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PERFIDI: Parametrically Enabled Relaxation Filters with Double Inversion

Stanislav Sykora ^a, Villiam Bortollotti ^b, Paola Fantazzini ^c

^aExtra Byte, Via Raffaello Sanzio 22C, Castano Primo, Italy I-20022

^bDICMA, University of Bologna, Viale Risorgimento 2, Bologna, Italy I-40100

^cDepartment of Physics, University of Bologna, Viale Berti Pichat 6/2, Bologna, Italy I-40127

Abstract

We present a novel approach to the nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) analysis of complex samples with a non-trivial distribution of longitudinal relaxation rates R_1 . The method, denominated PERFIDI, aims at separating signals arising from components with different R_1 's *prior* to actual data acquisition. Given any standard NMR / MRI pulse sequence, by itself insensitive to differences in R_1 's, it can be combined with a PERFIDI preamble which functions as a preliminary R_1 filter and confers the original technique sensitivity to the R_1 dimension. The article states the principles of the approach, including the way of accounting for instrumental imperfections, and shows how to build PERFIDI filters with specific filter profile functions. Using terms borrowed from electronics, these are classified as low-pass, high-pass and band-pass types. Also included are an experimental verification example and a discussion of potential applications of PERFIDI in various NMR areas.

Keywords: pulse sequence, inversion pulse, spectroscopy, imaging, relaxometry, relaxation, T1, Laplace transform, relaxation filter

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1. Introduction

The concept of PERFIDI [1] is illustrated in Figure 1. Given any 'standard' pulse sequence X, one combines it with a preamble of inversion pulses. The timing of the preamble is varied, using two or more settings, and the acquired data are linearly combined so as to enhance the effect of the preamble-timing differences. In a complex sample exhibiting different longitudinal relaxation rates R_1 (inverse of T_1), the result is a pre-selection of components according their R_1 values.

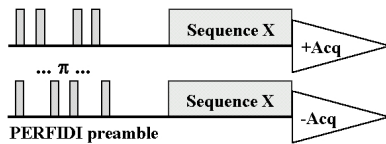


Fig.1. The concept of PERFIDI

It will be shown that PERFIDI introduce the possibility of avoiding some of the mathematical problems connected with Laplace transform inversion.

In general, the category of inversion problems we deal with most often is structured as follows: Let p be a material property and $s(p,t)$ an elementary transient signal from a homogeneous sample corresponding to the particular value of p . In a heterogeneous sample one expects a statistical distribution of the p -values according to a distribution

density function $w(p)$. The experimental signal from such a sample is then given by the integral transform

$$S(t) = \int w(p)s(p,t)dp \quad (1)$$

In practice, we assume $s(p,t)$, measure $S(t)$, and wish to *invert* Eq.(1) to recover $w(p)$. A simple minded solution of such inversion problems [2,3] involves the following steps:

- p and t are digitized following a digitization strategy (lin or log), so that $p \in \{p_i, i = 1,2,\dots,M\}$ and $t \in \{t_j, j = 1,2,\dots,N\}$.
- The integral transform (1) then becomes a matrix equation

$$wK = S, \text{ where} \quad (2)$$

$$w \equiv \{w_i = w(p_i)\} \text{ and } S \equiv \{S_j = S(t_j)\} \text{ and } K \equiv \{K_{i,j} = s(p_i,t_j)\}.$$

- The formal solution of Eq.(2) is

$$w = SK^{-1}. \quad (3)$$

Whether the simple approach can work depends upon the condition number [4] $C_n(K)$ of the kernel matrix K defined as the ratio between the largest (in absolute value) and the smallest singular values of K (singular values of a matrix are its diagonal elements after singular value decomposition). In a sense, $C_n(K)$ defines the noise amplification factor implicit in Eq.(3).

In practice, all kinds of situations arise. Thus in NMR spectroscopy p is the Larmor offset Ω , t is the FID sampling time and $s(p,t) = \exp(i\Omega t)$. This leads to an ortho-normal,

Fourier kernel \mathbf{K} whose condition number is 1, indicating an extremely stable inversion.

In NMR relaxometry, p is identified with a relaxation rate R , t with a pulse-sequence delay τ and $s(p,t) = \exp(-R\tau)$. It turns out that the condition numbers of the resulting Laplace kernels \mathbf{K} are extremely large (e.g., using a log distribution with 64 points spread over 4 orders of magnitudes, a simple Matlab program gives C_n of the order of 10^{20}).

In order to obtain meaningful results, such ill-condition cases [5] must be re-conditioned which, in general, involves a drastic reduction of admissible solutions. The most often used methods are:

- Decrease of the digitization resolution,
- Introduction of suitable *a-priori* knowledge, and
- Penalties on undesired features of $w(p)$.

The Laplace transform inversion is generally carried out by means of damped singular value decomposition [3,6,7] or by iterative fitting combined with various penalties. Hence a range of methods [8-10], of which the most reliable one appears to be UPEN [10].

The driving idea behind PERFIDI is the desire to separate the sample components according to their longitudinal relaxation rate R_1 *prior to data acquisition* rather than doing it mathematically *a-posteriori*.

Conceptually, there is nothing new in this. Virtually all NMR spectroscopy sequences can be in fact intended as a kind of filters on spin-system components possessing a desired characteristic such as a particular coupling pattern.

There are two types of precursors of this approach. In MRI one often uses particular acquisition parameter settings to obtain T_1 -weighed images. This is useful but it is difficult to make it rigorous in a quantitative way, due mostly to B_1 inhomogeneity which causes the efficiency of inversion pulses to vary across the sample. Another precursor consists in zeroing the magnetization of sample components with one or more particular values of T_1 , using one or more inversion pulses and suitable delays. This has two drawbacks: (i) again, it is difficult to achieve zero magnetization across the whole sample due to B_1 inhomogeneity and (ii) forcing the magnetization to be exactly null for selected values of T_1 dramatically decreases the signal magnitude for broad T_1 ranges and thus destroys the S/N ratio.

We present a category of R_1 filters based on a different line of reasoning. Rather than trying to zero the magnetization for some values of R_1 , we follow the analogy of electronic *band-pass* filters, concentrating primarily on the components which 'pass through' rather than those which are 'blocked'.

2. Construction of T_1 filters

To construct the R_1 filter sequences, we *intentionally* use only inversion RF pulses. This bias is motivated by the fact that inversion pulses

- have the largest effect on longitudinal magnetization,
- have a high tolerance to instrumental imperfections,
- produce the smallest amount of offset-related artifacts due to transverse magnetization components,
- can be made more precise by using composite pulses, and
- are compatible with optional, trailing gradient pulses for a more perfect suppression of transverse components.

In order to obtain reliable results we must also take into account the fact that, in practice, an inversion pulse always has a limited efficiency which varies across the sample volume due to B_1 inhomogeneity and other effects. Only taking the inversion pulse efficiency into account can one hope to obtain a method which works reliably under real conditions and on real, often imperfect, instruments.

An elementary inversion-sequence *slice* with an imperfect inversion is shown in Figure 2.

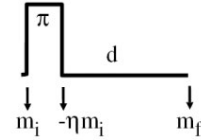


Fig.2. Elementary inversion-sequence slice.

The effect of such a slice on a sample component with relaxation rate r can be viewed as an operator $\mathcal{Q}_\eta(d,r)$ which converts an initial longitudinal magnetization m_i into a final longitudinal magnetization m_f by applying an inversion pulse (π) with inversion efficiency η , followed by a delay d . Explicitly, assuming a unit equilibrium magnetization $m_0 = 1$, the effect of $\mathcal{Q}_\eta(d,r)$ on m_i is

$$m_f = 1 - (1 + \eta m_i) e^{-rd} \quad (4)$$

The inversion-efficiency factors η can assume values ranging from 1 (perfect inversion) to -1 (no effect). In practice one encounters values lying anywhere between 0 and 0.9.

A PERFIDI preamble is a sequence composed of n consecutive elementary slices. Its effect on an initial sample magnetization m_i can be written symbolically as

$$F(r; d_1, d_2, \dots, d_n) \{m_i\} \equiv m_f \\ = \mathcal{Q}_\eta(d_n, r) \{ \dots \{ \mathcal{Q}_\eta(d_2, r) \{ \mathcal{Q}_\eta(d_1, r) \{m_i\} \} \} \}. \quad (5)$$

This leads to a recurrence relation with respect to n which admits an explicit solution. Putting $m_i = 1$ (i.e., starting with a relaxed sample), the solution can be written as:

$$F(r; d_1, d_2, \dots, d_n) \\ = 1 - (1 + \eta) \sum_{k=0}^{n-1} (-\eta)^k \exp(-r \sum_{j=n-k}^n d_j). \quad (6)$$

Notice that $F(r; d_1, d_2, \dots, d_n)$ is a polynomial with respect to the efficiency factor η .

To make the filter effect on components with the same value of r the same in every part of the sample, we should try to separate the effects of η from those of r . In other words, we need to achieve a factorization of the type

$$F(r; d_1, d_2, \dots, d_n) \equiv F(r, \{d_k\}) = E(\eta) f(r, \{d_k\}), \quad (7)$$

where $E(\eta)$ is a global efficiency factor independent of r and $f(r, \{d_k\})$ is an η -independent *filter profile*.

In general, the factorization is done by means of linear combinations (typically just sums and differences) of data acquired in separate scans in which the PERFIDI sequences assume different values for some intervals. The desired effect is the elimination of all the terms but one in the η -polynomial of Eq.(6).

3. A two-pulse PERFIDI filter



To see how this can be achieved, consider the simplest PERFIDI preamble composed of just two elementary slices (Figure 3).

Fig.3. Two-pulse PERFIDI sequence.

The first delay alternates between two different values upon alternate scans.

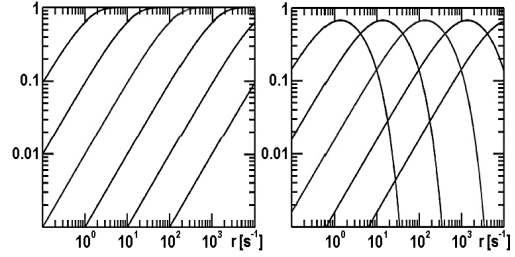
If one acquires two scans using the same delay d_2 in the second slice but different delays d_1 and D_1 in the first slice and subtracts the two data sets, the effect on a sample component with relaxation rate r is

$$F(r; d_1, d_2) - F(r; D_1, d_2) = \eta(1 + \eta) f_2(r; D_1, d_1, d_2), \quad (8)$$

Where

$$f_2(r; D_1, d_1, d_2) = (e^{-rd_1} - e^{-rD_1}) e^{-rd_2}. \quad (9)$$

Selecting different values of the delays D_1, d_1 and d_2 one can modify the filter profile in various ways. Figure 4 shows

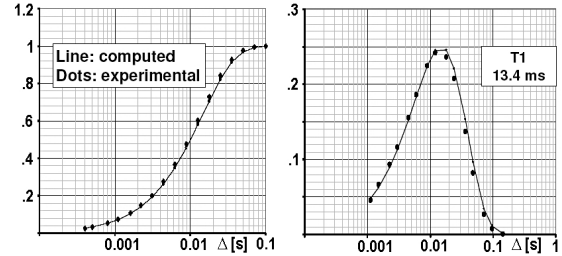


two sub-families of such filters. Each profile curve refers to a particular value of a single parameter Δ to which the delays d_1 and D_1 are proportional (d_2 is kept equal to zero).

Fig.4. Some two-pulse PERFIDI filter profiles. Horizontal axis: r . Vertical axis: $f_2(r, D_1, d_1, d_2)$ with $d_2 = 0$. Left graph: $d_1=0$, $D_1=\Delta$. Right graph: $d_1=0.15\Delta$, $D_1=0.85\Delta$. Δ is 1 second for the leftmost curve and decreases by 10 from left to right.

4. Experimental verification

Figure 5 shows the results of a verification of the effects of a two-pulse PERFIDI filter on a mono-exponential test



sample. The high degree of agreement ($\sim 1\%$) would be impossible to achieve had we not taken into account the limited inversion efficiency (η was in this case about 0.85).

Fig.5. Experimental verification of two-pulse PERFIDI filter. Sample: H_2O doped with Cu-EDTA; mono-exponential. Vertical axis: signal sampled by a 90° pulse just after the PERFIDI sequence and normalized with respect to a completely relaxed 90° pulse response. Horizontal axis: Δ . Filter settings: $d_2 = 0$; left graph: $d_1 = 0$, $D_1 = \Delta$; right graph: $d_1 = 2\Delta/3$, $D_1 = 4\Delta/3$. Solid lines connect calculated (theoretical) points, dots indicate experimental data.

A complete verification requires an extensive study which exceeds the scope of this presentation (in progress).

5. Principal features of PERFIDI filters

The following features of the PERFIDI filters are evident:

- The filter profiles depend only upon exactly known delays and not at all upon sample properties (specific values of T_1), nor upon instrumental factors (B_1 inhomogeneity).
- There is a close analogy between the relaxation filters and the frequency filters in electronics. In particular, we can distinguish between low-pass, high-pass and band-pass filter types.
- On a log(r) scale, simultaneous scaling (multiplication) of all delays of a PERFIDI filter shifts the filter profile left or right while leaving its shape intact.
- There are no zero-crossings, just attenuation's.

6. Examples of higher order filters

Using more than two elementary inversion slices opens the doors toward ever narrower filters with steeper slopes. When the number of inversion pulses increases, so does the number of possible factorization solutions.

The simplest of these consist in applying N cascaded two-pulse filters for a total of $2N$ inversion pulses. Naturally, it then takes 2^N separate scans to run through all the required delay-alternation settings but, as visible in the graphs, one ends up with filters whose cut-off regions exhibit 10N dB/decade slopes.

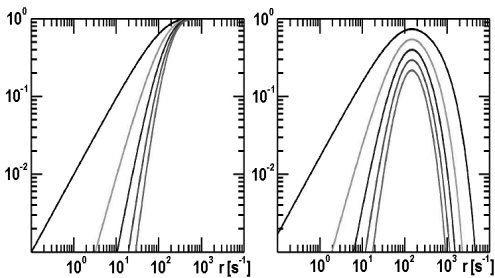


Fig.6. Examples of PERFIDI relaxation filters obtained by cascading 1 to 5 two-pulse filters, all of the type shown in Fig.4 for $\Delta = 10$ ms. Notice the increasing slope of the cut-off edges, the narrowing of the pass-through band and, in the case of band-pass filters, the decrease of center-band sensitivity.

For lack of space, we can not discuss phase cycling and the way it can be intertwined with delay-cycling. Likewise, we have to postpone the discussion of the use of gradient pulses for a better suppression of transversal components.

7. Exploitation of PERFIDI

Due to the fact that they can be combined with almost all established sequences, PERFIDI are bound to find useful applications in all branches of NMR.

Consider the simple example of PERFIDI combined with the plain 1D spectroscopy experiment. By carrying out a series of PERFIDI measurements with filters like those shown in Fig.4 and varying Δ , one obtains a 2D data set in which one axis is the usual spectral offset while the other is essentially the relaxation rate. The result is reminiscent of the Diffusion Ordered Spectroscopy (DOSY) sequence but with R_1 replacing the diffusion rate.

In MRI, PERFIDI open the following possibilities:

- Pre-selection of tissues according to T_1 .
- Enhanced contrast in the neighborhood of a particular value of T_1 (by working on the slope of a PERFIDI filter).
- Reinforcement of the effects of contrast agents.
- Reduction of the required amounts of contrast agents.

In NMR relaxometry, the advantages include:

- Pre-selection of a relaxation rate interval in routine essays.
- Splitting the total range of relaxation-range values into narrower sub-intervals before analysis by means of UPEN or similar algorithms.

An exciting possibility is related to the fact that the relaxation inversion kernel K^P for data obtained using PERFIDI is better behaved (its condition number is orders of magnitude smaller) than the plain Laplace inversion kernel K^L . It follows that PERFIDI can substantially improve the reliability and resolution of experimentally determined relaxation-rate distribution curves. Further verification and exploitation of this fact is underway and will be presented elsewhere.

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For more information, see the site: www.perfidi.net.

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