th differences (where d is usually 1 or 2):

$$S = \sum_{i=1}^m (\Delta^d z_i)^2. \quad (2)$$

A balanced combination of the two goals is the sum $Q = F + \lambda S$, where λ is a parameter by which the smoothness of z against the fit to the data y can be traded.

Some of the data points y_i may be missing; therefore, a new vector of weights w_i is introduced. Typically, $w_i = 1$, but when y_i is missing, the corresponding w_i is set to zero. The expression for Q is changed as follows:

$$Q = \sum_{i=1}^m w_i (y_i - z_i)^2 + \lambda \sum_{i=1}^m (\Delta^d z_i)^2. \quad (3)$$

The idea of penalized least squares is to find the series z that minimizes Q . Following Eilers,^[12] the minimization of the cost function Q is straightforward using matrix notation: Assuming second-order differences (i.e., $d = 2$), introducing $W = \text{diag}(w)$, and D a matrix such that $Dz = \Delta^2 z$, (3) can be written as

$$Q = (y - z)' W (y - z) + \lambda z' D' D z \quad (4)$$

with the explicit solution following from

$$\hat{z} = (W + \lambda D' D)^{-1} W y. \quad (5)$$

Eilers^[12] also provided Matlab code, which takes advantage of the sparse matrix features of Matlab:

```
m = length(y);
D = diff(speye(m), 2);
W = spdiags(w, 0, m, m);
z = (W + lambda * D' * D) \ (w * y);
```

The algorithm scales linearly with the length of the array due to the sparsity of the system, and the computations are extremely efficient even for very large data sets. For example, a vector with length $m = 10^6$ is smoothed in less than 50 ms using the C++ implementation of the algorithm available in Mnova software running under Win10, I7—7600 U @2.9 GHz.

The scalar parameter λ and the vector of weights w give the algorithm an enormous versatility, opening the range of applications. λ can vary over a wide range, depending on the application. For denoising, $\lambda = 1$ is not uncommon, whereas for solvent suppression, larger values (e.g., $\lambda = 10^6$) are used. On the other hand, by adjusting the weights, the algorithm can be used for both smoothing and interpolation operations as well as for baseline correction.

All these applications will be covered in the next section.

2.2 | Estimation of the smoothing parameter λ

As indicated by Equation 5, the output z is strongly influenced by the smoothing parameter λ and its value depends on the application. For example, optimal selection of λ may be different in smoothing operations than in NMR solvent suppression.

Nevertheless, it is important to understand the overall influence of λ on the raw data so that it can be adapted to different data processing problems. When λ tends to zero, hardly any penalization is imposed on the estimates, giving a nonsmoothed curve that closely resembles the input data. On the other hand, large values of the smoothing parameter will result in an oversmoothed curve with a poor fit. In the limiting case as $\lambda \rightarrow \infty$, penalty weight dominates, resulting in a straight line, which is the least squares regression line through the data for second-order differences. With third-order differences, a parabola is obtained in the limit.

Optimal values of λ should provide a smooth curve that reveals the true nature of the data while removing roughness and randomness.

Figure 1 illustrates the raw data, along with three smooth curves based on different penalty weights. For small values of λ , the data are overfit, whereas as λ increases, the method yields a smoother curve.

It may be desirable to have a data-driven method to determine automatically a suitable value for λ . Several approaches have been proposed in the literature, including the method of generalized cross-validation^[14] or L- and V-curves.^[15] Other common choices include those based on information theory such as Akaike information criterion or Bayesian information criterion.^[16]

Although these methods have shown some effectiveness, they introduce an extra computational load, which for many applications may not be necessary or convenient. Quoting Eilers,^[12] “it is advisable not to rely blindly on an automatic choice of the smoothing parameter”. From this author’s experience, it is usually enough to play with a few values of λ in the logarithm scale, tuning it until a visually pleasing result is obtained.

3 | APPLICATIONS

The most obvious and natural application of WS is the removal of unwanted signals (e.g., noise) of time series data or images with minimal altering of its original properties. This process is usually known as smoothing or denoising, two terms that are often used as loose synonyms and a distinction is seldom made.^[17]

In the context of data smoothing, WS has been applied in very different fields, including business and economy,^[18] Fourier transform (FT) near infrared spectroscopy,^[19] chromatography,^[20] or image processing.^[21,22] However, it would not be an understatement to say that the use of WS in NMR is not widespread. In fact, most of all the applications of the WS in NMR spectroscopy published to date have been focused on baseline correction (see below) rather than actual smoothing.

Apart from smoothing and baseline correction, a special application of WS can be found in the suppression of on-resonance signals (i.e., water) as an alternative to other well-established postprocessing methods such as wavelets or convolution filters.^[23]

3.1 | Smoothing

Smoothing can be considered a noise reduction process with the lowest possible signal distortion. This can be done either in the time or frequency domain, which, theoretically, should lead to the same results. Unlike other spectroscopy or chromatography techniques, frequency domain-based smoothing procedures are not widespread in NMR. This has historic roots: The usual way to enhance signal-to-noise ratio in NMR consists of applying a window function (e.g., a decaying exponential) to the acquired FID. This operation can be used to increase the sensitivity, enhance the resolution, or reduce truncation artifacts.

Occasionally, in order to save re-manipulation of an FID, it may be advantageous to smooth a frequency domain spectrum. Some methods have been proposed,

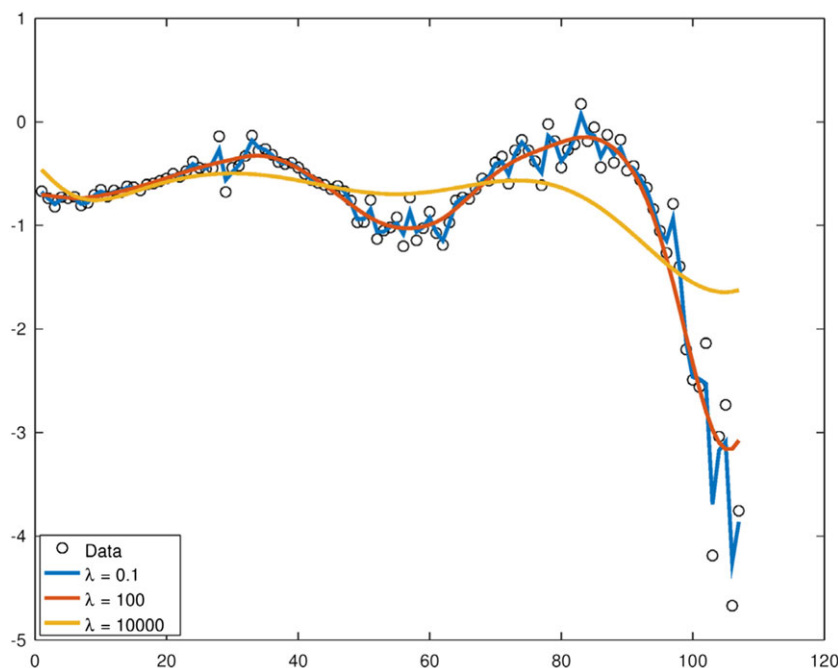


FIGURE 1 Whittaker smoother on simulated using three different penalty weights with a second-order differences. The larger λ is, the smoother the curve

usually as a preprocessing step before peak picking. Thus, for example, Cannistraci et al. used spatial filters,^[24] commonly employed in image processing, for the smoothing step of a 2D/3D peak picking algorithm. Another popular multidimensional peak picking algorithm, WaVPeak, uses wavelets for denoising.^[25] Wavelets smoothing has also been used for the analysis of NMR screening data.^[26] The Savitzky–Golay algorithm, probably the most popular method for smoothing and derivative calculation of analytical data, is a fundamental preconditioning step of global spectrum deconvolution,^[27–30] a powerful, automatic, peak picking algorithm available in Mnova.

Applications of WS for the smoothing of NMR spectra have been limited to the 1D-NMR spectrum shown in the original paper by Eilers,^[12] and no examples have been reported on 2D-NMR spectra. For the latter, the simplest procedure consists on smoothing first the rows using the same algorithm defined before for 1D smoothing and repeating the same procedure along the columns of the 2D data matrix. Different penalty weights can be applied to each dimension. This gives a very fast and effective algorithm, but other subtler possibilities exist.^[31]

A comparative example of the performance of the WS algorithm for the smoothing of an experimental 2D-HSQC spectrum is shown in Figure 2. This example is not intended to be a rigorous comparison among different smoothing techniques, which would require a more thorough analysis. The aim is to present, in a qualitative way, that WS can be a practical and competitive method for the smoothing of 2D NMR spectra. Figure 2a shows the aromatic region of an experimental 2D-HSQC spectrum of methyl 2-bromo-4-nitrobenzoate to which synthetic Gaussian noise was added. Figure 2b shows the result of applying a second difference WS with $\lambda_{\text{rows}} = 0.35$ and $\lambda_{\text{cols}} = 0.25$. Noise is significantly reduced, whereas the peak shapes are minimally distorted. The result obtained with 2D-WS is compared with two state-of-the-art denoising algorithms based on spatial filters. Figure 2d shows the result of applying a nonlocal means (NL-Means) denoising algorithm.^[32] Noise is further reduced, compared with WS, with an even superior peak shape preservation. However, this comes at the cost of a much higher computational burden. NL-Means filter has a complexity that is quadratic in the number of data points in the spectrum, which makes the method computationally more

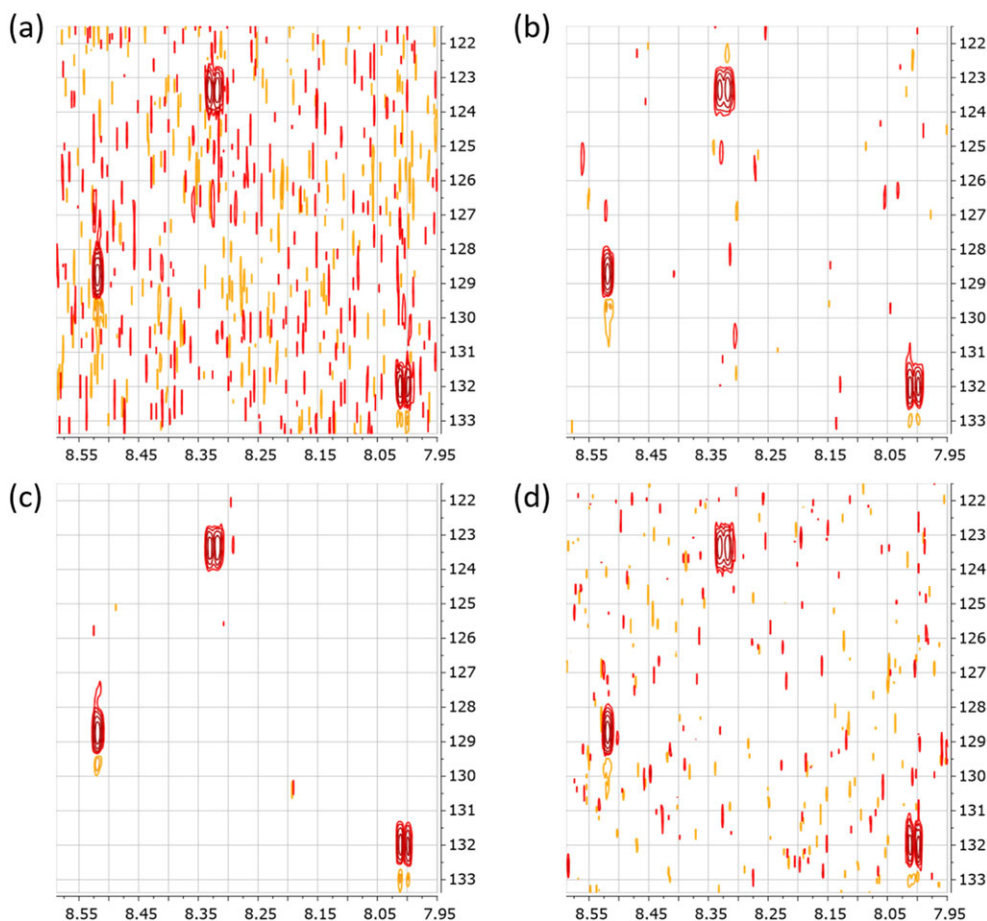


FIGURE 2 Comparison of Whittaker smoother (b), nonlocal means (c), and MMWF* (d) with an experimental 2D-HSQC spectrum with added Gaussian noise (a). All spectra are represented using the same contour level. See text for details

intensive than the other methods. Hence, for computational purposes, we have fixed a search window of 21×21 pixels and a similarity square neighborhood of 5×5 pixels. Finally, Figure 2d shows the result of applying a MMWF* filter^[24] using a kernel size of 7×7 . Similar results were obtained with different sizes. In this case, the smoothing results are slightly worse than those obtained with WS, but as mentioned before, it would not be fair to draw any conclusion based on one single case study. More research is certainly needed, but these results suggest that WS may be a competitive alternative to spatial filters for smoothing 2D NMR spectra, particularly considering its extremely fast performance. All these methods have been implemented in C++, and they are available in Mnova NMR software package. They have been parallelized using OpenMP for optimal performance.

3.2 | Interpolation

In Equations 4 and 5, the weights w_i were introduced to allow for missing values, but they also come in handy when interpolating on a discrete grid is needed (Figure 3). The procedure is straightforward and consists of setting to zero all w_i where the values need to be interpolated and to one otherwise. If no smoothing is necessary, λ can be set to a very small value (e.g., $\lambda = 10^{-6}$).

It can be shown that the interpolating values are piecewise third-degree polynomials when second-order differences are used, whereas for first-order differences, we get piecewise linear interpolation. In other words, a polynomial of degree $2d - 1$ is used for interpolation.

In NMR, interpolation can usually be achieved by zero filling (ZF) the FID. It is well known that doubling the FID enhances the actual digital resolution, whereas subsequent zero-fills improves the apparent digital

resolution, but does not increase the spectral information content. Nevertheless, large factors of ZF can be useful in different contexts, such as improving the performance of peak deconvolution algorithms due to the increased number of digital points available for the fitting procedure.

WS can be a very efficient alternative to ZF for several reasons: First, if the FID has not decayed smoothly to zero, ZF will introduce *sinc* artefacts in the FT spectrum, which must be removed by apodization, a process that would cause some degree of line broadening. Second, WS is more efficient computationally, particularly when the signal to be interpolated is already in the FT domain. Finally, WS can be applied to regions of interest of the spectrum as opposed to the standard ZF method, which can result in very large arrays (note that there is a selective discrete FT algorithm that can be helpful for increasing digital resolution locally without the penalty of large overall output size^[33,34]).

In general, interpolation does not add any inherent information, but it can render that information more visually obvious and thereby facilitate the computer analysis of the signals via, for example, peak picking, peak fitting, and integration. Ideally, one should aim to have at least five digital points per peak above half height for correct peak description, particularly in the case of noisy peaks.

3.3 | Baseline correction

The vector of weights w_i introduced in Equations 4 and 5 to deal with missing values gives WS an enormous versatility, making it useful not only for interpolation but also for other applications such as baseline correction, which is where WS has found most of its applications in NMR.

The first person who realized the potential of WS for baseline correction of analytical signals was Eilers himself.^[35] He proposed the use of asymmetric weights based on the analysis of the pointwise difference between the smoothed and raw data points. The essential idea is that these weights will get values close to zero in data points belonging to a peak and close to one when they belong to the pure baseline, but without actually having to perform a peak picking operation. The procedure is straightforward: Initially, all weights are set to one, and a new smoothed vector z_i is computed from y_i using Equation 5 with a given lambda (e.g., $\lambda = 10^6$). Next, a small scalar parameter p , the asymmetry parameter, is introduced, and new weights are calculated as follows:

$$w_i = \begin{cases} p, & y_i > z_i \\ 1-p, & y_i < z_i \end{cases} \quad (6)$$

The asymmetry parameter p is recommended to be set between 0.001 and 0.1. With these new weights, a new

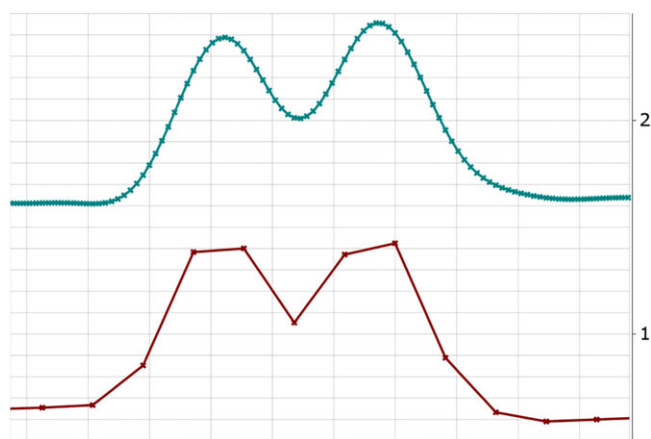


FIGURE 3 Result of interpolating a 1D trace of a HSQC spectrum by a factor of 10. The bottom panel corresponds to the original spectrum. The interpolated spectrum is shown in the upper panel

smoothed vector z_i is computed, and this process is repeated until the weight vector does not change anymore or it reaches the predefined number, for example, 5 or 10. This procedure by which weights w_i are chosen asymmetrically is known as penalized least squares, and the method has been coined as AsLS (asymmetric least squares). Matlab source code for this method can be obtained from the supporting information in Eilers^[35] and from a web page.^[36]

This method has been used for the baseline correction of chromatographic data sets. Zhang et al.^[37] modified the way in which the weights are calculated and applied it to NMR data sets as well as to chromatograms and Raman spectra. In this method, named as airPLS (adaptive iteratively reweighted penalized least squares), the weight vector w is obtained adaptively using an iterative method. The w of each iteration step t is obtained with the following expression

$$w_i = \begin{cases} 0, & y_i \geq z_i \\ \frac{t(y_i - z_i)}{e^{|d|}}, & y_i < z_i \end{cases} \quad (7)$$

where vector d consists of negative elements of the differences, $y - z$, in the t iteration step. The fitted vector z in the previous $t - 1$ iteration is a candidate of the baseline. If a data point y_i is greater than z_i (i.e., the candidate baseline data point), it can be regarded as a part of a peak, and hence, its weight is set to zero; otherwise, it is adjusted according to the second part of (7). Usually, a few iterations are needed for convergence.

This method was further modified by Baek et al.^[38] with the so-called arPLS algorithm (asymmetrically

reweighted penalized least squares), in which the weights are adjusted according to (8):

$$w_i = \begin{cases} 1, & y_i \leq z_i \\ \text{logistic}(y_i - z_i, m_{d^-}, \sigma_{d^-}), & y_i \geq z_i \end{cases} \quad (8)$$

where m_{d^-} , σ_{d^-} are the mean and the standard deviation of d^- , respectively. Given $d = y - z$, d^- is a part of d that is only defined on the region where $y_i \leq z_i$. The logistic function in (8) is a generalized logistic function, which is defined as follows:

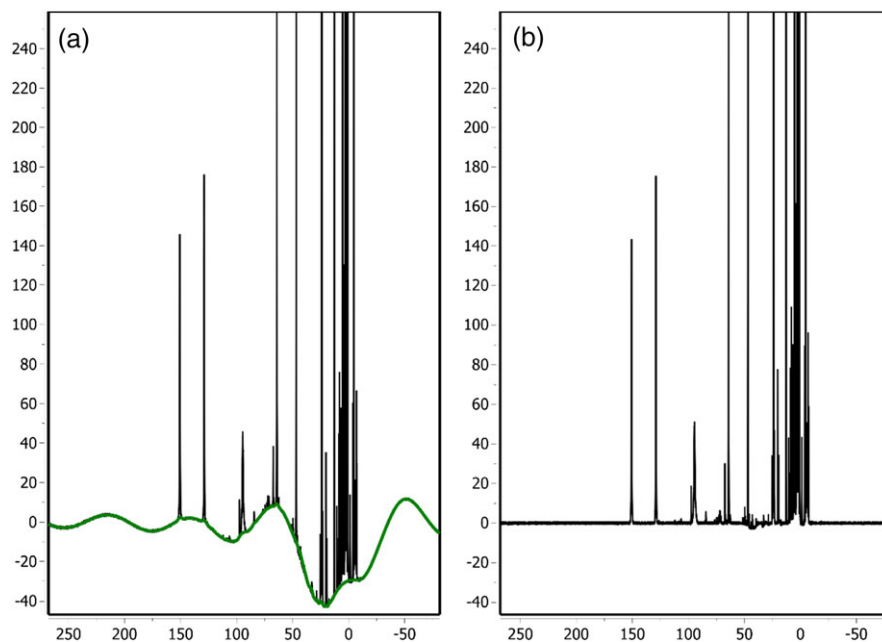
$$\text{logistic}(d, m, \sigma) = \frac{1}{1 + e^{2(d - (-m + 2\sigma))/\sigma}}. \quad (9)$$

This method has become popular in optical spectroscopy (e.g., Raman spectroscopy), but no applications have been reported to date for NMR spectra.

Cobas et al. proposed an alternative approach that takes advantage of the interpolation capabilities of the WS algorithm through the vector of weights.^[39] This consists of a three-step procedure: First, signal-free regions are identified using a modification of the iterative thresholding algorithm originally proposed by Dietrich et al.,^[40] equipped with a continue wavelet transform for an efficient derivative calculation. Next, a vector of weights w_i is defined with ones in those regions identified as pure baseline points and zeroes in those positions corresponding to signals. In the final step, the WS algorithm is executed using this vector w_i .

This method has proven to be very efficient with NMR spectra even in cases with wavy baselines, especially if the peaks are sharp and isolated (see Figure 4). However, it

FIGURE 4 Baseline modelling of a wavy ^{13}C nuclear magnetic resonance spectrum using the Whittaker smoother algorithm described by Cobas et al.^[39] (a) Original spectrum superimposed with the baseline model generated by the proposed algorithm and (b) corrected spectrum after subtraction of the baseline model



does not perform so well when the NMR spectrum contains complex multiplets with highly overlapped signals, such as those found in NMR spectra of biofluids.

3.4 | Solvent suppression

A frequently occurring problem in NMR spectroscopy is the observation of weak resonances in the presence of strong solvent peaks such as water. Many experimental pulse sequences have been developed for reducing those large solvent signals,^[41] but usually, they can still leave behind

a residual signal strong enough to obscure useful information. Data processing can help to further reduce the size of the troublesome solvent signal once the data have been acquired. Different methods of varied sophistication have been developed including convolution filters,^[42,43] wavelets,^[44] or singular value decomposition (SVD)-based procedures,^[45] to cite a few.

It was recently shown^[46] that WS can be used as an alternative to more sophisticated techniques. Its main advantage is the high speed, adding a very little computational burden to the overall NMR processing pipeline.

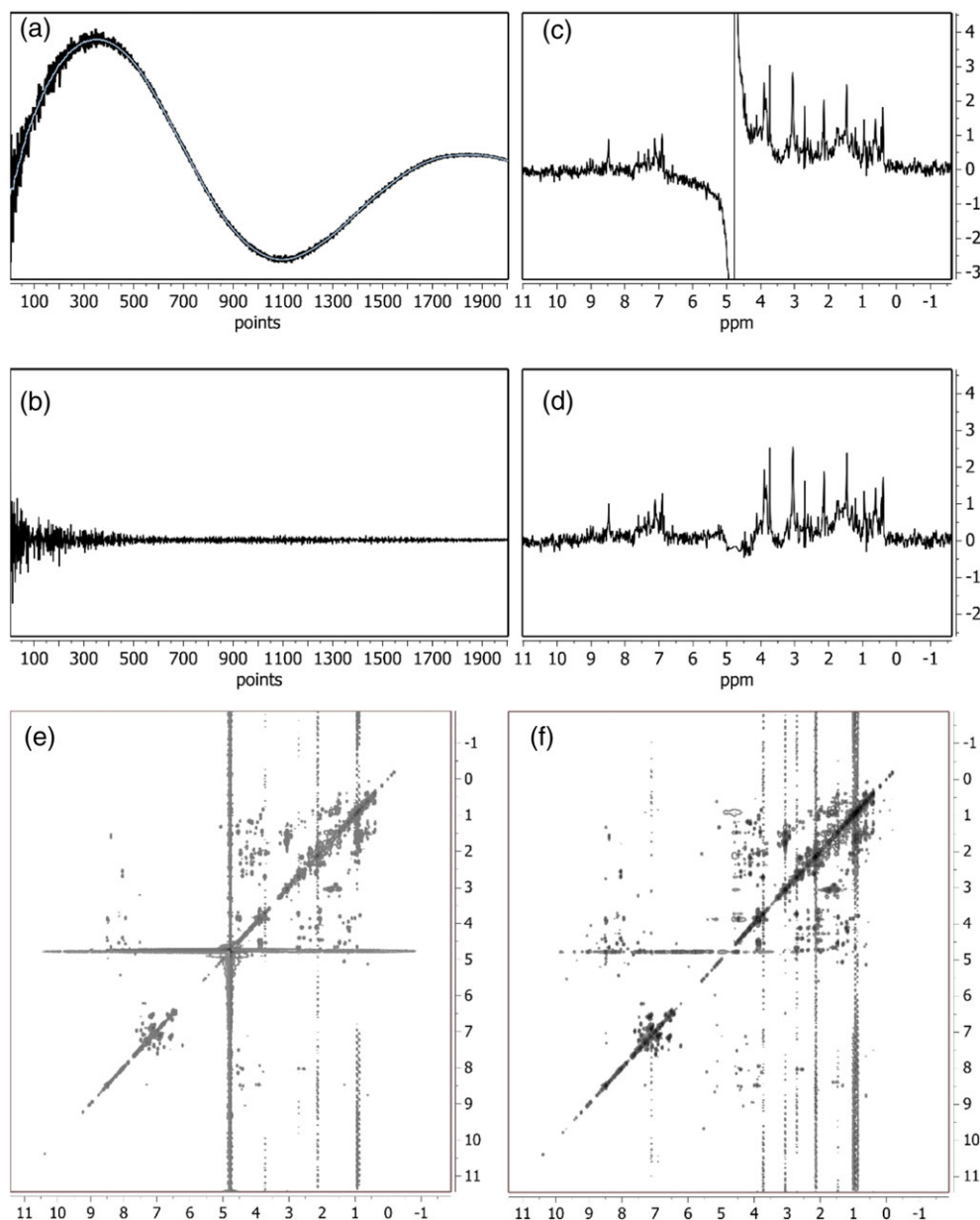


FIGURE 5 Water suppression with Whittaker smoother. (a) The real part of the first FID of a 2D TOCSY experiment. The residual water signal is fitted with the Whittaker smoother algorithm using a large smoothing parameter ($\lambda = 10^6$). Such trend is shown as a light blue line superimposed on the experimental FID. This operation is also applied to the imaginary part of the FID (not shown). (b) The corrected FID after the Whittaker smoother curve has been subtracted. (c, d) 1D spectrum with and without solvent suppression, respectively, and (e, f) treated and untreated 2D spectra

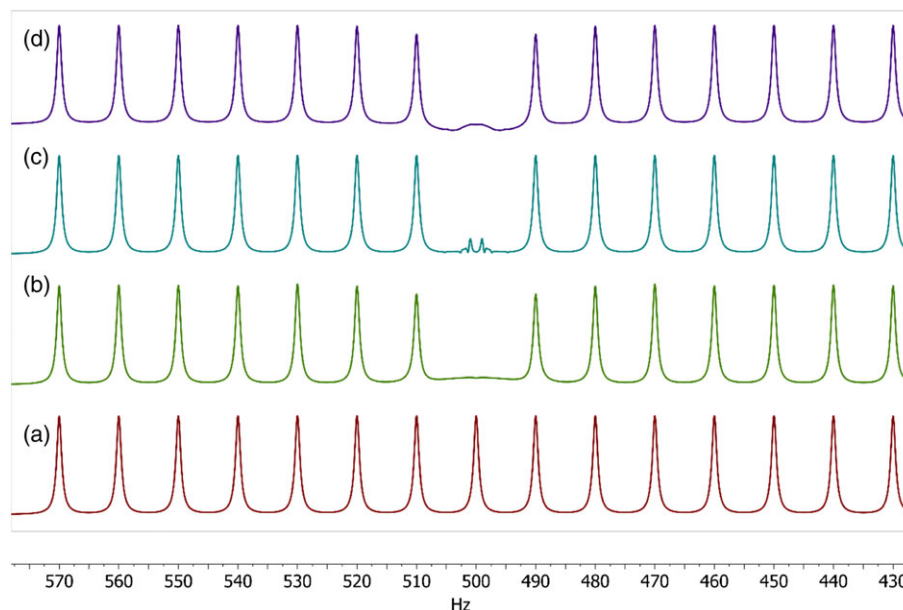


FIGURE 6 (a) Synthetic test spectrum sampled in the time domain using a spectral width of 1000 Hz and 64 K of complex data points with peaks separated by 10 Hz. The spectrum was obtained after applying a Fourier transform to the corresponding synthetic FID. (b) Test spectrum from (a) after applying a 64-point convolution filter to the FID followed by Fourier transform. (c) Spectrum from (a) after applying WAVEWAT suppressing 12 dyadic levels with a Daubechies 20 wavelet and mirror reflection of the FID. (d) Spectrum from (a) after applying WS procedure described in the text with $\lambda = 10^6$

The method assumes that the solvent signal is responsible for the low-frequency (i.e., on-resonance) component of the FID. This component is modelled using the WS (e.g., with a first-order difference) and subtracted from the original FID so that the FT of the modified FID yields a spectrum without the solvent peak. In practice, the original complex FID is fitted and subtracted separately on the real and imaginary parts as follows:

$$S_{Re}(t) = S_{Re}^{Or}(t) - S_{Re}^{WS}(t) \quad S_{Im}(t) = S_{Im}^{Or}(t) - S_{Im}^{WS}(t), \quad (10)$$

where $S_{Re}^{Or}(t)$ and $S_{Im}^{Or}(t)$ are the real and imaginary components of the untreated FID, respectively, and $S_{Re}^{WS}(t)$ and $S_{Im}^{WS}(t)$ are the result of applying WS to those data points to give the final corrected FID, $S_{Re}(t)$ and $S_{Im}(t)$, respectively.

The procedure is illustrated in Figure 5. The regular free induction decay (Figure 5a), corresponding to the first row of a 2D TOCSY spectrum, shows a large low-frequency component, originating from the residual H_2O signal. This component is removed in Figure 5b, after application of the method described above using $\lambda = 10^6$. The slow trend caused by the water resonance and modeled by the WS procedure is shown in Figure 5a as a light blue line superimposed over the acquired FID. Figure 5c–f compares the spectra corresponding to the untreated and treated FID.

A thorough analysis of the performance of the WS method for solvent suppression compared with other

methods is far beyond the scope of this review, but a cursory comparison with two other methods is provided here, employing a synthetic spectrum consisting of a series of equally spaced resonances with a separation of 10 Hz and a total spectral width of 1000 Hz. This analysis is analogous to the one used by Gunther et al.^[44] Figure 6a shows the central part of this test spectrum. All peaks have the same intensity and line width at half height of 1.0 Hz. Figure 6b shows the result after applying the method proposed by Marion et al.^[43] using a 64-point convolution filter to the FID followed by FT. It can be noticed that the filter produces slight distortions in the signals close to the peak in the center of the spectral width. The width of the distortion can be reduced by increasing the number of points of the convolution kernel.

Figure 3c shows the result of applying the WAVEWAT method,^[44] eliminating 12 dyadic levels with a Daubechies 20 wavelet. With this method, the central signal is suppressed without any distortion of other signals. Finally, Figure 3d depicts the spectrum obtained after applying the WS method, which resembles very closely the result obtained with the convolution method.

4 | CONCLUSIONS

WS is a versatile processing algorithm that has been widely applied in different fields. It can be implemented with a few lines of code (source code available from

Eilers^[12]) and adapted to different applications by changing the smoother parameter or the vector of weights. In this article, we have attempted to highlight some of its main applications in NMR spectroscopy, including smoothing, interpolation, baseline correction, and solvent suppression.

We hope that further applications in NMR will be developed as more NMR spectroscopists become aware of the useful properties of the WS method. In this context, an R software package, PepsNMR,^[46,47] has recently been published providing a complete pipeline for 1D-NMR processing, using algorithms that are based on the Whittaker smoother. This software can be found in Github (<https://github.com/ManonMartin/PepsNMR>).

ORCID

Carlos Cobas  <http://orcid.org/0000-0002-7494-7876>

REFERENCES

- [1] R. R. Ernst, in *Comput. Asp. Study Biol. Macromol. by Nucl. Magn. Reson. Spectrosc.*, Springer US, Boston, MA, **1991**, pp. 1–25.
- [2] (a) S. F. Gull, G. J. Daniell, *Nature* **1978**, 272, 686. (b) S. Sibisi, J. Skilling, R. G. Brereton, E. D. Laue, J. Staunton, *Nature* **1984**, 311, 446.
- [3] J. C. Barna, E. D. Laue, *J. Magn. Reson.* **1987**, 75, 384.
- [4] J. C. Barna, S. M. Tan, E. D. Lade, *J. Magn. Reson.* **1988**, 78, 327.
- [5] A. S. Stern, J. C. Hoch, *Magn. Reson. Chem.* **2015**, 53, 908.
- [6] H. L. Weinert, *Comput. Stat. Data Anal.* **2007**, 52, 959.
- [7] D. He, Q. Huang, J. Gao, *Entropy* **2012**, 14, 1306.
- [8] E. T. Whittaker, *Proc. Edinburgh Math. Soc.* **1922**, 41, 63.
- [9] R. Henderson, *Trans. Actuar. Soc. Am.* **1924**, 25, 29.
- [10] R. Henderson, *Trans. Actuar. Soc. Am.* **1925**, 26, 52.
- [11] A. C. Aitken, *Proc. R. Soc. Edinburgh* **1927**, 46, 36.
- [12] P. H. C. Eilers, *Anal. Chem.* **2003**, 75, 3631.
- [13] D. Garcia, *Comput. Stat. Data Anal.* **2010**, 54, 1167.
- [14] P. Craven, G. Wahba, *Numer. Math.* **1978**, 31, 377.
- [15] G. Frasso, P. H. Eilers, *Stat. Model. An Int. J.* **2015**, 15, 91.
- [16] S. U. Zuliana, A. Perperoglou, *Big Data Anal.* **2017**, 2, 6.
- [17] V. J. Barclay, R. F. Bonner, I. P. Hamilton, *Anal. Chem.* **1997**, 69, 78.
- [18] R. J. Hodrick, E. C. Prescott, *Comput. Stat. Data Anal.* **2015**, 29, 1–16.
- [19] H. Chen, W. Ai, Q. Feng, Z. Jia, Q. Song, *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.* **2014**, 118, 752.
- [20] L. Komsta, *Anal. Chim. Acta* **2009**, 641, 52.
- [21] K. Zheng, Y.-S. Chang, Y. Yao, *Compos. Part B Eng.* **2015**, 79, 351.
- [22] C. Atzberger, M. Wess, M. Doneus, G. Verhoeven, *Remote Sens.* **2014**, 6, 8617.
- [23] J. C. Hoch, A. Stern, *NMR Data Processing*, Wiley-Liss, New York **1996**.
- [24] C. V. Cannistraci, A. Abbas, X. Gao, *Sci. Rep.* **2015**, 5, 8017.
- [25] Z. Liu, A. Abbas, B.-Y. Jing, X. Gao, *Bioinformatics* **2012**, 28, 914.
- [26] N. Trbovic, F. Dancea, T. Langer, U. Günther, *J. Magn. Reson.* **2005**, 173, 280.
- [27] C. Cobas, F. Seoane, E. Vaz, M. A. Bernstein, S. Dominguez, M. Pérez, S. Sýkora, *Magn. Reson. Chem.* **2013**, 51, 649.
- [28] T. Schoenberger, S. Menges, M. A. Bernstein, M. Pérez, F. Seoane, S. Sýkora, C. Cobas, *Anal. Chem.* **2016**, 88, 3836.
- [29] C. Cobas, F. Seoane, in *ENC*, Santa Fe, **2008**.
- [30] M. A. Bernstein, S. Sýkora, C. Peng, A. Barba, C. Cobas, *Anal. Chem.* **2013**, 85, 5778.
- [31] P. H. C. Eilers, I. D. Currie, M. Durbán, *Comput. Stat. Data Anal.* **2006**, 50, 61.
- [32] A. Buades, B. Coll, J. M. Morel, *Multiscale Model. Simul.* **2005**, 4, 490.
- [33] S. Szalma, I. Pelczer, P. N. Borer, G. C. Levy, *J. Magn. Reson.* **1991**, 91, 194.
- [34] I. Pelczer, B. G. Carter, *Protein NMR Tech*, Humana Press, New Jersey **1997** 71.
- [35] P. H. C. Eilers, *Anal. Chem.* **2004**, 76, 404.
- [36] P. H. C. Eilers, H. F. M. Boelens, Baseline Correction with Asymmetric Least Squares Smoothing, https://zanran_storage.s3.amazonaws.com/www.science.uva.nl/ContentPages/443199618.pdf, last accessed 27/1/2018.
- [37] Z.-M. Zhang, S. Chen, Y.-Z. Liang, *Analyst* **2010**, 135, 1138.
- [38] S.-J. Baek, A. Park, Y.-J. Ahn, J. Choo, *Analyst* **2015**, 140, 250.
- [39] J. Carlos Cobas, M. A. Bernstein, M. Martín-Pastor, P. G. Tahoces, *J. Magn. Reson.* **2006**, 183, 145.
- [40] W. Dietrich, C. H. Rüdel, M. Neumann, *J. Magn. Reson.* **1991**, 91, 1.
- [41] G. Zheng, W. S. Price, *Prog. Nucl. Magn. Reson. Spectrosc.* **2010**, 56, 267.
- [42] D. Marion, M. Ikura, A. Bax, *J. Magn. Reson.* **1989**, 84, 425.
- [43] C. J. Craven, J. P. Waltho, *J. Magn. Reson. Ser. B* **1995**, 106, 40.
- [44] U. L. Günther, C. Ludwig, H. Rüterjans, *J. Magn. Reson.* **2002**, 156, 19.
- [45] G. Zhu, D. Smith, Y. Hua, *J. Magn. Reson.* **1997**, 124, 286.
- [46] R. Rousseau, PhD thesis. Institut de statistique, biostatistique et sciences actuarielles, Université catholique de Louvain, Belgium **2011**.
- [47] M. Martin, B. Legat, J. Leenders, J. Vanwinsberghe, R. Rousseau, B. Boulanger, P. H. C. Eilers, P. De Tullio, B. Govaerts, *Anal. Chim. Acta* **2018**, 1019, 1.

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