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Deconvolution Analysis of Dynamic Contrast-Enhanced Data Based on Singular Value Decomposition Optimized by Generalized Cross Validation

Kenya Murase*, Youichi Yamazaki, and Shohei Miyazaki

Department of Medical Physics and Engineering, Division of Medical Technology and Science, Course of Health Science, Graduate School of Medicine, Osaka University
1-7 Yamadaoka, Suita, Osaka 565-0871, Japan
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Purpose: To present an implementation of generalized cross validation (GCV) for automatically determining the regularization parameter—i.e., the threshold value in deconvolution analysis based on truncated singular value decomposition (TSVD) of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) data—and to investigate the usefulness of this approach in comparison with TSVD with a fixed threshold value (TSVD-F).

Methods: Using computer simulations, we generated a time-dependent concentration of the contrast agent in the volume of interest (VOI) from the arterial input function (AIF) modeled as a gamma-variate function under various cerebral blood flows (CBFs), cerebral blood volumes (CBVs), and signal-to-noise ratios (SNRs) for three different types of residue functions (exponential, triangular, and box-shaped). We also considered the effects of delay and dispersion in AIF. The TSVD with GCV (TSVD-G) and TSVD-F with a fixed threshold value of 0.2 were used to estimate CBF values from the simulated concentration-time curves in the VOI and AIF, and the estimated values were compared with the assumed values. Additionally, the optimal threshold value was determined from the threshold value in TSVD-F giving the mean CBF value closest to the assumed value and was compared with the threshold value determined with TSVD-G.

Results: With TSVD-G, the CBF estimation was substantially improved over a wide range of CBFs for all types of residue functions at the cost of more noise than was seen with TSVD-F. The dependency of the threshold value determined with TSVD-G on the CBF, CBV, and SNR was similar to that of the optimal threshold value, with some discrepancy being observed for the box-shaped residue function, although they did not always agree in terms of absolute value.

Conclusion: Given an improved SNR, TSVD-G is useful for quantification of CBF with deconvolution analysis of DCE-MRI data.

Keywords: deconvolution analysis, singular value decomposition, generalized cross validation, dynamic contrast-enhanced MRI, cerebral blood flow

Introduction

The use of an intravascular contrast agent in combination with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is becoming a well-established technique for measuring cerebral perfusions such as cerebral blood flow (CBF) and cerebral blood volume (CBV).1,2 This technique is playing an increasingly important role in the diagnosis, assessment, and management of acute stroke patients.3,4 According to the indicator dilution theory5 for intravascular contrast agents, the time-dependent concentration of the contrast agent in the volume of interest (VOI) \([C_{VOI}(t)]\) is given by

\[
 k_h C_{VOI}(t) = \frac{C_{BF} C_{AIF}(\tau) R(t - \tau) \, d\tau}{0}.
\]

In Eq. [1], \(C_{AIF}(t)\) is the time-dependent concentra-
An example of residue function \([R(t)]\) as a function of time. Figures (a), (b), and (c) show the exponential, triangular, and box-shaped residue functions, respectively. In these cases, the cerebral blood flow (CBF) and cerebral blood volume (CBV) were assumed to be 60 ml/100 g/min and 4 ml/100 g, respectively.
where the total number of frames, respectively. It should be noted that these curves were obtained by converting the corresponding signal-time curves with the equation given by Rosen et al., and $C_{VOI}(t)$ was magnified 10 times for clarity.

Quantification of CBF
Quantification of CBF with TSVD

If it is assumed that the functions $C_{AIF}(t)$ and $R(t)$ in Eq. [1] are constant over short time intervals, $\Delta t$, Eq. [1] is reduced to

$$k_0 C_{VOI}(t_i) = C_{AIF}(t) \sum_{l=1}^{n} C_{AIF}(t_l) R(t_l - t_i),$$

where $t_i$ and $n$ denote the time of the $i$th frame and the total number of frames, respectively. It should be noted that it was assumed that $t_i = 0$ and the duration of each frame was equal when converting Eq. [1] to Eq. [2]. When $k_0$ is assumed to be unity for simplicity, the convolution in Eq. [2] can then be formulated as a matrix equation

$$\hat{c} = \hat{A} \cdot \hat{b},$$

where

$$\hat{A} = \begin{pmatrix} C_{AIF}(t_1) & 0 & \cdots & 0 \\ C_{AIF}(t_2) & C_{AIF}(t_1) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ C_{AIF}(t_n) & C_{AIF}(t_{n-1}) & \cdots & C_{AIF}(t_1) \end{pmatrix},$$

and

$$\hat{b} = C_{VOI}(t_1) \begin{pmatrix} R(t_1) \\ \vdots \\ R(t_n) \end{pmatrix}.$$

With SVD, the matrix $\hat{A}$ in Eq. [3] can be expressed as the product of an $n \times n$ column-orthogonal matrix $\hat{U}$, an $n \times n$ diagonal matrix $\hat{W}$, and the transpose of an $n \times n$ orthogonal matrix $\hat{V}$, i.e.,

$$\hat{A} = \hat{U} \hat{W} \hat{V}^T = \hat{U}[\text{diag}(w_i)] \hat{V}^T,$$

where $w_i$ ($i = 1, 2, \cdots, n$) are the diagonal elements of $\hat{W}$ (the singular values) that are nonnegative and that can be ordered such that

$$w_1 \geq w_2 \geq \cdots \geq w_n \geq 0.$$  

The SVD constructs the matrices so that the inverse of $\hat{A}$ can be written as

$$\hat{A}^{-1} = \hat{V}[\text{diag}(1/w_i)] \hat{U}^T,$$

where $\hat{U}^T$ is the transpose of $\hat{U}$. The matrix $\hat{b}$ can then be calculated as

$$\hat{b} = \hat{V}[\text{diag}(1/w_i)] (\hat{U}^T \hat{c}),$$

i.e., Eq. [7] is used to solve for $\hat{b}$, which contains the elements of $R(t)$.

With TSVD, if $w_i$ was smaller than the maximal value of $w_i$ multiplied by a threshold value, $1/w_i$ in Eq. [7] was replaced by zero. We denote TSVD with a fixed threshold value as TSVD-F. Unless specifically stated, the threshold value was fixed to 0.2 in this study. The CBF value was obtained from the maximum value of $\hat{b}$ calculated from Eq. [7].

Determination of Optimal Threshold Value

To investigate the optimal threshold value in TSVD-F, we varied the threshold value from 0.01 to 0.7 in increments of 0.01 and estimated the CBF values. After 1,000 runs for each threshold value, the threshold value giving the mean CBF value closest to the assumed value was chosen as the optimal threshold value.
Quantification of CBF with TSVD with GCV

GCV is based on statistical considerations; namely, that a good value of the regularization parameter should predict missing data values. With this approach, no a priori knowledge of the error norms is required. GCV leads to choosing \( \lambda \) as the minimizer of the GCV function \( g(\lambda) \) defined by

\[
g(\lambda) = \frac{\| \hat{A} \hat{b}_\lambda - \hat{c} \|_2^2}{(T(\lambda))^2},
\]

where \( T(\lambda) \) is defined by

\[
T(\lambda) = \text{trace}(I_n - \hat{A} \hat{A}^T).
\]

\( \lambda \) is a regularization parameter corresponding to the threshold value to truncate \( 1/w_i \) in \( \hat{A}^{-1} \) when \( w_i \) is smaller than the maximum value of \( w_i \) multiplied by this value. \( I_n \) in Eq. [9] denotes the identity matrix of order \( n \), and \( \hat{A}^T \) is the inverse of \( \hat{A} \) in which the diagonal elements in Eq. [6] \((1/w_i)\) were truncated (\( \hat{A}_\lambda \)). \( \hat{b}_\lambda \) in Eq. [8] is the solution of Eq. [3] with \( \hat{A}_\lambda \) instead of \( \hat{A} \) and is expressed as

\[
\hat{b}_\lambda = \hat{A}_\lambda^T \hat{c}.
\]


\[
g(\lambda) = \frac{\| \hat{A} \hat{A}^T \hat{c} - \hat{c} \|_2^2}{\text{trace}(I_n - \hat{A} \hat{A}^T)^2}.
\]

In this study, the threshold value was varied from 0.01 to 1.0 in increments of 0.01, and the GCV value was calculated with Eq. [11] for each threshold value. The threshold value rendering the minimum GCV value was then determined, and the CBF value was estimated from the maximum value of \( \hat{b}_\lambda \) calculated with Eq. [10] using this threshold value. We denote TSVD with a threshold value rendering the minimum GCV value as TSVD-G.

Simulation of Delay and Dispersion in AIF

The effects of delay and dispersion in AIF were also considered in the simulations according to the method described in detail in our previous papers. To illustrate the effects of delay and dispersion in AIF, Fig. 3 shows an example of \( C_{\text{AIF}}(t) \) with and without delay and dispersion. Figure 3(a) shows \( C_{\text{AIF}}(t) \) without delay and dispersion and that with a delay of 5 s by the solid and dotted lines, respectively. In these cases, statistical noise was neglected to focus on the effects of delay and dispersion in AIF.

Study Conditions and Statistical Analysis

To investigate the relationship between the assumed and estimated CBF values and the dependency of the threshold value determined with TSVD-G and the optimal threshold value on CBF, the CBF value was varied from 10 to 200 ml/100 g/min in increments of 10 ml/100 g/min for a CBV of 4 ml/100 g; SNRs of 20, 50, and 100; and three residue functions. In these cases, the effects of delay and dispersion in AIF were neglected.

To investigate the dependency of the threshold value determined with TSVD-G and the optimal threshold value on CBV, the CBF value was varied.
from 2 to 10 ml/100 g in increments of 1 ml/100 g for a CBF of 60 ml/100 g/min, SNRs of 20, 50, and 100 and three residue functions. The effects of delay and dispersion in AIF were also neglected in these cases.

To investigate the dependency of the threshold value determined with TSVD-G and the optimal threshold value on SNR, the SNR value was varied from 10 to 200 in increments of 10 for a CBF of 60 ml/100 g/min; a CBV of 4 ml/100 g; and three residue functions. In these cases, the effect of dispersion in AIF was neglected.

To investigate the effect of delay in AIF on the CBF estimation, the delay time was varied from 1 to 10 s in increments of 1 s for a CBF of 60 ml/100 g/min; a CBV of 4 ml/100 g; SNRs of 20, 50, and 100; and three residue functions. In these cases, the effect of delay in AIF was neglected.

To investigate the effect of dispersion in AIF on the CBF estimation, the dispersion constant was varied from 1 to 10 s in increments of 1 s for a CBF of 60 ml/100 g/min; a CBV of 4 ml/100 g; SNRs of 20, 50, and 100; and three residue functions. In these cases, the effect of delay in AIF was neglected.

A Monte Carlo simulation of 1,000 runs was performed for each condition. The mean and the standard deviation (SD) of the estimated CBF values for 1,000 runs were calculated.

**Results**

Figure 4 shows an example of the GCV value as a function of threshold value. In this case, the CBF, CBV, and SNR were taken as 60 ml/100 g/min, 4 ml/100 g, and 50, respectively, and $R(t)$ was assumed to be exponential. The threshold value rendering the minimum GCV value was adopted as a regularization parameter in TSVD-G.

First, we investigated the relationship between the assumed and CBF values estimated with TSVD-G in comparison with that estimated with TSVD-F. The results are shown in Fig. 5, in which (a), (b), and (c) show cases for SNR = 20; (d), (e), and (f) for SNR = 50; and (g), (h), and (i) for SNR = 100. The upper, middle, and lower panels show cases in which $R(t)$ was assumed to be exponential, triangular, and box-shaped, respectively. In these cases, CBV was assumed to be 4 ml/100 g and the effects of delay and dispersion in AIF were neglected. The open and closed symbols represent the estimated CBF values with TSVD-G and TSVD-F, respectively. As shown in Fig. 5, TSVD-G leads to a substantial improvement in the CBF estimation in terms of linearity over a wide range of CBFs at the cost of greater noise than is seen with TSVD-F for all types of residue functions. The SD of the estimated CBF values with TSVD-G was greater by a factor of approximately 3 than that of the CBF values estimated with TSVD-F.

Second, we investigated the relationship between the threshold value determined with TSVD-G and the optimal threshold value for various conditions. As previously described, the threshold value in TSVD-F giving the mean CBF value obtained from 1,000 simulations closest to the assumed value was defined as the optimal threshold value. Figure 6 shows the dependency of these threshold values on CBF. As in Fig. 5, (a), (b), and (c) indicate cases in which $R(t)$ was assumed to be exponential, triangular, and box-shaped, respectively. The open and closed symbols represent the threshold value determined with TSVD-G and the optimal threshold value, respectively. Figure 7 shows the dependency of these threshold values on CBV, while Fig. 8 shows the dependency on SNR. As in Figs. 6 (a), (b), and (c) in Figs. 7 and 8 indicate cases in which $R(t)$ was assumed to be exponential, triangular, and box-shaped, respectively, and the open and closed symbols represent the threshold value determined with TSVD-G and the optimal threshold value, respectively. As shown in Figs. 6, 7, and 8, the dependency of the threshold values determined with TSVD-G on CBF, CBV, and SNR was similar to that of the optimal threshold value except for the case where $R(t)$ was assumed to be box-shaped [Figs. 7(c) and 8(c)], although the
Fig. 5. Relationship between the assumed and estimated CBF values. Figures (a), (b), and (c) show cases for SNR = 20; (d), (e), and (f) for SNR = 50; and (g), (h), and (i) for SNR = 100. The upper, middle, and lower panels represent cases in which $R(t)$ was assumed to be exponential, triangular, and box-shaped, respectively. In these cases, CBV was assumed to be 4 ml/100 g and the effects of delay and dispersion in AIF were neglected. Open and closed symbols represent the CBF values estimated with deconvolution analysis based on truncated singular value decomposition (TSVD) with the threshold value determined by GCV (TSVD-G) and TSVD with a fixed threshold value of 0.2 (TSVD-F), respectively. Error bars represent the standard deviation (SD) for 1,000 simulations. The solid line represents the line of identity.

Finally, we investigated the effects of delay and dispersion in AIF on the CBF values estimated with TSVD-G in comparison with those estimated with TSVD-F. Figure 9 indicates the CBF values estimated with TSVD-G and TSVD-F by open and closed symbols, respectively, as a function of delay time in AIF, while Fig. 10 shows the same as a function of dispersion constant in AIF. As in the above figures, (a), (b), and (c) in Figs. 9 and 10 indicate cases in which $R(t)$ was assumed to be exponential, triangular, and box-shaped, respectively. In these figures, the mean CBF values obtained from 1,000 simulations are shown. In
Fig. 6. Dependency of the threshold value determined with TSVD-G and the optimal threshold value on CBF. Figures (a), (b), and (c) indicate cases in which \( R(t) \) was assumed to be exponential, triangular, and box-shaped, respectively. In these cases, the CBV and SNR were assumed to be 4 ml/100 g and 50, respectively, and the effects of delay and dispersion in AIF were neglected. Open symbols represent the threshold values determined with TSVD-G, while closed symbols represent the optimal threshold values determined from the threshold value in TSVD-F giving the mean CBF value obtained from 1,000 simulations closest to the assumed value. Error bars represent the SD for 1,000 simulations.

Fig. 7. Dependency of the threshold value determined with TSVD-G and the optimal threshold value on CBV. Figures (a), (b), and (c) indicate cases in which \( R(t) \) was assumed to be exponential, triangular, and box-shaped, respectively. In these cases, the CBF and SNR were assumed to be 60 ml/100 g/min and 50, respectively, and the effects of delay and dispersion in AIF were neglected. Open symbols represent the threshold values determined with TSVD-G, while closed symbols represent the optimal threshold values. The error bar represents the SD for 1,000 simulations.

Discussion

As previously described, several regularization methods have been proposed to stabilize the solution of an ill-posed problem such as that of Eq. [1]. Among these methods, the Tikhonov regularization method is the most popular, and it has been applied to quantification of blood flow with dynamic functional imaging.\(^9\,11,12\) Although this approach has proved to be useful,\(^9\,11,12\) Koh et al.\(^11\) pointed out the importance of the choice of regularization matrix when applied to quantification of blood flow. With a very poor choice of regularization matrix, the resulting predictions in flow values can be misleading and such poor predictions can persist even with a high SNR. This represents a potential drawback of this method compared to regularization in standard form. In these cases, CBF, CBV, and SNR were assumed to be 60 ml/100 g/min, 4 ml/100 g, and 50, respectively. As shown in Figs. 9 and 10, the CBF values estimated with TSVD-G were somewhat less affected by the delay in AIF than those estimated with TSVD-F, while the dispersion in AIF affected both CBF values estimated with TSVD-G and TSVD-F in a similar manner. Similar results were obtained for other conditions of CBF, CBV, and SNR.
the case of regularization in standard form with methods such as TSVD, the accuracy and consistency of prediction improve with the increase in SNR largely independently of the shape of the underlying residue function. They suggested the use of this method only with the availability of reliable prior information on residue function; otherwise, regularization in standard form may still be preferable.

The key step for any regularization method is choosing the optimal regularization parameter. Various methods have been proposed for choosing this parameter. One of the simplest and most popular methods is the L-curve criterion (LCC). Alternative strategies include the use of the discrepancy principle, the quasi-optimality criterion and the GCV. Of these methods, the GCV does not require knowledge of the error, but extracts the information from the data itself.

In this study, we have implemented a GCV that automatically determines the regularization parameter, i.e., the threshold value in TSVD, and investigated the feasibility of the GCV approach for quantification of CBF with DCE-MRI in comparison with TSVD-F. Our results demonstrated that TSVD-G substantially improved the CBF estimation in terms of linearity over a wide range of

Fig. 8. Dependency of the threshold value determined with TSVD-G and the optimal threshold value on SNR. Figures (a), (b), and (c) indicate cases in which $R(t)$ was assumed to be exponential, triangular, and box-shaped, respectively. In these cases, CBF and CBV were assumed to be 60 ml/100 g/min and 4 ml/100 g, respectively, and the effects of delay and dispersion in AIF were neglected. Open symbols represent the threshold values determined with TSVD-G, while closed symbols represent the optimal threshold values. Error bars represent the SD for 1,000 simulations.

Fig. 9. Relationship between the estimated CBF values and delay time in AIF. Figures (a), (b), and (c) indicate cases in which $R(t)$ was assumed to be exponential, triangular, and box-shaped, respectively. In these cases, the CBF, CBV, and SNR were assumed to be 60 ml/100 g/min; 4 ml/100 g; and 50, respectively, and the effect of dispersion in AIF was neglected. The open and closed symbols represent the CBF values estimated with TSVD-G and TSVD-F, respectively, which are the mean CBF values obtained from 1,000 simulations.
CBFs for all types of residue functions studied, although the SD of the CBF values estimated with TSVD-G was much larger than that of the CBF values estimated with TSVD-F (Fig. 5). These results suggest the need to reduce statistical noise in the DCE-MRI data when using TSVD-G. This would be possible with methods such as wavelet transform, anisotropic diffusion method, and spline interpolation. In general, the SNR depends on several factors such as the pulse sequence used. Calamante et al. reported that the typical SNR values obtained in vivo on a pixel-by-pixel basis were 36 and 30 for gray and white matter, respectively. When the methods mentioned above are used to reduce statistical noise in the DCE-MRI data, the SNR is expected to be improved relative to these values. Thus, the accuracy of CBF estimation when combined with these methods would be close to that in the case of SNR = 50 shown in this study.

As shown in Figs. 6–8, the threshold value determined with TSVD-G changed depending on the CBF, CBV, and SNR in a manner similar to the optimal threshold value, with some discrepancy being observed for the box-shaped residue function. These findings do not conflict with our previous results. However, these two threshold values did not always agree in terms of absolute value. When the residue function was exponential or triangular, the threshold values determined with TSVD-G were greater than the optimal threshold values; however, when the residue function was box-shaped, they tended to be smaller than the optimal threshold values. Although the CBF estimation was substantially improved with TSVD-G as previously described, the CBF values estimated with TSVD-G were still somewhat smaller than the assumed values for the exponential or triangular residue function, while they became greater than the assumed values at a higher SNR for the box-shaped residue function (Fig. 5). These variations in result are believed to be attributable to the following: the performance of the threshold values determined with TSVD-G depends on the type of residue function, and, as mentioned above, they are overestimated for the exponential or triangular residue function and underestimated for the box-shaped residue function compared to the optimal threshold values.

Regarding the effects of delay and dispersion in AIF (Figs. 9 and 10), the CBF values estimated with TSVD-G were affected in a manner similar to those estimated with TSVD-F, although they were somewhat less sensitive to the delay in AIF. Our results suggest that the effects of delay and dispersion in AIF should be carefully considered even when the TSVD-G approach is used. As pointed out by Calamante et al., while the error introduced by the delay can be corrected with information on the arrival time of the bolus, the correction for the dispersion is less straightforward and requires a model for the vasculature. Ostergaard et al. incorporated a more complicated vascular model into a DCE-MRI study in an effort to account for the effects of delay and dispersion in AIF. In that study, they applied a modified version of the vascular model described by Kroll et al. The vasculature was modeled as a major feeding artery with a fixed relative dispersion and a delay determined by its volume fraction in a series with small
parallel vessels with relative flows and weights according to a given flow heterogeneity. This method could be used to correct for the dispersion, but further validation will be necessary. Recently, Alsop et al.\textsuperscript{23} have proposed a method to measure the AIF local to each voxel in order to minimize dispersion effects. This method will be useful for the detection and correction of significant distortions in AIF. Investigation and implementation of these methods will be the subjects of a future study.

Recently, Sourbron et al.\textsuperscript{24} have investigated the performance of the GCV and LCC for the selection of the truncation threshold in TSVD using both simulated data and simulated images and concluded that both GCV and LCC are equivalent, but GCV has an advantage over LCC in terms of calculation time. When compared to TSVD-F, the TSVD-G approach presented here requires additional calculation time for determination of the regularization parameter. The TSVD-F approach took about 73 s for 1,000 runs with Matlab (The MathWorks Inc., Natick, MA, U.S.A.) on a Pentium 4 (2.8 GHz) with 2 GB RAM, while the TSVD-G approach took about 294 s. However, it would be possible to shorten this calculation time by minimizing the number of steps with which the threshold value is varied. As its premise, the dependency of the accuracy in CBF estimation on the number of steps must be investigated, and this will also be the subject of a future study. On the other hand, the advantages of the TSVD-G approach are twofold: Eq. [11] can be used to easily obtain the regularization parameter from only the concentration-time curve data in AIF and VOI, and this approach can be easily incorporated in existing TSVD-F algorithms with only minor modifications.

In conclusion, the TSVD-G approach is useful for quantification of CBF with deconvolution analysis of DCE-MRI data. However, our results suggest that this approach requires improvement of the SNR in DCE-MRI data. In addition, further studies with clinical data are necessary to establish the usefulness of this approach. These studies are currently in progress.

References


