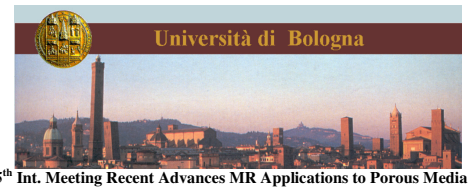
EXAMPLES OF MARGINAL RESOLUTION OF NMR RELAXATION PEAKS USING UPEN AND DIAGNOSTICS



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Errors of Fit, Noise, Quality of Fit

$$R_r^2 = \left(\sum_{i=1}^{N} B_i E_i^2\right) / N$$

The E_i 's are the errors of fit. For T_2 data, signal amplitude s_i may represent a window average of B_i echoes. R_r (R for noise: *rumore, Rauschen*) is an estimate of individual-echo error of fit, using a compromise weighting to give equal weights at long and short times, rather than $\Sigma(B_i E_i)^2/\Sigma B_i$ to give the best statistical estimate of the ensemble average echo noise R. This compromise weighting is used for all the R's.

If there is a slowly-varying error of fit in addition to random noise, one may get a better estimate of the noise from R_v (v for variation), computed from differences of the E 's for second-nearest neighbors, since a non-random slowly-varying error of fit would not greatly affect these differences.

$$R_v = \frac{1}{2(N-2)} \sum_{i=1}^{N-2} \left(\sqrt{B_i} E_i - \sqrt{B_{i+2}} E_{i+2}\right)^2$$

If there are random errors only, R_r should be somewhat less than R_v , because the fitting minimizes the errors, rather than differences of errors. Having separate estimates of the random noise and the overall error of fit can warn us if the data are not, or cannot be, adequately fit. Thus, the quality-of-fit parameter

$$R_{rv} = \ln(R_r / R_v)$$

should normally be negative, as it usually is for artificial data corresponding to positive exponential components plus random noise. A value of R_v=0.05 usually indicates data problems, and values over 0.1 normally indicate serious data problems.

UPEN: Uniform PENalty inversion of multiexponential decay data

Minimize (error)^2 + penalty

$$\sum_{i=1}^{N} B_i \left(g_0 + \sum_{k=1}^{M} g_k \exp(-t_i / T_k) - s_i\right)^2$$

$$+ \sum_{k=1}^{M} A_k g_k^2 + \sum_{k=2}^{M-1} C_k \left(g_{k-1} - 2g_k + g_{k+1}\right)^2$$

The first line is weighted (error of fit)^2 ; the second is the penalty.

B_i is the weighting factor, g_k the computed amplitude, t_i is data time, T_k is relaxation time, s_i is signal amplitude. A_k is amplitude penalty coefficient (=0 for times covered by data).

C_k is curvature penalty coefficient (with negative feedback applied to the penalty through c_k).

$$c_k = \beta_p \Delta_Q^2 \left(g_{k+1} - g_{k-1}\right)^2 + \beta_c \max\left[\left(g_{j-1} - 2g_j + g_{j+1}\right)^2\right]_{j=k-1,k,k+1}$$

$$C_k = R^2 \Delta_Q / \left(\beta_0 + c_k\right)$$

$$A_k = R^2 \Delta_Q / \left(\beta_0 + \beta_a g_k^2\right)$$

β_p is the slope (*pendenza*) compliance parameter.
β_c is the curvature compliance parameter.
β_a is the amplitude compliance (for outside data range).
β_0 is the compliance floor (not critical, but not zero).
β_{00} (normally = 1) multiplies the other β's.
Δ_Q is data point time spacing in Nepers.

Abstract

The multiexponential inversion program UPEN by the authors [J. Magn. Reson. 1998; **132**: 65-77; Ibid. (In press)] employs negative feedback to a regularization penalty to implement variable smoothing when both sharp and broad features appear on a single distribution of relaxation times. This allows a good fit to relaxation data that correspond to a sum of decaying exponentials plus random noise, but it usually does not give a good fit to data that are distorted by systematic errors from instrument problems, which can cause erroneous "resolution" or erroneous non-resolution of peaks. UPEN provides a series of diagnostic parameters to help identify such data problems that can lead to interpretation errors, and, in particular, to warn when a close call on the resolution or non-resolution of nearby peaks might be questionable. Examples are given from a series of T_2 data sets from desiccated bone samples, with examples where the presence of two peaks is required by good data, examples where the presence of two peaks is negated by good data, and examples where the resolution or non-resolution of peaks cannot be trusted because of instrumental distortions revealed by UPEN diagnostic parameters. It is suggested that processing relaxation data with UPEN in nearly real time could permit retaking data while a sample is still available if the diagnostic parameters show instrumental problems.

Resolution of Two Equal Lines

[UPEN I: JMR **132**, 65-77 (1988), Eqs. 11-12]

$$y = (\ln Y)^2 / 12 \qquad E_2 \approx y^2 / \left(6.87 + 15.9y + 7.2y^2\right)$$

$$SNR \geq \sqrt{\Delta_q} / E_2$$

E_2 is the least maximum absolute error of fit to a rectangular distribution of relaxation times by 2 sharp lines, a factor of Y apart. The data time spacing in Nepers is Δ_q, which for T_2 data without discarded points is T_{EE}/T, where T is relaxation time of the minimum between the peaks, and T_{EE} is the spacing of the echoes employed. If the peaks are of comparable size and are the only significant features on the distribution, SNR is the signal-to-noise ratio. If the peaks are disparate, only the signal in the smaller peak is counted. Additional major features make resolution more difficult. The above SNR value is for marginal resolution; several times higher SNR is required for firm resolution. If the two tentative peaks do not have zero inherent line width, Y must be reduced by about the mean halfwidth (on a logarithmic time scale).

Linewidth due to the Noise

[UPEN I: JMR **132**, 65-77 (1988), Eqs. 13-14]

$$w = 3\Delta_q^{1/4} / \sqrt{SNR} \quad ,$$

where w is the halfwidth of the line and SNR counts only the signal in the line. Nearby features widen the line.

Significance Criterion for Improvement in Fit

[UPEN I: JMR **132**, 65-77 (1988), Eq. 15]

Under some conditions, to suggest a significant change in the quality of a fit, the relative change in error of fit should be at least

$$1 / \left(N\sqrt{2\Delta_q}\right) \ ,$$

with the same adaptation to T_2 data as mentioned above. N is the number of (possibly windowed) data points used in the computation.

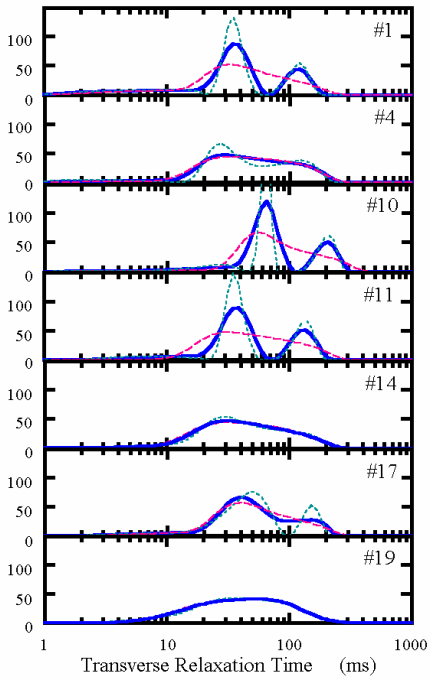

Fig. 1. Relaxation time distributions. Heavy solid curves are for $\beta_{00} = 1$; light short-dashes are for $\beta_{00} = 2^{3/2}$ and long dashes for $\beta_{00} = 2^{-3/2}$. Parts of the dashed curves may be hidden by the heavy solid curve.

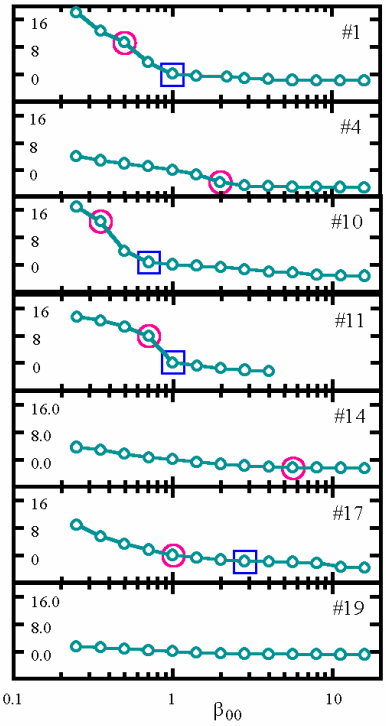

Fig. 2 Percent errors of fit as functions of β_{00}, normalized to those for $\beta_{00} = 1$. The point with the large circle is the last one giving a monotonic curve. The point with the large square is the first one with two peaks separated to, or nearly to, baseline.

The multiexponential inversion program UPEN [1, 2] provides a series of diagnostic parameters to help identify data problems and warn of possible misinterpretation of computed results. The variable smoothing feature of UPEN permits the fitting of *ideal* data to within the level of random noise, usually somewhat better, since a fitting procedure accommodates somewhat to the noise. The parameter R_r is the rms error of fit, using the compromise weighting for T_2 data described in Ref. [2]. R_v is the rms error computed from differences of errors of second-nearest neighbors in order to remove the contribution of a smooth and slowly-varying error of fit, as might result from some systematic data distortion of instrumental origin, as described in [2]. A large positive value of the parameter $R_{rv} = \ln(R_r/R_v)$ is then an indication of data distortion, that is, that the data could not be fit adequately by a sum of positive exponentials. In particular, one should beware of interpreting sharp detail from a computed distribution of relaxation times when there is a warning of a high R_{rv}.

With UPEN there is normally no user adjustment of smoothing parameters, although adjustment of a global compliance parameter β_{00}, normally =1, is sometimes warranted in the case of the marginal resolution of features such as a pair of peaks. In some cases an increase of β_{00} by a factor of 2 or less may lead to the appearance of resolved peaks. Ref. [1] gives criteria for the relative decrease in R_r needed for the resolved peaks to be required by the data, and for the signal-to-noise ratio (SNR) required for marginal resolution of equal sharp peaks a factor of Y apart.

Sets of T_2 relaxation data taken by CPMG sequences were from a series of desiccated bone samples taken from a pig femur [3]. It is not the purpose of the present work to interpret these data physically or to further describe the experimental procedures, but merely to present some closely related sets of relaxation data that show both legitimate differences in the distributions of relaxation times and also illustrate some of the problems in identifying when the NMR data require, rather than just permit, the resolution of two peaks.

The distributions of relaxation times computed by UPEN are shown for seven of these samples in **Fig. 1**. The vertical scale shows percent of total signal per Neper of relaxation time. The heavy solid curve in each is for the normal processing, with the smoothing compliance $\beta_{00} = 1$. The light short-dashed curve is with β_{00} increased by three factors of $2^{1/2}$; the long-dashed curve has β_{00} decreased by three factors of $2^{1/2}$. Eqs. (11-12) of Ref. [1], using data densities as described in Ref. [2], suggest that SNR>45 is needed for marginal resolution of two inherently-narrow peaks at the spacing shown in **Fig. 1**, with two to three times this SNR needed for firm resolution. The SNR values for the seven samples are 190, 100, 261, 118, 113, 289, 94, respectively. Eq. (15) of Ref. [1] suggests that, to be significant, a small increase in β_{00} that leads from one peak to two well-resolved peaks should decrease the error about 7% in addition to the amount that the error is decreased simply by making a better fit to the noise, about a percent, by the same size step at slightly larger β_{00}. Fig. 2 shows error of fit relative to that for β_{00}=1, with the vertical interval 8%, about the amount corresponding to a significant decrease in the error. In Fig. 2 the point with the largest β_{00} that does not give a distribution with a minimum between two peaks has a large circle around it. The point with the smallest β_{00} that gives a minimum to baseline or near baseline has a large square around it.

In Fig. 1 it may be noted that all curves are monotonic with $\beta_{00} = 2^{-3/2} = 0.354$. In UPEN the smoothing penalty, which is inversely proportional to β_{00}, has a factor of the noise-squared, so $\beta_{00} = 2^{-3/2}$ is equivalent to overestimating the noise by a factor of $2^{3/4} = 1.68$. Note that the large circles in Fig. 2 are all on or after this point. Two samples, #10 and #17, showing somewhat opposite behavior, are disqualified by large R_{rv} values, even for very large β_{00}, that is, even if greatly undersmoothed. Sample #10 shows two peaks in Fig. 1 when using the normal β_{00}=1or even $2^{-1/2}$ (as can be noted also from Fig. 2), and shows a sharp off-scale peak at $\beta_{00} = 2^{3/2}$. There is also an abrupt decrease in error for a single step in β_{00}, which, without the large R_{rv}, would suggest resolution of the peaks. Sample #17, on the other hand, shows two separated peaks only when β_{00} is increased to $2^{3/2}$, and this is not accompanied by a significant decrease in the error. However, neither of these data sets can be trusted, because of the high R_{rv} values.

Samples 1 and 11 show abrupt changes in error just below $\beta_{00} = 1$ and have acceptably low values of R_{rv}, making it reasonably clear that the resolved peaks are required by these data.

Curves 4, 14, and 19 do not show any such action in Fig. 2. In Fig. 1, curve 4 barely shows a minimum even with $\beta_{00} = 2^{3/2}$. Even raising β_{00} to 16 does not give separated peaks for these three samples. However, for $\beta_{00} = 1$, these three curves have somewhat steeper sides and flatter tops than do single Gaussians. The lack of resolution into two peaks does not imply lack of observable structure. Thus, from the seven sets of data displayed, two are shown to fit the conditions for two resolved peaks, three are shown not to be compatible with the conditions for two resolved peaks, and two must be discarded because of systematic errors that could affect resolution in either direction.

The UPEN program contains further diagnostic means to detect different kinds of data and processing problems. It is suggested that, in circumstances where data problems are likely, processing with UPEN in nearly real time could permit retaking data while a sample is still available.

Acknowledgments

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