Multi-Regularization Reconstruction of One-Dimensional $T_2$ Distributions in Magnetic Resonance Relaxometry with a Gaussian Basis

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We consider the inverse problem of recovering the probability distribution function of $T_2$ relaxation times from NMR transverse relaxometry experiments. This problem is a variant of the inverse Laplace transform and hence ill-posed. We cast this within the framework of a Gaussian mixture model to obtain a least-square problem with an $L_2$ regularization term. We propose a new method for incorporating regularization into the solution; rather than seeking to replace the native problem with a suitable mathematically close, regularized, version, we instead augment the native formulation with regularization. We term this new approach ‘multi-regularization’; it avoids the treacherous process of selecting a single best regularization parameter $\lambda$ and instead permits incorporation of several degrees of regularization into the solution. We illustrate the method with extensive simulation results as well as application to real experimental data.

1 Introduction

1.1 Inverse Problems in Magnetic Resonance

In the study of magnetic resonance (MR) and magnetic resonance imaging (MRI), measurements and determination of $T_2$ relaxation times by magnetic resonance spectroscopy (MRS) is one of the main applications. Physically speaking, $T_2$ relaxation time represents the time constant for decay of transverse magnetization for specific tissue in atomic levels, therefore, due to the fact that different materials possess their unique $T_2$ values, the inverse problem is then considered to be recovering those values from data acquired by the noninvasive MR tests. Signals obtained from measurement usually exhibit behaviors of mono- or multi-exponential decay whose governing equation can be initially expressed as weighted summation of exponential functions:

$$y_{ob}(t) = \sum_{i=1}^{M} c_i e^{-t/T_{2,i}}$$

(1.1)

where $c_i$ and $T_{2,i}$ represent characteristics (concentration and relaxation time) of the $i$-th material in the sample. The addition parameter $M$ denotes the pre-determined number of components.
As an alternative to the model in Eq. (1.1), a more general representation in the form of Fredholm integral equation of the first kind, is introduced:

\[ y_{ob}(t) = \int_{T_{2,\text{min}}}^{T_{2,\text{max}}} G(t, T_2) f(T_2) dT_2 \]  

(1.2)

where \( G(t, T_2) = e^{-\frac{t^2}{T_2}} \) is called the kernel and \( f(T_2) \geq 0 \) is called the \( T_2 \) relaxation time distribution. As a consequence, Eq. (1.1) can be seen as a special case for Eq. (1.2) where the \( T_2 \) distribution \( f(T_2) \) becomes summation of \( M \) Dirac Delta functions at \( T_2 = T_{2,i} \). On the other hand, Equation (1.2) can also be recognized as a truncated Laplace transform, whose inverse transform is a well-known ill-posed problem. In this case, the associated inverse problem is to determine the distribution \( f(T_2) \) given discrete measurements from \( y_{ob}(t) \). Practically, the observable data \( y_{ob} \in \mathbb{R}^m \) comes as discretized values and the goal is to determine a discretized version of the \( T_2 \) distribution \( f_{\text{true}} \in \mathbb{R}^n \) subject to the forward map

\[ y_{ob} = A f + n, \quad f \geq 0 \]  

(1.3)

where \( A \in \mathbb{R}^{m \times n} \) is the kernel matrix with entries \( A_{i,j} = e^{-\frac{t_i^2}{T_{2,j}}} \Delta T_2 \), and \( n \) is denoted as additive noise. The positivity constraint \( f \geq 0 \) is physically intrinsic in the sense that, all \( T_2 \) values of any material are always non-negative. Inheriting the smoothing property of the integral operator in (1.2), \( A \) is a smoothing operation whose condition number can be so large that any direct inversion without regularization such as using pseudo-inverse or non-negative least squares (NNLS) can be extremely unstable.

From the perspective of inverse problems, determination of discrete \( T_2 \) distribution \( f \) can be seen as a constrained version of inverse Laplace transform and integral equation whose ill-posedness can be often addressed by regularizations. And in inverse problems, Tikhonov-typed Regularization is often considered as a powerful tool in stabilizing such ill-posedness. It is performed by minimizing the cost function involving observable data and one regularization term which requires a regularization parameter \( \lambda \). The regularization parameter needs to be appropriately chosen so as to reach a balance between the model error and solution norm.

1.2 Methods of Parameter Selection

In magnetic resonance applications, the classical Tikhonov regularization of reconstructing \( f \) given \( A \) and \( y_{ob} \), reads

\[ f_\lambda = \text{argmin}_{f \geq 0} \left\{ \|A f - y_{ob}\|_2^2 + \lambda^2 \|f\|_2^2 \right\}. \]  

(1.4)

Again the regularization parameter \( \lambda \) acts as a trade-off between the the size of regularized solutions and the fit to observable data. Additionally, prior knowledge of the solution \( f \), such as sparsity or smoothness that depends on the actual application, can be applied to the minimization problem by varying the regularizing term \( \|f\|_2 \) to \( \|f\|_p \), with \( p \geq 1 \) in most cases.

In Tikhonov regularization, the problem of selecting \( \lambda \) has been studied for decades, however, there is no universal approach. Classical methods such as L-curve [11, 10, 8, 9, 3], generalized cross-validation (GCV) [5, 19, 20], discrepancy principle (DP) [13, 14, 15] and so on are used to choose one \( \lambda \) by certain criteria. For example, in L-curve method, the optimal \( \lambda \) lies near the corner of the L-shaped curve practically, and the L-curve is the log-log plot of the solution norm against residual norm; Selecting \( \lambda \) using GCV is to locate the minimum of the GCV function; DP seeks \( \lambda \) such that the residual norm is proportional to the norm of noise by a fixed constant. All existing parameter selection methods seek only one optimal \( \lambda \) and its corresponding regularized solution, and discard all others obtained from regularization with different values of \( \lambda \). A survey of the methods can be found in [1]. Distinct from all current methods, we propose a new method termed Multi-Regularization (Multi-Reg) in section 2. Recovered approximation by Multi-Reg is formed by a linear combination of regularized solutions across a range of proposed \( \lambda \)'s, as oppose to selecting one \( \lambda \) and its associated approximation.
1.3 Gaussian Mixture Model and Application to Determining $T_2$ Distributions

Gaussian mixture model is an approach of representing a probability density function by a weighted sum of Gaussian distribution functions [17]. Gaussian mixture models are often considered as a means of unsupervised learning problems where a cluster of data is assumed to be governed by a Gaussian density function $g(\mu_i, \sigma_i)$, with $\mu_i$ and $\sigma_i$ represent the mean and standard deviation of a single Gaussian density in one dimension. In the application of determining the one-dimensional $T_2$ relaxation distribution, the idea of representing the distribution $f(T_2)$ in terms of a weighted sum of Gaussian density functions, is to solve for the unknowns $\mu_i, \sigma_i$ so that the problem of determining a $T_2$ distribution can be formed as an non-linear least squares problem:

$$\{\sigma_i, \mu_i\}_{i=1}^M = \arg\min_{\{\sigma_i, \mu_i\}} \|y_{ob} - A \sum_{i=1}^M g(\sigma_i, \mu_i)\|_2^2$$

(1.5)

where $g(\sigma_i, \mu_i)$ denote the discretized Gaussian density function with standard deviation $\sigma_i$ and mean $\mu_i$. This approach has the advantage of significantly reducing the size of unknowns [16]. However, this nonlinear form requires heavily on the prior knowledge of how many Gaussian functions are needed to represent the end distribution, and the intrinsic ill-posedness of the linear problem in Eq. (1.3) is altered, which is beyond the scope of study in this paper.

Instead, it is still possible to treat the problem of determination of $T_2$ distribution based on the Gaussian mixture assumption as simply a least squares problem by providing a dictionary of Gaussian functions to choose from:

$$c^* = \arg\min_{c \geq 0, \sum_i c_i = 1} \|y_{ob} - (AG)c\|_2^2,$$

(1.6)

where columns of matrix $G$, termed $\{g_i\}$, represent different Gaussian distributions and $c$ is the vector of coefficients assigned to each proposed distribution. The least squares problem is then considered as finding the coefficients of the proposed Gaussian distribution functions such that problem (1.6) is satisfied.

The problem is usually severely ill-posed due to the non-orthogonality of Gaussian functions that form the dictionary, and can lead to extremely unstable solutions.

2 Multi-Reg: Multi-Regularization method

2.1 Intuition

In general, in the case of a given underlying function $f_{true} \geq 0$, a common procedure of simulation aims to test the performance of a certain parameter selection method, is performed following the steps below:

1. Generate noiseless observation: $y_{clean} = Af_{true}$.
2. Manually add noise with pre-selected SNR: $y_{noisy} = y_{clean} + n$.
3. Solve Tikhonov regularization problem (1.4) with different proposed $\lambda_j$ to get regularized solution $f_{\lambda_j}$.
4. Choose one regularized solution $f_{\lambda^*}$ according to certain parameter selection method.
5. Compare the end result $f_{\lambda^*}$ with the underlying distribution $f_{true}$.

The common ground for all existing parameter selection methods is that, the “optimal” parameter is chosen among a list of proposed values and the associated regularized solution follows. That is the same way to say that, in the view of all proposed regularized solutions, existing methods assign coefficients $[0, 0, \cdots, 0, 1, 0, \cdots, 0]$ to the candidates, in which at index $i$, the $i$-th regularized solution is selected. However, in general, there is no best method of parameter selection, and depending on the actual applications of the inverse problems, various methods perform differently. This means that there is no guarantee that
the selected $i$-th regularized solution according to a conventional method ought to be the optimal while other methods might return different values.

To put the problem of parameter selection in a greater framework, that is, the end solution is considered to be a vector of coefficients assigned to different regularized solutions. So the end solution is not restricted to sparse solutions such as $[0, 0, \cdots, 0, 1, 0, \cdots, 0]$. Providing that $f_{\text{true}}$ is given, we can certainly obtain better recovery than classical parameter selection methods for (1.4) with a little help of “cheating”, which is by solving for $\{\alpha_j\}_1^N$ that satisfy

$$f_{\text{true}} \approx \sum_{j=1}^{N} \alpha_j f_{\lambda_j}$$

(2.1)

where $\{\alpha_j\}_1^N$ solve the following least square problem

$$(\alpha_1, \alpha_2, \cdots, \alpha_N) = \arg\min_{\alpha \geq 0} \left\| f_{\text{true}} - \sum_{j=1}^{N} \alpha_j f_{\lambda_j} \right\|^2$$

(2.2)

In other words, from the perspective of Eq. (2.2), all traditional parameter selection methods only arrive at a single regularized solution $f_J$ that corresponds to special choices of $\{\alpha_j\}_1^N$ where $\alpha_J = 1$ for some $J$ and all other $\alpha_j = 0$ for $j \neq J$. Given the observation above, we wonder if similar idea can be applied to this inverse problem in practice where $f_{\text{true}}$ is not known, as a result, the problem now becomes to determine $\{\alpha_j\}_1^N$ while the underlying $f_{\text{unknown}}$ is not given:

$$f_{\text{unknown}} \approx \sum_{j=1}^{N} \alpha_j f_j$$

(2.3)

In addition to regarding $\{f_j\}_1^N$ as one set of representing functions for $f_{\text{unknown}}$ as in (2.3), we also take advantage of the assumption that $f_{\text{unknown}}$ can be represented by linear combinations of Gaussian functions $\{g_i\}_1^M$ in order to be consistent with the non-negativity $f_{\text{unknown}} \geq 0$. Therefore the other representation of $f_{\text{unknown}}$ yields

$$f_{\text{unknown}} = \sum_{i=1}^{M} c_i g_i$$

(2.4)

Additional information maybe available depending on the applications. For MR relaxometry, $f(T_2)$ is regarded as a probability distribution of $T_2$ times, whose integral over the whole $T_2$ space equals 1. In Eq. (2.4) this means $\sum_{i} c_i = 1$. To link the two expressions (2.3) and (2.4), we propose to approximate the regularized solutions $f_{\alpha_j}$ as a linear combination of the regularized solutions $\{g_{ij}\}_1^N$, where noise polluted Gaussian $g_{ij}$ is obtained after step 1 - 3 for each Gaussian function $g_i$ with respect to $\lambda_j$.

2.2 Multi-Reg method with prior information of Gaussian sums

2.2.1 Theory

Given noisy observation $y_{\text{ob}} \in \mathbb{R}^m$, we obtain the regularized solutions $f_j =: A_{\lambda_j}^{-1} y_{\text{ob}}$ (as a short of $f_{\lambda_j}$) by solving (1.4). Note that the inversion operator $A_{\lambda_j}^{-1}$ is symbolic and not the usual form of pseudoinverse because of the non-negativity constraints. We first assume the underlying distribution $f_{\text{unknown}}$ can be written as a linear combination of $f_j$, and the goal is to seek coefficients $\{\alpha_j\}_1^N$ as well as $f_{\text{unknown}}$ according to

$$f_{\text{unknown}} \approx \sum_{j=1}^{N} \alpha_j f_j =: f_{\alpha}$$

(2.5)

and note that both $f_{\text{unknown}}$ and $\alpha_j$ need to be determined.
In addition, if a Gaussian distribution \( g_i \in \mathbb{R}^n \) is provided, it can be approximated as a linear combination \( g_{ij} \in \mathbb{R}^n \), which are regularized solutions after the procedure \( g_i \rightarrow Ag_i \rightarrow Ag_i + n \rightarrow g_{ij} \) or simply written as
\[
g_{ij} = A^{-1}_{\lambda_j} (Ag_i + n). \tag{2.6}
\]
Then follow the intuition of Multi-Reg
\[
g_i \approx \sum_{j=1}^{N} \beta_{ij} g_{ij} \tag{2.7}
\]
where random noise realizations \( n \) share the same SNR tailored to the experimental data \( y_{ob} \). In fact, as \( n \) is random, the corresponding \( g_{ij} \) and \( \beta_{ij} \) are random variables whose values differ for each different \( n \). So we average both \( g_{ij} \) and \( \beta_{ij} \) over \( n \) run times of noise realizations to get the mean values of \( g_{ij} \) and \( \beta_{ij} \).

Numerically the coefficients \( \beta_{ij} \) can be obtained by solving the LS problem
\[
\beta_{ij} = \arg \min_{\beta_{ij} \geq 0} \left\| g_i - \sum_{j=1}^{N} \beta_{ij} g_{ij} \right\|, \quad i = 1, 2, \ldots, M \tag{2.8}
\]
Using the presumptive representation for our distribution \( f_{unknown} \) that can be seen as sum of proposed Gaussian functions \( \{g_i\}_{i=1}^{M} \), we have
\[
f_{unknown} \approx \sum_{i=1}^{M} c_i g_i =: f_c \tag{2.9}
\]
and note that coefficients \( c_i \) need to be determined since \( f_{unknown} \) is not known. By the assumption of (2.9) that the original distribution is represented in terms of Gaussian functions, we can further assume each regularized recovery \( f_j \) can be represented by regularized solutions \( g_{ij} \) as well:
\[
f_j \approx \sum_{i=1}^{M} x_{ij} g_{ij} \tag{2.10}
\]
so coefficients \( x_{ij} \) satisfy the following LS problem, where each minimization is over index \( i \) with one minimization problem for each \( j \):
\[
x_{ij} = \arg \min_{x_{ij} \geq 0} \left\| f_j - \sum_{i=1}^{M} x_{ij} g_{ij} \right\|, \quad j = 1, 2, \ldots, N \tag{2.11}
\]
In conclusion, once the dictionary of Gaussian distributions \( \{g_i\}_{i=1}^{M} \) is defined and given the noisy data \( y_{ob} \), and the statistics of the noise in the experiment is known, we would be able to calculate the sets of coefficients \( \{\beta_{ij}\} \) and \( \{x_{ij}\} \) from the regularized solutions \( \{f_j\} \) and \( \{g_{ij}\} \) and our task becomes to seek coefficients \( \{\alpha_j\}_{j=1}^{N}, \{c_i\}_{i=1}^{M} \) in (2.5) and (2.9).

Now equating the equations (2.5) and (2.9) together with (2.7) and (2.10), we arrived at an equation in terms of the obtained variables \( \beta_{ij}, x_{ij} \) and \( g_{ij} \):
\[
\sum_{j=1}^{N} \alpha_j f_j \approx \sum_{i=1}^{M} c_i g_i \tag{2.12}
\]
\[
\Rightarrow f_{\alpha} = \sum_{j=1}^{N} \alpha_j \sum_{i=1}^{M} x_{ij} g_{ij} \approx \sum_{i=1}^{M} c_i \sum_{j=1}^{N} \beta_{ij} g_{ij} = f_c
\]
Then we can solve for \( \alpha_j \) and \( c_i \) at the same time by solving the following LS problem
\[
\begin{cases}
(\alpha^*, c^*) = \arg \min ||f_{\alpha} - f_c||_2 \\
\text{subject to } \alpha^* \geq 0, \ c^* \geq 0, \text{ and } \sum_i c_i^* = 1,
\end{cases} \tag{2.13}
\]
note that the solution \((\alpha^*, c^*)\) is unique, provided the additional equality constraint on \(\sum_{i=1}^{M} c_i^* = 1\).

Hence the final recovery \(f^*\) will be

\[
  f^* = \sum_{j=1}^{N} \alpha_j f_j \quad \text{or} \quad f^* = \sum_{i=1}^{M} c_i g_i
\]

(2.14)

### 2.2.2 Numerical Implementation

Before diving into the detailed computations, some notations shall be declared:

\[
  \mathbf{L}_\alpha = \begin{bmatrix} \mathbf{g}_{11} & \mathbf{g}_{21} & \cdots & \mathbf{g}_{M1} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{g}_{1N} & \mathbf{g}_{2N} & \cdots & \mathbf{g}_{MN} \end{bmatrix} \in \mathbb{R}^{M \times MN}
\]

(2.15)

\[
  \mathbf{L}_c = \begin{bmatrix} \mathbf{g}_{11} & \mathbf{g}_{12} & \cdots & \mathbf{g}_{1N} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{g}_{M1} & \mathbf{g}_{M2} & \cdots & \mathbf{g}_{MN} \end{bmatrix} \in \mathbb{R}^{M \times MN}
\]

(2.16)

note that the column size of \(\mathbf{L}_\alpha\) is \(MN\) and \(\mathbf{L}_c\) is \(MN\), the row size of two matrices are the same, which is the number of nods for \(T_2\).

\[
  \mathbf{x}_{\text{vec}} = \begin{bmatrix} x_{11} & x_{21} & \cdots & x_{M1} \\ \vdots & \vdots & \ddots & \vdots \\ x_{1N} & x_{2N} & \cdots & x_{MN} \end{bmatrix} \in \mathbb{R}^{MN}
\]

(2.17)

\[
  \beta_{\text{vec}} = \begin{bmatrix} \beta_{11} & \beta_{12} & \cdots & \beta_{1N} \\ \vdots & \vdots & \ddots & \vdots \\ \beta_{M1} & \beta_{M2} & \cdots & \beta_{MN} \end{bmatrix} \in \mathbb{R}^{MN}
\]

(2.18)

where the sizes of \(\mathbf{x}_{\text{vec}}\) and \(\beta_{\text{vec}}\) are same as number of columns for \(\mathbf{L}_\alpha\) and \(\mathbf{L}_c\), respectively.

\[
  \mathbf{c}_{\text{vec}} = \begin{bmatrix} c_1 & c_1 & \cdots & c_1 \\ \vdots & \vdots & \ddots & \vdots \\ c_M & c_M & \cdots & c_M \end{bmatrix} \in \mathbb{R}^{MN}
\]

(2.20)

where \(\mathbf{c}_{\text{vec}} \in \mathbb{R}^{MN}\) and \(\mathbf{c}_{\text{vec}} \in \mathbb{R}^{MN}\) share the same size with \(\mathbf{x}_{\text{vec}}\) and \(\beta_{\text{vec}}\) as well.

According to (2.5) and (2.9)

\[
  \mathbf{f}_\alpha = \mathbf{L}_\alpha \cdot \text{diag} (\mathbf{x}_{\text{vec}}) \cdot \mathbf{c}_{\text{vec}}
\]

(2.21)

\[
  \mathbf{f}_c = \mathbf{L}_c \cdot \text{diag} (\beta_{\text{vec}}) \cdot \mathbf{c}_{\text{vec}}
\]

(2.22)

hence the minimization problem (2.13) can be explicitly written as

\[
  \begin{cases}
  (c^*, \alpha^*) = \arg\min \| \mathbf{L}_\alpha \cdot \text{diag} (\mathbf{x}_{\text{vec}}) \cdot \mathbf{c}_{\text{vec}} - \mathbf{L}_c \cdot \text{diag} (\beta_{\text{vec}}) \cdot \mathbf{c}_{\text{vec}} \|_2 \\
  \text{subject to } c_i \geq 0, \alpha_j \geq 0, \sum_i c_i = 1
  \end{cases}
\]

(2.23)

Assume the solution is stacked in the form of

\[
  \mathbf{s} = [\alpha_1, \alpha_2, \cdots, \alpha_N, c_1, c_2, \cdots, c_M]^T \in \mathbb{R}^{N+M}
\]

(2.24)

problem (2.23) can be further simplified to the classical form of constrained least square problem: find \(\mathbf{s}^* \in \mathbb{R}^{N+M}\) such that

\[
  \begin{cases}
  \mathbf{s}^* = \arg\min_{\mathbf{s} \geq 0} \| \mathbf{B} \mathbf{s} \|_2 \\
  \text{such that } \sum_{j=N+1}^{N+M} s_j = 1
  \end{cases}
\]

(2.25)

where

\[
  \mathbf{B} = \mathbf{L}_\alpha \cdot \text{diag} (\mathbf{x}_{\text{vec}}) \cdot \mathbf{T} \mathbf{T}_\alpha - \mathbf{L}_c \cdot \text{diag} (\beta_{\text{vec}}) \cdot \mathbf{T} \mathbf{T}_c \in \mathbb{R}^{m \times (N-1+M)}
\]

(2.26)

\[
  \mathbf{T} \mathbf{T}_\alpha = \mathbf{I}_N \otimes \begin{bmatrix} 1 \\ \vdots \\ 1 \\ \vdots \\ 1 \end{bmatrix}_{M}
\]

(2.27)
\[ \mathbf{T}_c = \mathbf{I}_M \otimes \begin{bmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{bmatrix} \cdot [\mathbf{0}_{M \times N} \quad \mathbf{I}_M] \in \mathbb{R}^{MN \times (N+M)} \]  

(2.28)

Remarks:

1. The computational procedure can be divided into two parts: offline computation and online computation. For offline computation, \( \{g_i\}, \{g_{ij}\} \) and \( \{\beta_{ij}\} \) will be determined for only once. As for online part, each time a noisy measurement \( y_{ob} \) is given, the corresponding \( \{f_j\}, \{x_{ij}\} \) and \( (c^*, \alpha^*) \) can be obtained and final recovery is denoted as (2.14).

2. To solve for \( \{\beta_{ij}\} \) in (2.7), note that \( g_{ij} \) depends on the noise and for a fixed \( g_i \), the resulted \( \beta_{ij} \) depends on the added noise \( n \) as well, in other words, both \( g_{ij} \) and \( \beta_{ij} \) are actually random variables. One could perform the same task described in (2.7) for \( n_{run} \) times and take the mean values for \( g_{ij} \) and \( \beta_{ij} \).

The pseudocode for offline and online computations read as follows:

**Algorithm 1: Offline Computation**

**Data:** Pre-determined \( \{\lambda_j\}, \{g_i\}, n_{run} \) and noise SNR

**Result:** \( \{g_{ij}\} \) and \( \{\beta_{ij}\} \) to be stored

initialization;

for \( k = 1, 2, \cdots, n_{run} \) do

for \( i = 1, 2, \cdots, M \) do

\( y_{(i)}^{\text{clean}} = A g_i; \)
\( y_{(i)}^{\text{noisy}} = y_{(i)}^{\text{clean}} + n; \)

for \( j = 1, 2, \cdots, N \) do

\( g_{ij} = \text{argmin}_{g \geq 0} \left\{ \|Ag - y_{(i)}^{\text{noisy}}\|_2^2 + \lambda_j^2 \|g\|_2^2 \right\}; \)

end

end

Average \( g_{ij} \) to get \( g_{ij} \);

\( \beta_{ij} = \text{argmin}_{\beta_{ij} \geq 0} \left\| g_i - \sum_{j=1}^N \beta_{ij} g_{ij} \right\|_2. \)

end

**Algorithm 2: Online Computation**

**Data:** \( y_{ob}, \{\lambda_j\}, \{g_{ij}\}, \{\beta_{ij}\} \)

**Result:** \( f^* \)

initialization;

for \( j = 1, 2, \cdots, N \) do

\( f_j = \text{argmin}_{f \geq 0} \left\{ \|Af - y\|_2^2 + \lambda_j^2 \|f\|_2^2 \right\}; \)
\( x_{ij} = \text{argmin}_{x_{ij} \geq 0} \left\| f_j - \sum_{i=1}^M x_{ij} g_{ij} \right\|_2; \)

end

\((c^*, \alpha^*) = \text{argmin}_{c, \alpha \geq 0, \sum_i c_i = 1} \left\| \sum_{j=1}^N \alpha_j \sum_{i=1}^M x_{ij} g_{ij} - \sum_{i=1}^M c_i \sum_{j=1}^N \beta_{ij} g_{ij} \right\|_2; \)

\( f^* = \sum_j \alpha_j^* f_j \) or \( f^* = \sum_i c_i^* g_i \).
3 Case study: inversion of one-dimensional continuous NMR relaxometry

The one-dimensional continuous NMR relaxometry signal admits the form [2, 12, 21, 6]

\[ y_{\text{ob}}(t) = \int_0^\infty e^{-\frac{t}{T_2}} f_{\text{true}}(T_2) \, dT_2 + n(t) \]  

(3.1)

\( y_{\text{ob}}(t) \) denotes the observational signal at time \( t \), \( T_2 \) are relaxation times, \( f_{\text{true}}(T_2) \geq 0 \) denotes the continuous \( T_2 \) distribution function and \( n(t) \) is the additive Gaussian noise for which the statistics of the noise can be obtained. The truncated forward problem of (3.1)

\[ y_{\text{ob}}(t) = \int_{T_{\text{start}}}^{T_{\text{end}}} e^{-\frac{t}{T_2}} f_{\text{true}}(T_2) \, dT_2 + n(t) \]  

(3.2)

can be discretized as (1.3)

\[ y_{\text{ob}} = Af_{\text{true}} + n, \quad f_{\text{true}} \geq 0 \]  

(3.3)

where \( y_{\text{ob}} \in \mathbb{R}^m, f_{\text{true}} \in \mathbb{R}^n, n \in \mathbb{R}^n \), and entries of matrix \( A \in \mathbb{R}^{m \times n} \) is given by \( A_{ij} = e^{-\frac{t_j}{T_2}} \Delta T_2 \). In this case, we define the SNR of the noise as follows

\[ \text{SNR} = \frac{\max |y_{\text{ob}}|}{\text{RMS}(n)} \]  

(3.4)

Gaussian Mixture Model (GMM) is considered as a powerful tool to represent an arbitrary probability distribution by a weighted sum of Gaussian distributions [16, 4, 7] and GMM works for reconstruction of \( T_2 \) distribution because of the nature of non-negativity for \( f_{\text{true}} \). Therefore the associated inverse problem to (1.3) for Multi-Reg is

\[ f_j = \arg\min_{f \geq 0} \left\{ \|Af - y_{\text{ob}}\|_2^2 + \lambda_j^2 \|f\|_2^2 \right\} \]  

(3.5)

subject to the prior information that \( f \) can be represented as a linear combination of Gaussian distributions.

3.1 Study of parameter settings for implementation of Multi-Reg

In order to proceed with the offline computation, a few parameters need to be pre-determined, such as the number of regularization parameters \( N \), number of Gaussian functions \( M \), choice of Gaussian functions \( g_i \), and the number of noise realizations \( n_{\text{run}} \) added in the time-domain representation for each simulated distribution in (2.6).

We use the following biexponential form of \( f_{\text{sim}}(T_2) \) in the \( T_2 \) domain for simulation

\[ f_{\text{sim}}(T_2) = \frac{1}{\sqrt{2\pi}\sigma_1^2} e^{-\frac{(T_2-\mu_1)^2}{2\sigma_1^2}} + \frac{1}{\sqrt{2\pi}\sigma_2^2} e^{-\frac{(T_2-\mu_2)^2}{2\sigma_2^2}} \]  

(3.6)

where \( \mu_1 \) is set to 20ms, and \( \mu_2 \) is determined by the ratio of peak separation (RPS) \( \frac{\mu_2}{\mu_1} \), which consists of 8 evenly spaced values between 1 and 8; \( \sigma_1 = \sigma_2 \) which contains 10 evenly spaced values between 2 and 8. There are \( 8 \times 10 = 80 \) different biexponential distributions in total.

Discretized \( T_2 \) values consist \( n = 200 \) evenly spaced nodes within the range \([1, 200]\). The discretized time-domain signal \( y_{\text{sim}} \) for truncated forward problem

\[ y_{\text{sim}} = Af_{\text{sim}} + n \]  

(3.7)

is defined on \( t \in [0.3, 800] \) with \( m = 150 \) evenly spaced nodes, with \( A_{ij} = e^{-\frac{t_j}{T_2}} \). The SNR of the additive noise is set to be 500. For the Tikhonov regularization (3.5) used in Multi-Reg, the range of regularization parameter is from \( 10^{-6} \) to 10.
To test performance of Multi-Reg on the 80 simulated signals $y_{\text{sim}}$, we represent the simulation result using heat maps to indicate the relative error over a wide range of Gaussian peak separations and widths where the relative error is defined as

$$
\varepsilon = \frac{\|f^* - f_{\text{sim}}\|_2}{\|f_{\text{sim}}\|_2}
$$

(3.8)

where $f^*$ is the reconstructed distribution using Multi-Reg [18]. Moreover, the criteria for evaluating the performance of each setting for Multi-Reg is the mean value of the heat map matrix (where the $(i,j)$-th element of the matrix stands for the relative error corresponds to the $i$-th $\sigma$ and $j$-th RPS).

To achieve good settings of Multi-Reg, we study different possible configurations of the dictionary $\{g_i\}_1^M$ by varying the total number $M$, the standard deviations $\sigma_k$ for the Gaussian functions, as well as the number of regularization parameters $n_\lambda$, and number of repetitive tests $n_{\text{run}}$. Since there are infinite such compositions, there is no way to analyze each possible configuration numerically, so we tested a few possible different settings and pick the one that has the smallest mean error of the heatmaps. In general, we tested 7 groups of dictionaries, for each dictionary $\{g_i\}_1^M$ in group $k$, the standard deviations $\sigma_k$ of all Gaussian functions $g_i$ equals $k$, and the mean values of all Gaussian distributions are set to be equally spaced along the $T_2$ axis depending on the number $M$, which means that, as $M$ increases, the mean values of Gaussian functions become closer. For each group, we tested various settings, as are shown below.

### 3.1.1 Choosing $M$

Different $M$ in the finite set $\{g_i\}_1^M$ with uniform standard deviation $\sigma_k = k$ for each $g_i$ and for $k = 1, 2, \cdots, 7$. To do this, for a given value of $M$, we vary the number of Gaussians by means of changing the number of evenly spaced $\mu_i$ within the range of $T_2 \in [1, 200]$ for each $g_i$. The proposed values of $M$ are chosen within $\{100, 120, 140, 160, 180, 200, 240, 260, 280\}$, the performance (indicated by the mean values of the heatmaps) of Multi-Reg under the different settings of $\{g_i\}_1^M$. Other variations are fixed where the number of repetitive noise realizations $n_{\text{run}} = 10$, and number of regularization parameters $n_\lambda = 10$.

As a result, we arbitrarily choose configuration $\sigma_k = 7$ and with $M = 220$ as our proposed set of Gaussian distributions, simply because it shows the smallest averaged relative error among all other configurations.
3.1.2 Choosing $n_\lambda$

The regularization parameters are chosen to be the $n_\lambda$ logarithmically spaced points between $10^{-6}$ and 10. Unlike in L-curve or GCV that a finer grid of regularization parameters is preferred than a coarse one, a good number of regularization parameters $n_\lambda$ for Multi-Reg should seek for a balance between reducing the ill-posedness for solving the LS problems (2.8) and (2.11) and expanding the space spanned by $\{f_j\}$. This means on one hand, $n_\lambda$ should be small so that solutions to (2.8) and (2.11), $\{\beta_{ij}\}$ and $\{x_{ij}\}$ are stable; on the other hand, $n_\lambda$ should be large so that each $f_j$ may be able to show various regularized results.

While we fix all other settings of the method, where the $M = 220$ and $n_{run} = 10$, we plot the trajectories of mean values of the heatmaps against various numbers of $n_\lambda$.

![Figure 2: $L^2$ norms of heat maps for different number $n_\lambda$ of regularization parameters, where the regularization parameters range from $10^{-6}$ to 10.](image)

We see that the “best” scenario is when $n_\lambda = 12$ for $\sigma_k = 7$, as it resulted in a smaller mean values of the heatmaps.

3.1.3 Choosing $n_{run}$

To choose $n_{run}$, we proposed a set of values $\{1, 2, 4, 8, 16, 32, 64\}$ to choose from while fixing all other parameters where $n_\lambda = 12$, $M = 220$. We plot the trajectories of the mean values as functions of $n_{run}$, shown in Fig. 3.
It is seen from the trajectories that, when $\sigma_k = 6$, and the associated $n_{\text{run}} = 32$, the mean values of heatmaps are minimal among all configurations considered for the test of choosing $n_{\text{run}}$.

In summary, during the limited number of testings, the Gaussian function dictionary is chosen to be formed as follows: $M = 220$, $n_\lambda = 12$, $n_{\text{run}} = 32$ and with uniform standard deviation $\sigma = 6$.

### 3.2 Simulation results: comparison between Multi-Reg and other parameter selection methods

After the preferred settings of Multi-Reg is determined, we would be ready to proceed online computations once new observational data $y_{\text{obs}}$ is given. We will use heat maps to represent the differences between various underlying distributions and recoveries using Multi-Reg, together with L-curve and GCV. For L-curve and GCV recovery, we follow used Tikhonov Regularization to determine coefficients of the same given Gaussian basis $\{g_i\}$ as is used in the offline computation for Multi-Reg, and increased the number of regularization parameter to 40 evenly logspaced nodes from $10^{-5}$ to 10, in order to achieve a higher resolution of L-curve and GCV curve. After the simulation, we averaged the the heat maps as well as their corresponding $L^2$ norm over 40 times. Each time of simulation, we manually added different noise realizations with same SNR. Results are shown below:
Figure 4: Comparisons of the heat maps of recoveries using Multi-Reg, GCV and L-curve, on noisy signals generated by various distributions.

To better compare the results between Multi-Reg and the other two methods, and indicate regimes in detail, we plot the fractions of the relative-error heat maps matrices: $\frac{\text{Multi-Reg}}{\text{GCV}}$ and $\frac{\text{Multi-Reg}}{\text{L-curve}}$ as below, i.e. in the regime where the ratio is less than 1, Multi-Reg performs better and otherwise when the ratio is larger than 1, in the sense of relative errors.
Figure 5: Ratio of average relative errors of Multi-Reg/GCV methods, over 20 noise realizations with SNR=500, corresponding to a range of peak widths and separations for two Gaussian peaks of equal standard deviation.

Figure 6: Ratio of average relative errors of Multi-Reg/L-curve methods, over 20 noise realizations with SNR=500, corresponding to a range of peak widths and separations for two Gaussian peaks of equal standard deviation.
Figure 7: Example showing different recoveries with comparable relative errors, where Multi-Reg recovery correctly displays the number and location of the underlying distributions.

Figure 8: Another example showing different recoveries with comparable relative errors, where Multi-Reg recovery correctly displays the number and location of the underlying distributions.

and examples consist of more than two Gaussian distributions whose coefficients are random:
Figure 9: Examples showing that recoveries using Multi-Reg provide more information of the underlying distributions while the relative errors of Multi-Reg are comparable or even larger than L-curve or GCV when more than two Gaussian distributions with random coefficients are given. In the results above, both L-curve and GCV select the same regularized solutions based on their parameter selection criterion.

3.3 Numerical results on experimental data

To test the performances of Multi-Reg as well as other regularization parameter selection methods with respect to real experimental data, two sets of experiments are conducted and their noisy observations are collected.

3.3.1 Recoveries of Muscle Data

- Data acquisition: After informed consent, data were obtained from a 62-year-old male using a 3T whole-body clinical scanner (Achieva, Philips) with a SENSE Flex-M coil. $T_2$-weighted scans were collected along the axial plane within the thigh with $TE/TR = 6 ms/5 sec$, 72-echo train, in-plane resolution of $3 \times 3 mm$ reconstructed to isotropic $0.98 mm$, and $10 mm$ slice thickness. The data were collected before and after 45-sec intense quadriceps extension exercise.
- Problem settings: $T_2 \in [6, 350]$ with 250 equally spaced nodes. $SNR \approx 533.0789$. Simulations were tailored to experiments on in vivo human thigh muscle in terms of $TE$, $T_2$, and noise level.
- Optimal basis setting for Multi-Reg: the basis consists of 2 sets of Gaussians where the first set has $n_{Gaussian} = 250$ and $\sigma = 2$, the second set of Gaussians has $n_{Gaussian} = 100$ and $\sigma = 3$, $n_{run} = 20$, $\gamma_i$ are chosen to be the $n_{\lambda} = 8$ logarithmically spaced points between $10^{-6}$ and 10.
Figure 10: Recoveries for muscle datasets: quadriceps (top) and medial (mid) and hamstrings (right). Less regularized recoveries are selected by the GCV method, which successfully located the two water pools in each muscle but also resulted in high peaks near 1ms; Over-regularized approximations are selected by the L-curve method, which failed to locate the extracellular water. Multi-Reg recoveries display a combination of both features in a way that it reveals two water pools while reducing the sparsity.

3.3.2 Recoveries of mouse spinal cord data

- Data acquisition: Data were obtained on formalin-fixed and washed 10 mm lengths, of cervical and lumbar spinal cord from a 4 month-old male C57BL/6 mouse, with cross-sectional lengths $2 \times 3$
mm. The samples were imaged in Fluorinert (Sigma-Aldrich, St. Louis, MO, USA) using a 9.4 T Bruker Avance III NMR spectrometer and a Micro2.5 imaging probe equipped with a 5 mm diameter solenoidal coil. Spectroscopic transverse relaxation decay data were obtained using a Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence, with TR/TE = 10 s/300 s, 4096 echoes, and NEX = 32, with saturation slabs restricting data acquisition to a 2 mm slice.

- Problem settings: $T_2 \in [1, 400]$ with 600 equally spaced nodes. $SNR \approx 2200$. Simulations were tailored to experiments on in vivo mouse spinal cord in terms of $TE$, $T_2$, and noise level.

- Optimal basis setting for Multi-Reg: the basis consists of 1 set of Gaussians where $n_{Gaussian} = 200$ and $\sigma = 2$, $n_{run} = 20$, $\gamma_i$ are chosen to be the $n_\lambda = 10$ logarithmically spaced points between $10^{-5}$ and $10^{-1}$.

![Recoveries for Spinal Cord Region 1](image1)

![Recoveries for Spinal Cord Region 2](image2)

Figure 11: Recoveries for spinal cord datasets: cervical (left) and lumbar (right) spinal cord. Multi-Reg shows similar efficiency of GCV, while L-curve tends to select over-regularized recovery as is shown in the left figure.

4 Conclusion

In this paper, we develop a new parameter selection method for the constrained standard form of Tikhonov regularization. Instead of choosing one regularized solution as the "best" approximation to the underlying $T_2$ distribution using conventional methods such as L-curve or generalized cross-validation (GCV), we used a combination of multiple regularized solutions as well as representation of a over-complete dictionary of Gaussian functions to express the unknown distribution function.

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