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REVIEW

Quantitative Data Analysis of *In Vivo* MRS Data Sets

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The different characteristics between frequency domain and time domain analysis techniques are detailed for their application to *in vivo* MRS data sets. With the aim of quantitative analysis of MRS signals, i.e. estimation of parameters in the physical model function that describes the MRS experiment, it is considered desirable to avoid any preprocessing of the data, resulting in a preference for time domain parameter estimation techniques. A historical overview is provided for the time domain analysis methods presented in the literature, and a number of time domain methods are described in detail. Finally, the MRUI software package, providing an interactive graphical user interface for a variety of time domain methods, is summarized. © **1997 John Wiley & Sons, Ltd.**

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INTRODUCTION

It has been long recognized that for quantitation of MRS (magnetic resonance spectroscopy) data, the conventional technique of peak area integration in the Fourier transform (FT) spectrum is far from ideal. Underlying broad resonances from immobile compounds, baseline distortion due to missing initial data points, closely overlapping resonances and low signal-to-noise ratios (SNRs), combined with the need for selection of the integration intervals, lead to biased, inaccurate and operator-dependent results. Especially for *in vivo* MRS, operator bias may become a prohibitive factor. From the early 1980s, new methods have been presented in the NMR literature which estimate the relevant parameters via a mathematical model function, describing either the measured time domain signal [usually in the form of a free induction decay (FID)] or its FT spectrum. First, the different characteristics of time domain (TD) methods and frequency domain (FD) methods, fitting a model function of Lorentzian or Gaussian lines to the FT spectrum, are summarized.

WHY TIME DOMAIN FITTING?

The first answer to this question is simple: because the MRS data are measured as a time series (the FID or spin echo). For this reason, it is even logical to estimate the model function parameters from the raw data, avoiding Fourier transformation and any other preprocessing techniques required to obtain a useful spectrum. This greatly reduces the number of sources of operator bias. Despite this, the emphasis for quantitation has been on the FT spectrum for a long time, simply because the MRS data have always been presented through their FT spectra. Theoretically, with the Fourier transform being a linear operator, all information contained in the time domain signal is still present in the frequency domain spectrum. However, if experimental conditions cause a non-ideal FID to be measured, then the FT will result in a distorted spectrum.[1]

- Missing data points, whether at the beginning or the end of an FID, cause a convolution of the 'ideal' FT spectrum (the FT of the complete FID) with a sinc function, which may impede accurate quantitation in the frequency domain. The characteristics of the sinc convolution involved are different for FIDs truncated at the beginning or at the end:
  - Short data series (the FID effectively truncated before it has died out) introduce high-frequency, low-amplitude oscillations throughout the spectrum.
  - If the delay time is different from zero, if a number of initial data points is missing (e.g. due to phase-encoding), or if the first few data points of the FID have been perturbed by receiver distortions and have therefore been omitted from the analysis, a low-frequency oscillation with moderate amplitude will distort the spectrum.

  Correction methods for the previous two phenomena exist (these are often based on a TD method such as linear prediction, estimating the missing data points by extrapolation[2–4]), but introduce more approximations, operator dependences and generally also systematic errors in the final parameters. When operating in the time domain, truncation of the measured

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FID, either at the beginning or at the end, has no negative effects, as the model function which is fitted to the data can be identically truncated. Broad resonances from large and less mobile molecules arise from signals with very short relaxation times: these will decay rapidly to zero, within the first few data points. It is therefore possible to eliminate the distorting effect of these large and less mobile molecules from the TD analysis by deliberately excluding these initial data points from the fit.

- Non-uniform sampling requires extra corrections before the Fourier transform can be carried out satisfactorily.[5] TD analysis methods can incorporate non-uniform sampling simply by applying the same sampling scheme to the TD model function.[6]
- Many conventional FD fitting methods rely on correct phasing of the resonances. Only the most recent FD fitting methods can include individual phase factors. All phases are naturally included in the TD model function and can be fitted either fully individually or in relation to an overall zero order phase, which itself can be fitted or supplied by the spectroscopist.
- An advantage of FD analysis is that it is very easy to analyze selectively a small region of interest in the spectrum. Frequency-selective fitting leads to a reduced number of data points, yielding shorter calculation times. Especially for *in vitro* MRS, with large numbers of data points and many peaks, this may be an important advantage. However, frequency-selective fitting in the time domain has also become feasible.[7/10]

Given the aim of the quantitation–accurate estimation of the biochemically relevant parameters of the model function that describes the measured MRS signal—it is preferable to avoid any (approximate) preprocessing of the data, and this is automatically achieved when performing the quantitative data analysis in the time (measurement) domain. However, whatever the choice of analysis domain, it remains highly desirable to display the FT spectrum for interpretation of the data and fitting results. Moreover, the FT spectrum can be easily exploited to supply starting values for non-linear least squares fitting algorithms.

Exponentially damped sinusoid	*Lorentzian or Gaussian peak*
Resonance frequency ν	Position ν on frequency axis
Damping factor α or β	line width (full width at half-maximum FWHM) for Lorentzian $h = \alpha/\pi$ and for Gaussian $h = (1/\pi)\sqrt{(\beta 4 \ln 2)}$
amplitude a	total integrated area under the peak $A = a/2$, for both Lorentzian and Gaussian. The height of the real part of a Lorentzian is a/α, the height of the real part of a Gaussian is $a\sqrt{(\pi/4b)}$. For the Gaussian the height relation is much more complex
phase ϕ	Phase of the Lorentzian or Gaussian peak ϕ

THE MODEL FUNCTION

The N data points of the measured FID x_n can be modeled as a sum of K (for K spectral resonances) exponentially decaying sinusoids (model function $\hat{x}_n$) plus noise ε_n:

$$x_n = \hat{x}_n + \varepsilon_n = \sum_{k=1}^{K} a_k \, e^{i(\phi_0 + \phi_k)} d(t_n) e^{i 2\pi \nu_k t_n} + \varepsilon_n$$

$$n = 0, 1, \ldots, N-1 \quad (1)$$

with $d(t_n)$ is the exponential decay function that governs the FID due to the transverse relaxation (the effective T_2^*). The two most prominent decay functions that occur in MRS spectral fitting are the linear exponential decay (yielding Lorentzian lineshapes after Fourier transform) and the quadratic exponential decay (Gaussian lineshapes). A combination of the two yields a so-called Voigt lineshape:

$$\begin{aligned} &\text{Lorentzian:} && d(t_n) = e^{-\alpha_k t_n} \\ &\text{Gaussian:} && d(t_n) = e^{-\beta_k t_n^2} \\ &\text{Voigt:} && d(t_n) = e^{-\alpha_k t_n - \beta_k t_n^2} \end{aligned} \quad (2)$$

The model function parameters for the kth ($k = 1, \ldots, K$) sinusoid are its amplitude at time zero a_k, its resonance frequency ν_k, damping factor α_k (or β_k in the case of a Gaussian lineshape) and individual phase ϕ_k. ϕ_0 is the zero-order phase (overall phase of the spectrum), and the time points are $t_n = n\Delta t + t_0$, where Δt is the sampling interval ('dwell time') and t_0 the delay time between the effective time origin and the first data point acquired (or the first data point included in the fit if initial data points are rejected on purpose). The measurement noise ε_n is for most spectral analysis methods assumed to be white and Gaussian (complex).[11] $i = \sqrt{-1}$ is the imaginary unity. The parameters of the time domain model function Eqn (1) relate to their frequency domain analogues as follows:

In general, fitting the model function $\hat{x}_n$ to the measured FID x_n involves a least-squares (LS) procedure.[12] On the assumption that Eqn (1) correctly describes the *in vivo* MRS signal from K resonances, $4K$ unknown parameters have to be estimated. Of these, the damping factors α_k and the frequencies ν_k appear in the model function in a *non-linear* fashion (in terms of the running variable t_n), whereas the amplitudes a_k and phases ϕ_k are linear parameters. Owing to the non-linear parameters the LS procedure will usually be iterative. However, by making full use of the mathematical properties of the exponential decay model [this is only valid for the Lorentzian decay in Eqn (2)], all $4K$

parameters can be estimated using matrix algebra, i.e. non-iteratively. Of the many TD analysis methods presented in the NMR literature, the iterative and non-iterative methods will be discussed separately.

NON-ITERATIVE MODEL FITTING

The first TD methods that appeared in the NMR literature were based on the linear prediction (LP) principle, which could be used to estimate data points based on a known series of points (for a review, see Refs 13 and 14). Initially, its purpose was to reconstruct a full FID, after which FT would yield an undistorted spectrum, followed by FD spectral analysis. Kumaresan and Tufts[15] suggested combining the LP method with singular value decomposition (SVD) and model order reduction, in order to permit the estimation of the model function parameters directly from the available time points via the signal poles $z_k = e^{(\alpha_k + i2\pi\nu_k)\Delta t}$. Barkhuijsen *et al.*[16] introduced a version of this LPSVD algorithm, dedicated to MRS spectral analysis, which became very popular. In the following years, improved versions of the LPSVD were published, using the Householder triangularization decomposition for increased computation speed (LPQRD)[17] or total least squares for increased accuracy (LPTLS)[18]. Gesmar and co-workers[14,19] extended the LPSVD method to handle large numbers of data points and large numbers of peaks. Tang and Norris[7] devised an LP version, which could selectively analyze a particular region of interest from the MR spectrum (LP-ZOOM). Kölbel and Schäfer[20] introduced the continuous regularization principle into the LPSVD method to allow automatic determination of the number of resonating components (LPSVD(CR)). Diop and co-workers[21,22] proposed the use of the Cadzow enhancement procedure for more consistent and less noise-sensitive parameter estimates (EPLPSVD). The combination of the latter two methods would permit fully automatic LP analysis of MRS data.[23] A statistical approach to LP spectral analysis was offered by the modified Prony method,[24] determining final estimates on the basis of a large number of LP runs using different prediction lengths. A clear disadvantage of this method is the extraordinarily long calculation time involved. However, all LP methods suffer from two specific problems: the root selection (which roots represent signal components and which arise from noise features), and the actual rooting of the prediction polynomial, which becomes increasingly demanding for larger numbers of spectral components.[14] This, together with noise-related systematic errors (as discussed by Diop *et al.*[22]) introduced by preceding Cadzow enhancement (also less efficient because extra SVDs involved), puts a limit to the circumstances under which the LP methods will still be successful.

A more robust alternative was provided by the State-space theory of Kung *et al.*[25] Based on the Vandermonde decomposition of the Hankel data matrix (indirectly solved via SVD), it would carry out the entire parameter estimation process on matrix algebra alone, avoiding the root selection and polynomial rooting involved with the LP methods.[26] As with LPSVD, it was the group from Delft who first exploited the improved algorithm, and presented an MRS-dedicated version under the name of HSVD.[27] Again, improved versions were published, using the Householder triangularization decomposition for increased computation speed (HQRD)[28] or total least squares for increased accuracy (HTLS)[29], the latter optionally preceded by a minimum variance (MV) enhancement procedure for more reliable parameter estimation at the cost of an extra, although smaller, SVD.[30] A disadvantage of these methods was that an entire SVD always had to be carried out on the Hankel data matrix, the size of which is directly proportional to the number of data points. Owing to the complete SVD, the calculation times would increase by approximately a power of three if the number of data points in the fit was doubled. Millhauser *et al.*[31] pointed out that using Lanczos recursion, the SVD of the data matrix could be reduced to any desired number of largest singular values, i.e. only to the significant signal components. Another reduction in calculation time was brought about by intelligent exploitation of the Hankel symmetry of the data matrix, as indicated by Hansen.[32] Pijnappel[33] combined both algorithms into a new HLSVD State-space method with, depending on the application, calculation times up to hundreds of times faster than previous HSVD versions.[34] Because the HLSVD method can do a very rapid fit if only the largest components are involved, it can be efficiently applied to remove large unwanted features from the signal, such as a residual water resonance, or large lipid resonances. The use of HLSVD for water removal is detailed in Ref. 35.

Other non-iterative time domain methods based purely on linear algebra are MUSIC,[36] the generalized Pisarenko method,[37] ESPRIT[38] and the matrix pencil method.[39]

In general, all non-iterative spectral analysis methods have the following characteristics:

- All model parameters are estimated in a single step; these methods can be very fast.
- Linear processes do not need starting values for the non-linear parameters to be estimated. This significantly reduces the workload for the operator.
- Operator interaction on the whole can be kept to a minimum. For this reason, the non-iterative or non-interactive methods are sometimes called 'black box' methods.
- The model function is restricted to an exponential decay model. However, non-Lorentzian signal components can be represented by multiple Lorentzians.[26]
- Only very limited prior knowledge about the signal can be imposed on the fitting process, such as the number of resonances present. A first attempt to introduce prior knowledge of frequencies and damping factors into a State-space method is presented in Ref. 40.

Especially the last item may be of vital importance when considering spectral analysis of *in vivo* MRS data, where the signal quality is usually poor. At low SNR, considerable peak overlap, and with problematic spectral baselines, the ability to impose biochemical and/or

experimental prior knowledge on the model fit may be crucial in order to arrive at consistent and reliable parameter estimates.[41]

ITERATIVE MODEL FITTING

Iterative (optimization) methods fit the model function of Eqn (1) directly to the time domain data in non-linear least squares sense, via

$$\min_{a,\phi,\alpha,\nu} \sum_{n=0}^{N-1} |x_n - \hat{x}_n|^2 = \sum_{n=0}^{N-1} \left| x_n - \sum_{k=1}^{K} a_k e^{i(\phi_0+\phi_k)} d(t_n) e^{i2\pi\nu_k t_n} \right|^2 \quad (3)$$

where a, ϕ, α and n are the parameter vectors containing the amplitudes, phases, damping factors and frequencies, respectively. General characteristics of such methods are as follows:

- The model parameters are estimated in a series of iteration steps, which need convergence to a global minimum in the minimization (fitting) process to reach the correct values for the parameter estimates.[12] Evidently, a global search over the entire parameter space would make computation times prohibitively long, and most iterative methods are local optimizers, relying on reasonable starting values. Recently, genetic algorithms have been demonstrated to reach the global minimum,[42] although computation times are still slow.
- Starting values for the first iteration step are required for all non-linear parameters (damping factors α_k and frequencies ν_k). These can be obtained from a rapid black box method, or from the FT spectrum of the FID (peak positions and widths).
- There are no limitations concerning the mathematical structure of the model function (this feature allows the introduction of Gaussian or Voigt lineshapes).
- It is possible to impose biochemical prior knowledge of the metabolites under investigation on the fitting process. Examples of prior knowledge are:
  - *Amplitudes*—Certain molecules have different groups that resonate at different frequencies (owing to different chemical environments) and contain different numbers of equivalent atoms (*e.g.* the CH_2 and CH_3 group of creatine in ^{1}H MRS). For such structures an amplitude ratio (e.g. 2:3 for creatine) can be imposed on the fitting of the two respective amplitudes, reducing the number of free parameters by one.
  - *Frequencies*—Molecules with coupled resonances will produce multiplet resonances, the frequency splittings in which are known from their coupling constants (e.g. 7 Hz for lactate in ^{1}H MRS). These frequency relationships can be imposed on the estimation of the respective frequencies, further reducing the number of free parameters.
  - *Damping factors*—Although coupled spins resonate at different frequencies, their linewidths are identical. This can be imposed as a 1 : 1 ratio in fitting the respective damping factors.
  - *Phases*—If the delay time t_0 of the FID is negligible, all resonances have identical phases (with a few exceptions). Hence only one phase has to be fitted for the entire signal, or for a large group of resonances. If this phase were known from the spectrometer settings (or after phasing the spectrum), its value could be fixed and no phase would have to be estimated at all. On the other hand, the overall phase f_0 can be estimated, as can the delay time t_0.

  It can be seen that imposing relevant biochemical prior knowledge leads to a reduction in the number of parameters to be estimated, and hence to shorter calculation times, better convergence behavior and improved results.
- With the use of a maximum likelihood (ML) fitting routine, there are no systematic errors in the parameter estimates, and the statistical errors can be approximated by their theoretical lower limits, the so-called Cramér Rao lower bounds, on condition that the noise ε_n be white and Gaussian.[12]
- User interaction may be extensive when starting values and parameter constraints are to be supplied manually.

Various spectral analysis methods, based on non-linear least-squares optimization of Eqn (3), have been presented in the NMR literature. A number of these, such as NLTD,[43] NLLS[44] and general ML fitting,[45] are mere variations to the non-linear least-squares problem of Eqn (3). Chen *et al.*[46] described a parallel implementation of such an ML method. However, these methods have not been described to implement biochemical prior knowledge as outlined above. An iterative fitting method developed purely for MRS, complete with input facility for parameter relationships based on biomolecular and/or experimental prior knowledge, was published by van der Veen *et al.*[47] under the name VARPRO. This term stands for the variable projection method, an algorithm suggested by Golub and Pereyra.[48] It separates the linear and non-linear parts of the model function in Eqn (1), so that the fitting process is separated into one non-linear least-squares algorithm in which only the frequencies and damping factors are optimized, and a subsequent linear least-squares (non-iterative) algorithm in which the amplitudes and phases are fitted. Especially VARPRO's capacity to include prior knowledge has made it a reliable tool for accurate and consistent spectral analysis, even in challenging data sets with low spectral quality.[9,26,41,47,49] Another iterative TD fitting method with the ability of implementing biochemical prior knowledge was published by de Graaf and Bovée.[50] The original VARPRO spectral analysis method has undergone a number of important improvements, such as the introduction of frequency-selective fitting.[8] This permits the fitting of a limited number of resonances of interest, without suffering from systematic errors caused by the difference of the fitted model function and the measured data, due to the peaks excluded from the fit. Should the number of signal peaks be overestimated (i.e. too many resonances used to fit a signal), then this will become clear by the redundant model resonance being fitted either to a noise feature (unrealistically narrow linewidth and a

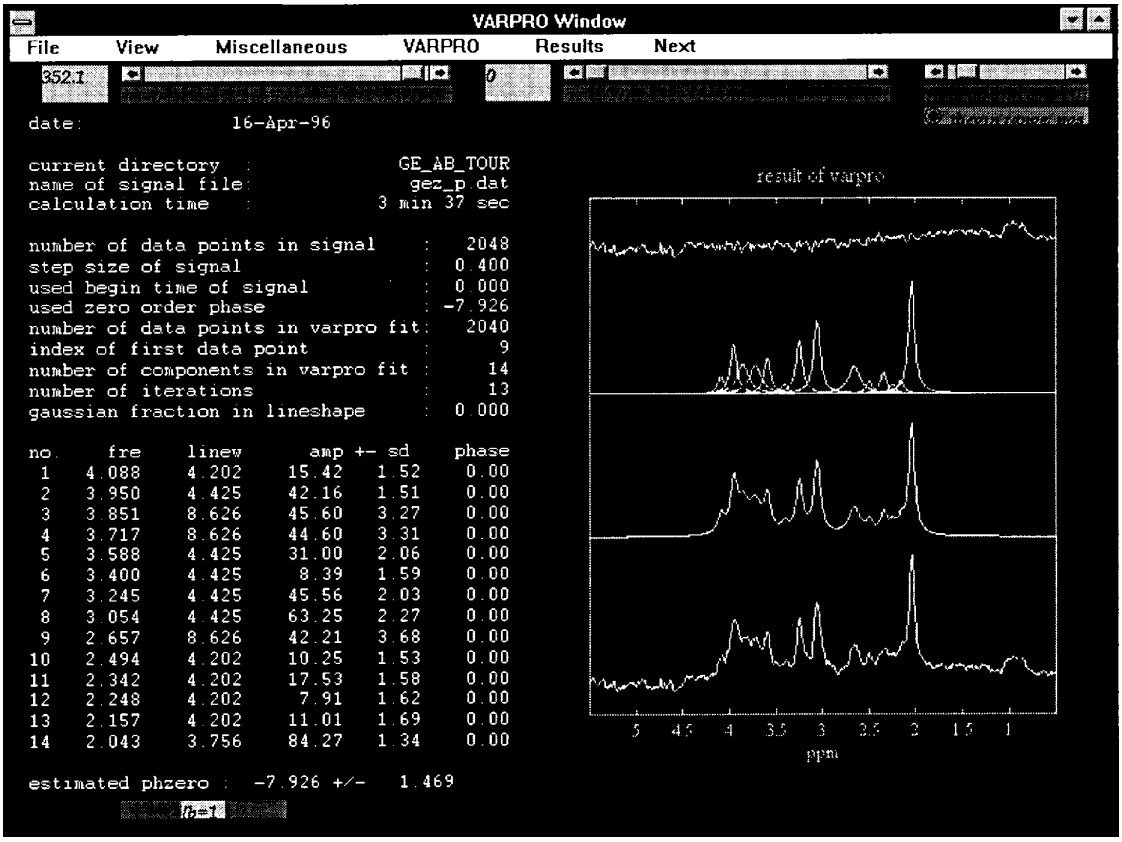

Figure 1. Example of the MRUI spectral window, here after the VARPRO method has converged on an *in vivo* ^{1}H MRS signal (from the occipital lobe in the brain of a healthy male volunteer, using the STEAM pulse sequence with an echo time of 30 ms on a GE/Signa 1.5T clinical scanner). The residual water resonance was removed from the experimental signal using HLSVD. The results are displayed in a table and as plots of the original spectrum (lowest trace), of the FT of the signal reconstructed from the parameters estimated by VARPRO (second trace up), of the individual Lorentzians (third trace up) and of the residual which is the difference between the original spectrum and the reconstruction (top trace). The pull-down menus canbe seen at the top of the MRUI spectral window, as well as the sliders for phasing the spectra (for display only, VARPRO can estimate the zero-order and individual phases; see the zero-order phase in the bottom left corner). The table lists frequencies in the same units as the spectral axis (ppm in this case), linewidths in Hz and amplitudes (plus standard deviations based on a Carmér Rao calculation) in arbitrary units.

small amplitude parameter with a large standard deviation), or it could be used for a composite fit of a resonance the lineshape of which did not correspond exactly to the model function used (e.g. by involving a broader baseline component). Such a situation should become clear from inspection of the reconstructed model spectrum according to the individually fitted resonances, which can be displayed after the fit (automatically done in the MRUI software, see next section). Recently an improved method has been presented under the name AMARES (Advanced Method for Accurate, Robust and Efficient Spectral fitting).[51] It features a faster and more robust optimization algorithm, a pre-programmed switch between Lorentzian, Gaussian or Voigt model lineshape, the possibility of fitting spin echoes in addition to FIDs and extended possibilities on the implementation of biochemical prior knowledge.

COMBINATION OF METHODS AND USER SOFTWARE

It is obvious that both non-iterative and iterative fitting methods have their advantages and disadvantages, and each should be used when most appropriate. With their ease of use, short calculation times and possibilities for full automation, non-iterative methods should be used where possible. When the quality of the data becomes poor, or the resolution becomes low owing to extensive peak overlap, iterative methods, implementing all available prior knowledge, need to be utilized for reliable parameter estimation. In fact, application of prior knowledge may reduce the fitting problem to such an extent that the iterative methods turn out to be faster than non-iterative methods on the same data set. However, in this case the non-iterative methods may still play an important role, e.g. for the removal of large unwanted resonances, such as residual water or lipid peaks.

One remaining problem that has troubled many published spectral analysis algorithms is the accompanying software package and its ease of use. Many powerful algorithms were programmed by physics- or mathematics-related research groups, targeted at performance alone, without much regard for their accessibility. The recently presented MRUI software package[52] provides a graphical interface to a number of the non-iterative and iterative TD methods discussed above, in a fashion transparent to the user. It provides facilities for supplying starting values ('peak-picking' or

via a black box method) and prior knowledge, an FID Maths library of preprocessing functions, conversion routines (including automatic interpolation routines for sequentially measured FIDs in order to correct for half-dwell-time differences between the real and imaginary parts of the data points), display/plot features, etc. The spectroscopist or biochemist is enabled to handle an arsenal of sophisticated mathematical algorithms, in much the same manner as he/she would analyze the data with his/her spectrometer software. An example of the MRUI interface for the VARPRO parameter function is displayed in Fig. 1; see the caption for details of the analyzed spectral data. The MRUI software is available upon request (http://mrui-web.uab.es/mruiwww/mruiwww/mrui_hom.html).[53,54] This Internet WWW site also depicts a number of examples on the use of the MRUI package, complete with instructions and illustrations. A hard copy of the software manual, which also exhibits algorithm theory, general spectral analysis theory and prior knowledge implementation tips, can be downloaded.

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