Journal of Magnetic Resonance 196 (2009) 23–32

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

# IRIS-HSVD algorithm for automatic quantitation of *in vivo* $^{31}$P MRS

Xin Wang [a], Jing-Huei Lee [a,b,*]

[a] Department of Biomedical Engineering, P.O. Box 670586, University of Cincinnati, 231 Albert Sabin Way, Room 6153A, MSB, Cincinnati, OH 45267, USA
[b] Center for Imaging Research, P.O. Box 670583, University of Cincinnati, Cincinnati, OH 45267, USA

ARTICLE INFO

*Article history:*
Received 10 March 2008
Revised 26 September 2008
Available online 30 September 2008

*Keywords:*
Magnetic resonance spectroscopy
Quantification
Hankel singular value decomposition
Iteration
Automation
$^{31}$P

ABSTRACT

The rapid development of $^{31}$P magnetic resonance spectroscopy (MRS) has enhanced non-invasive measurement of brain metabolites, which is important for biomedical research. The accuracy and efficiency of data post processing and quantification is paramount for MRS applications. One of the difficulties with *in vivo* $^{31}$P MRS data quantification is the separation of broad line-width resonances from chemical compounds' resonances under a low signal-to-noise ratio condition. Furthermore, the chemical shift of some compounds caused by pH and $Mg^{2+}$ concentration can be troublesome. This work aims to develop an automatic algorithm using a state-space based quantification approach to solve the above mentioned problems. To achieve this aim, we utilized an HSVD based adaptive optimizing prior knowledge algorithm, which uses so called "interference" signals to optimize prior knowledge iteratively for parameter optimization. We termed this algorithm IRIS-HSVD, which stands for Iterative Reduction of Interference Signal HSVD. The Monte Carlo evaluations of the algorithm were conducted with simulated data using *in vivo* parameters commonly obtained from a 4 T scanner. The performance of this algorithm using simulated data was compared to those of other automatic methods including HSVD and HTLS-PK. Examples of *in vivo* $^{31}$P data obtained from brains of healthy subjects on a 4T MRI scanner were also presented, which demonstrated the superiority of the new method. The results were compared with those using AMARES.



## 1. Introduction

Magnetic resonance spectroscopy (MRS) has become increasingly important in biomedical research because of its ability to measure *in vivo* biochemical information. Multi-voxel $^{31}$P MRS is a useful tool for the study of *in vivo* energy metabolites in humans and animals [1,2]. However, spectral analysis can be tedious and time consuming, particularly for multi-voxel data acquired using 2D or 3D MRS. Additionally, it suffers from a low signal-to-noise ratio (SNR), spectral overlapping, chemical frequency variation influenced by a biophysiological environment, and significant baseline artifacts. These issues can be attributed to (1) a low natural concentration of $^{31}$P biochemical compounds in *in vivo* samples, (2) the variation of certain $^{31}$P resonances by the influence of physiological environment, (3) the origination of some signals from immobile compounds (presumably from bone marrow and/or cell membranes), and/or (4) imperfect hardware. These complications continue to challenge the development of an automatic algorithm for MRS data quantification, which is strongly needed to further advance this methodology to widespread clinical applications.

The algorithms developed for MRS data analysis based on the state-space approach are rapidly increasing due to significant improvements in quantitation robustness and accuracy [3]. The state-space methods often employ tools such as the Singular Value Decomposition (SVD) [4] or the orthogonal matrix triangularization (also known as QR decomposition) [5,6] to distinguish the signal and noise subspaces. Compared to the frequency domain methods [7], the state-space approach has less sensitivity to phase errors and greater tolerance of spectral overlap, baseline distortions and/or missing data samples [8,9].

The SVD, as well as its derivative methods such as Hankel SVD (HSVD) [10,11], Hankel Lanczos SVD (HLSVD) [12] and Linear Prediction SVD (LPSVD) [13,14], provide nearly automatic quantification approaches, although their results are often prone to lack of physical and/or physiological meaning (i.e., specificity and accuracy). It was demonstrated that the accuracy of these approaches can be improved by introducing Hankel Total Least Squares (HTLS) techniques [15]. Furthermore, incorporating prior knowledge with subspace methods (or, in general, any methods) could further improve performance robustness. For example, simulated spectra by spin physics were utilized to obtain a theoretical estimation of the frequencies and damping factors of targeted resonances in QUEST (quantitation based on quantum estimation), which can also handle baseline distortions [16]. Prior knowledge of signal frequencies and damping factors can also serve as the starting

* Corresponding author. Address: Department of Biomedical Engineering, P.O. Box 670586, University of Cincinnati, 231 Albert Sabin Way, Room 6153A, MSB, Cincinnati, OH 45267, USA. Fax: +1 513 558 7164.
*E-mail address:* jing-huei.lee@uc.edu (J.-H. Lee).

1090-7807/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.jmr.2008.09.024

estimation values in AMARES (advanced method for accurate, robust, and efficient spectral fitting) [19]. In addition, constrained signal frequencies and damping factors were used in methods such as the frequency domain SVD [20], Extended Relaxation Based Estimator (E-RELAX) [21], and Metropolis Frequency-Selective (MeFres) [22]. The chemical shift relationship of certain chemical species was also used to improve algorithm accuracy and robustness in the Knowledge Based SVD (KNOB-SVD) [23] and the Knowledge Based Total Least Square (KNOB-TLS) methods [24]. Both algorithms estimated the relative chemical frequency using a fixed chemical shift between α- and γ-ATP and demonstrated an improvement in performance compared to the AMARES, HTLS, and HTLS-PK algorithms.

To date, few studies have focused on *in vivo* $^{31}$P MRS conditions, in which chemical frequency changes could be caused by biophysiological and/or physical variations (e.g., pH value and $Mg^{2+}$ concentration, and spatial $B_0$ variations). In this work we propose an algorithm termed Iterative Reduction of Interference Signal HSVD (IRIS-HSVD), which utilizes interference signals to optimize prior knowledge iteratively to separate baseline components and to estimate parameters for *in vivo* 3D $^{31}$P MRS data that suffer from a low SNR. In 3D MRS experiments, whole brain $^{31}$P MRS data may contain spectra with varying chemical shifts caused by $B_0$ inhomogeneity in different locations in addition to those due to biophysiological variants. Thus, an adaptive, baseline tolerant, and automatic algorithm is strongly desired. The IRIS-HSVD iteratively separates the signal subspace from noise and baseline subspaces by the QR decomposition. During each iteration, the interference signal (see below), which resulted from inaccurate prior knowledge, is identified and utilized to optimize the parameter estimation. The resulting signal frequencies and damping factors corrected by the interference signal are then used as the "new" prior knowledge for the next iteration. This procedure continues until the interference signal is minimized. This algorithm utilizes a constrained decision making mechanism and is fully automated and relatively robust.

## 2. Materials and methods

### 2.1. FID signals modeling

The complex time domain free induction decay (FID) signal is often modeled by the sum of exponentially damped sinusoids given in Eq. (1).

$$\begin{aligned} y_n &= \bar{y}_n + e_n = \sum_{k=1}^{K} c_k z_k^n + e_n \\ z_k &= e^{(-d_k + i f_k)2\pi\Delta t} \\ c_k &= a_k e^{i\phi_k} \end{aligned} \tag{1}$$

where $y_n$ represents the original signal, $\bar{y}_n$is the estimated signal, $e_n$ is a complex white Gaussian noise, and $n$ is the index of data samples. The value K is the number of different frequencies and $z_k$ refers to the $k_{th}$ signal pole with a frequency of $f_k$ and a damping factor of $d_k$ (the reciprocal of the transverse relaxation time constant, $T_2^*$), and $\Delta t$ is the data sampling time interval [8,18]. The value $c_k$ is the complex amplitude of $z_k$, $a_k$ is the absolute magnitude, and $\varphi_k$ is the phase.

In this work, we develop an algorithm based on the state-space approach to solve Eq. (1). Since details of the state-space method can be found elsewhere [25], we are brief here. In short, by arranging $y_n$ ($n = 0, \ldots, N-1$) in Eq. (1) into a special $L$ by $M$ Hankel matrix as shown in Eq. (2), the parameters $z_k$ and $c_k$ can be estimated by computing the SVD of $\mathbf{H} = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^{\mathbf{H}}$, where $\mathbf{\Sigma}$ is a diagonal matrix containing the singular values, $\mathbf{U}$ and $\mathbf{V}$ is an $L$ by $L$ and $M$ by $M$ unitary matrix, respectively, and $\mathbf{H}$ denotes Hermitian conjugation [8,11].

$$\mathbf{H} = \begin{bmatrix} y_0 & y_1 & \cdots & y_{M-1} \\ y_1 & y_2 & \cdots & y_M \\ \vdots & \vdots & \vdots & \vdots \\ y_{L-1} & y_{N-M} & \cdots & y_{N-1} \end{bmatrix} \tag{2}$$
$$L \geqslant K, \quad M \geqslant K, \quad N = L + M - 1$$

### 2.2. Baseline distortion modeling

As mentioned above, broad line-width peaks and/or hardware imperfection can cause baseline distortion. In this work, we assume that the broad line-width signals causing baseline distortion can be represented by an assortment of fast decaying exponentially damped sinusoids and can be considered in the singular values of the HSVD solution. This is reasonable since the fast decaying part of FID is likely, in most *in vivo* $^{31}$P MRS, the signal from macromolecule-bonded compounds such as cell membrane phospholipids.

### 2.3. Determine the number of poles

To compute the singular values is straightforward; however, it is no trivial matter to determine the number of singular values, $k$, to represent the estimated signal, $\bar{y}_n$, which may include broad line-width components. Several methods have been proposed to determine the number of singular values, but the decision of the number of singular values to be used can be difficult [9]. In ideal cases, we should choose a maximum number of $k$ to represent $y_n$ with as little noise as possible. Some investigators have recommended the use of the ratio of $\sigma_{m+1}/(\sigma_m - \sigma_{m+1})$ as a guideline for choosing the value of $k$ [25]. The values $\sigma_m$ and $\sigma_{m+1}$ are the smallest accepted and the largest rejected singular value of the Hankel matrix in Eq. (2), respectively, where $m$ (i.e., $k$) and $(m+1)$ are the indices of the singular values. However, in this study, we used the ratio of $\sigma_{m+1}\sigma_m/(\sigma_m - \sigma_{m+1})^2$ as the function of singular value index ($m$) instead of $\sigma_{m+1}/(\sigma_m - \sigma_{m+1})$. Otherwise, the decision making procedure is the same as the original method proposed by de Groen [25]. This ratio provides a compatible tool for determining the number of poles to be used and will be used through this work.

### 2.4. Prior knowledge and adaptive optimization processes

As noted, the HSVD method does not necessarily return the solutions (poles) with physiological and biochemical meaningful frequencies and damping factors. What it yields in most cases is a mathematically best "fit" to $y_n$. This drawback is particularly apparent in *in vivo* data when the SNR is significantly low. Therefore, known information such as frequencies and damping factors can be helpful for parameters optimization and fast converging in data analysis. Perhaps the most challenging task in the development of an algorithm for MRS quantitation is to have the ability of self-correction for prior knowledge when needed. It is shown that the phase change of a signal pole is strongly correlated with its frequency deviation from the original value [17]. Therefore, one may utilize phase alternation information to assist in correcting frequency mismatch if needed in the optimization process. Indeed, we found that the frequency difference of a pole from its "true" value can be approximated by the product of its phase change and its damping factor, that is, $\Delta f_k \cong \Delta p_k * d_{k0}$. We have demonstrated this relationship in Fig. 1. To assess this relationship, a set of $^{31}$P MRS data was simulated by varying the frequency of certain peaks (Pi, α-, β-, and γ-ATP) using parameters listed in Table 1. Briefly, two baselines were added to the simulation data with SNR levels ranging from 100 to 1100. (see Section 2.7 for details) Note that the frequencies of Pi, α-, β-, and γ-ATP peaks varied linearly between −1