Evaluation of model-independent deconvolution techniques to estimate lung parenchymal perfusion

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Abstract

Dynamic contrast enhanced (DCE) MRI has become a useful technique for measuring perfusion in many applications. The theoretical basis for perfusion quantification is the central volume principle, which requires deconvolution of the measured arterial input and tissue concentration curves to derive a residue function ($R$) and mean blood perfusion. Deconvolution methods generally differ in assumptions of the global shape of $R$, computational stability and oscillations in estimated $R$. Therefore, several deconvolution methods to estimate $R$ and blood perfusion are evaluated in this study. Among these are model-dependent and model-independent techniques. All methods were applied to series of Monte Carlo simulations to evaluate the accuracy to reproduce different underlying shapes of $R$ and blood perfusion. Of the model-independent approaches the use of B-splines with Tikhonov regularization had a reasonable accuracy in perfusion estimations and was less biased than all model-dependent approaches. This technique is most promising for application to experimental data.

Keywords:  magnetic resonance ■ blood flow ■ deconvolution ■ perfusion ■ residue function
Introduction

DYNAMIC CONTRAST ENHANCED (DCE) MRI has become a useful technique for measuring perfusion in many applications. The theoretical basis for perfusion quantification is the central volume principle, which was originally introduced by Zierler and Meier. Application of this theory requires deconvolution of the measured arterial input and tissue concentration curves to derive a residue function and mean blood perfusion. Since this is an ill-posed problem, constraints should be applied to treat this problem. One type of constraint is by assuming that the residue function can be described by a mathematical function, a model-dependent approach. However, since the vascular structure is not known a-priori, this assumption has caused some to reject these methods. Others have proposed model-independent approaches. In this paper we compared a series of model-dependent and model-independent deconvolution techniques to determine the residue function and blood perfusion. All techniques were applied on simulation data contaminated with white noise. The accuracy and stability was evaluated for different kinds of simulated residue functions.

Methods

Problem definition

The central volume principle states that the transport of an injected tracer is linear and time-invariant. The response in a tissue \( C_T(t) \) to an arbitrary arterial input concentration curve \( C_a(t) \) is then given by the convolution integral of this input with the tissue impulse response or residue function, \( r(t) \). Let \( t \in \mathbb{Z} \) the discrete-time points with sequence \( t = 0 \ldots N - 1 \), the discrete-time convolution yields:

\[
C_T(t) = \Delta t \sum_{\tau=0}^{t} r(\tau) \cdot C_a(t - \tau) + \epsilon(t), \quad \text{with } C_a(t) = 0 \text{ for } t < 0
\]  

(1)

where \( \Delta t \) is the sampling interval and \( \epsilon \) the signal noise. For a more compact notation (1) can be notated as

\[
C_T = A \cdot r + \epsilon,
\]

(2)

where

\[
C_T = \begin{bmatrix}
C_T(t_1) \\
\vdots \\
C_T(t_N)
\end{bmatrix}, \quad r = \begin{bmatrix}
r(t_1) \\
\vdots \\
r(t_N)
\end{bmatrix}
\]
and \( A \in \mathbb{R}^{N \times N} \) a Toeplitz matrix, yielding:
\[
A = \Delta t \cdot \begin{bmatrix}
C_s(t_1) & 0 & \cdots & 0 \\
C_s(t_2) & C_s(t_1) & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
C_s(t_N) & C_s(t_{N-1}) & \cdots & C_s(t_1)
\end{bmatrix}.
\]

In these equations, the impulse response or residue function \( r \) is assumed as a monotonically decaying function, whose initial amplitude provides a measure of mean blood perfusion in ml/min/g².

In principle, the solution vector \( \hat{r} \) (i.e. the residue function that should be determined) can be solved by inversion of \( A \). However, since \( A \) is numerically ill conditioned even small amounts of noise on the data may result in physiologically meaningless solutions. Different approaches exist to improve the stability of \( \hat{r} \). One approach is using regularization methods to improve the condition of the problem whose solution is more satisfactory than the ordinary solution. Another approach is choosing a parameterization of \( r \) in order to reduce the number of parameters that needs to be estimated. Both approaches are discussed below.

**Regularization of the problem**

The linear problem can be formulated as:
\[
\hat{r} = \arg \min \left\| C_r(t) - Ar \right\|_2^2.
\]

This problem can be solved using the (generalized) singular value decomposition (SVD), but to ensure that \( \hat{r} \) is not too sensitive to perturbations the problem needs to be regularized.

**SVD truncation**

The simplest form of regularization is by truncating the smallest singular values (i.e. the singular values that causes the solution to oscillate) such that the solution is smoother than the unregularized solution. In this study, the optimal threshold below which singular values are to be removed is determined empirically and is considered as a percentage of the largest singular value.

**SVD with Tikhonov regularization**

A more gradual regularization without an abrupt cut-off for the singular values is Tikhonov regularization (also called damped least squares). In this situation, one augments the
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linear equations with linear side constraints, \(\lambda^2 \| Lr \|^2\), where \(L\) is a matrix operator and \(\lambda\) a weighting factor. \(L\) should be chosen based on a priori information and the optimal \(\lambda\) should then be computed\(^3\). The solution is obtained using the generalized SVD. The simplest choice for \(L\) is the identity matrix, but is normally not appropriate to reduce oscillations in the solution vector. Other choices of \(L\) with increased regularization are the first or second derivative operator (defined as \(L = \text{bidiag}(-1, 1)\) and \(L = \text{tridiag}(1, -2, 1)\), respectively).

A common method to derive the optimal value of \(\lambda\) is the \(L\)-curve criterion (LCC), which is based on the premise that the optimal value of \(\lambda\) is a compromise between the seminorm \(\| Lr \|^2\) versus the residual norm \(\| C_r - Ar \|^2\). A plot of these norms often reveals a characteristic \(L\)-shaped curve, with the assumption that the corner represents the point of optimal balance between both norms\(^3\).

**Choosing a parameterization**

Another approach to determine the residue function is choosing a parameterization, which reduces the number of parameters that should be estimated.

**System identification**

Assuming that the final samples in the data sequences are not of great importance, we may consider the first \(M\) samples only, such that a finite impulse response (FIR) predictor is obtained:

\[
\hat{C}_r(t, \theta) = \phi^T(t) \theta
\]

where

\[
\theta = \begin{bmatrix}
\tau_0 \\
\tau_1 \\
\vdots \\
\tau_{M-1}
\end{bmatrix}, \quad \phi(t) = \begin{bmatrix}
C_s(t) \\
C_s(t-1) \\
\vdots \\
C_s(t-M+1)
\end{bmatrix}
\]

Thus, the predictor is a scalar product between a known data vector \(\phi(t)^T\) and parameter vector \(\theta\). Subsequently, \(\theta\) is estimated by numerical minimization of a cost criterion, for which we considered the quadratic error:

\[
\hat{\theta} = \arg \min_{\theta} \frac{1}{N} \sum_{t=0}^{N-1} \| C_r(t) - \hat{C}_r(t, \theta) \|_2^2
\]

where \(\hat{\theta}\) is the optimal parameter vector and \(\hat{C}_r(t, \theta)\) the estimated tissue curve. Inserting (4) in (5) we get
\[ \hat{\theta} = \left[ \frac{1}{N} \sum_{i=1}^{N} \phi(t) \phi^T(t) \right]^{-1} \frac{1}{N} \sum_{i=1}^{N} \phi(t) C_T(t) \]
\[ = \left[ \frac{1}{N} \Phi \Phi^T \right]^{-1} \frac{1}{N} \Phi C_T. \]

Note that, for \( M = N \), matrix \( \Phi^T \) is similar to \( A \) in (2), and that the cost-criterion (5) is similar to (3).

The disadvantage of the FIR predictor, however, is the lack of adequate freedom in describing the properties of the disturbance term. Therefore, a more suitable approach is the prediction error estimate of an output-error model. Output error models are used to determine the deterministic transfer from input to output, with the assumption that uncertainties due to disturbances and the finite truncation can be lumped as an additive perturbation at the output. The general output-error structure is given by:

\[ \hat{C}_{OE}^T(t, \theta) = \phi^T(t) \theta, \]

where

\[ \theta = \begin{bmatrix} b_0 \\ b_1 \\ \vdots \\ b_{B-1} \\ f_1 \\ \vdots \\ f_F \end{bmatrix}, \quad \phi(t) = \begin{bmatrix} C_s(t) \\ C_s(t-1) \\ \vdots \\ C_s(t-B+1) \\ C_T(t-1) \\ C_T(t-2) \\ \vdots \\ C_T(t-F) \end{bmatrix}, \]

and where \( B \) and \( F \) are the numbers of samples considered of the inputs and outputs respectively. These orders should be provided as an initial condition. Inserting (7) in (5) we get a non-linear least squares problem, which can be solved using the Gauss-Newton method. Initially, \( B \) and \( F \) were set to 1 and 3. After the identification process, it was checked whether all poles were located in the right side of the complex plane, and if necessary, \( F \) was reduced to obtain a stable solution.

**B-splines**

Another way to constrain the solution vector is a representation using a basis of smooth B-splines, which has been proposed by Verotta and has also been successfully applied in myocardial perfusion. The solution of the residue function in a basis of B-splines can be represented by:
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\[ r(t) = \sum_{j=1}^{p} B_j^{(k)}(t) \cdot \alpha_j, \quad (8) \]

where \( B_j^{(k)} \) is the \( j \)-th B-spline of order \( k \) for an equally distributed knot sequence containing \( P+k \) knots (equal distribution is not a requirement but would suffice and is also used in\(^6\)). The vector \( \alpha \) represents the real valued B-spline coefficients. Estimated tissue concentration can now be expressed as:

\[ \hat{C}^{\text{spline}}_T(t, \theta) = \phi^T(t) \theta, \]

where

\[ \theta = \begin{bmatrix} \alpha_1 \\ \vdots \\ \alpha_p \end{bmatrix}, \quad \phi(t) = \begin{bmatrix} B_1^{(k)}(t) \\ \vdots \\ B_p^{(k)}(t) \end{bmatrix}, \]

which is also a linear problem and can thus be solved as in (6). The matrix \( \Phi \Phi^T \) is ill-conditioned, therefore we apply Tikhonov regularization before inverting this matrix. In this study we used B-splines of order 4 and evaluated the optimal number of break points. Multiplicity at the end-points was equal to the order and one for the interior knots.

**Model-based deconvolution**

Two model-dependent techniques were included for comparison purposes.

**Exponential model**

The first technique is known as the generalized kinetic model and is closely related to the so-called one-compartment Toft model\(^7\). This model assumes that the solution of \( r(t) \) is represented by an exponential function, ignoring the contribution of intravascular tracer to the total tissue concentration. The solution of \( r(t) \) is obtained in a non-linear least squares sense.

**Fermi model**

The second technique is not based on a pharmacokinetic model, but assumes that the solution of \( r(t) \) is represented by a Fermi function. This function has been motivated by the empirical observation that it closely resembles the impulse response for an intravascular tracer\(^8\). Also in this situation, the solution of \( r(t) \) is obtained in a non-linear least squares sense.
Data analysis

The performance of the deconvolution techniques was tested by application to a series of Monte Carlo simulations. Output data was contaminated with white noise sequences with signal-to-noise ratio (SNR) of 12, 15, 18 and 21 dB. For each noise level, 500 different noise realizations were generated.

A gamma variate model was used to simulate the first-pass of the arterial input:

\[
C_{a}^{\text{first-pass}}(t) = K \cdot (t-t_0) \cdot t^\alpha \cdot e^{-(t-t_0)/\tau},
\]

where \(K, \alpha\) and \(\tau\) are model parameters and \(t_0\) the bolus arrival time (values used were \(K=3, \alpha=3, \tau=3\) and \(t_0=0\)). Recirculation component was also modeled by convolving the gamma variate in (10) with an exponential function with a delay of 15 s and time constant of 30 s. Perfusion was set at half the value at first pass to compensate for leakage of contrast agent from the vascular space into the interstitial space. The obtained function was added to (10) to obtain the arterial input \(C_a(t)\) (Figure 1).

To test the performance of the different methods to estimate the residue function \(r(t)\) and its initial height (=blood perfusion), different shapes of potential residue curves were chosen. Four different models were considered, which were simulated with a constant perfusion \((P)\) of 1, 3, 10 and 20 ml/min/g:

**Exponential**

\[
r(t) = P \cdot e^{-t/\tau},
\]

with \(\tau = 3\).
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Fermi

\[ r(t) = P \cdot \frac{2}{1 + e^{-t/\tau}} , \]

with \( \tau = 3 \).

Lorentzian

\[ r(t) = P \cdot \frac{(\frac{1}{2} \Gamma)^2}{t^2 + (\frac{1}{2} \Gamma)^2} , \]

with \( \Gamma = 3 \).

Gamma variate

\[ r(t) = \frac{P}{(a \cdot \tau)^{3} \cdot e^{-t} \cdot e^{-t/\tau}} , \]

with \( \tau = 3 \) and \( a = 3.5 \). This function was used to simulate the case of bolus dispersion. Perfusion was estimated as the maximum of the residue curve. Note that, this function is only used as a theoretical case. Evaluation of the effect of dispersion on estimates of perfusion and \( r(t) \) would require a separate study. Figure 2 shows examples of residue curves when simulated using the four different residue functions and parameters as described.

The output \( C_t(t) \) was determined by convolving the residue function with \( C_a(t) \). Data was simulated with a sample period of 1 s and total simulation length was 50 s (Figure 1). Estimated \( r(t) \) was compared to simulated \( r(t) \) using the root-mean square error (RMSE). The last 10 s of \( r(t) \) was removed before the RMSE calculation to minimize the sensitivity of border effects at the end of the \( r(t) \).
Results

The results of the different deconvolution techniques using a series of underlying residue functions are presented in Figure 3. The data are presented for SNR = 15 dB and perfusion of 3 ml/min/g. The left panels show estimates of perfusion and the right panels show the RMSE between simulated and estimated \( r(t) \), further indicated as RMSE. Table 1 shows a global comparison of all techniques based on all simulations with different noise levels and simulated blood perfusions.

The model-dependent deconvolution techniques all yielded bias in estimated perfusion that increased for higher simulated perfusion. Results were less biased when the underlying (simulated) \( r(t) \) was described by the chosen function. RMSE was largest for the gamma variate residue function.

With respect to the model-independent techniques, the truncated SVD approach yielded significant oscillations in estimated \( r(t) \), resulting in a persistent underestimation of perfusion for all but gamma variate \( r(t) \). RMSE was moderate with only a small confidence interval. Removing too many singular values lead to an increased underestimation of perfusion. Removing too little eigenvalues lead to unstable solutions. The optimal threshold to optimize between these extremes was 5% of the largest singular value. Oscillations in \( r(t) \) were reduced by Tikhonov regularization when matrix \( L \) was a first order derivative operator and were almost completely dissolved by choosing \( L \) as a second order derivative operator. Despite, estimated perfusion was still biased, which was even larger compared to the truncated SVD technique. The subsequent parts of \( r(t) \) were well identified by Tikhonov regularization.

Application of additional constraints to the solution of \( r(t) \) by a basis of B-splines resulted in a reduced bias of estimated perfusion. Despite Tikhonov regularization, B-splines occasionally aggravated oscillations in estimated \( r(t) \), irrespective of the choice of \( L \). The occurrence of these unwanted oscillations was sensitive to the number of break points; e.g. with 10 break points unstable solutions occurred in ±30% of cases, while with 5 break points only ±2% of solutions was unstable. This number was assumed to be optimal. Further reducing the number of break points resulted in reduced accuracy of estimated \( r(t) \) and in significant border effects at the final part of \( r(t) \) (i.e. deviation from true \( r(t) \)).

The system identification approach using an output error model was most robust to noise for a single pole in case the underlying \( r(t) \) was equal to an exponential, Fermi or Lorentzian function. In this situation, it behaves just like the exponential model-based deconvolution. For the gamma variate function best results were obtained for two poles and a single zero. Pre-filtering the input and output data using optimal cut off frequencies did not affect the optimal model orders.
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**Figure 3** - Estimation results of blood perfusion and RMSE of estimated $r(t)$ by application of different deconvolution techniques for SNR = 15 dB and perfusion of 3 ml/min/g. All techniques were applied on simulation data generated using different underlying residue functions: (A) exponential, (B) Fermi, (C) Lorentzian and (D) gamma variate function. Results are shown using boxplots, with the central marks represent the median estimates and the edges of the boxes represent the 25th and 75th percentiles. The simulated (true) blood perfusion is constant for all underlying residue functions and indicated by a solid gray line. Note that the y-limits of the right panel of (D) differ from the other panels.
Discussion

In this study, the performance of different deconvolution techniques was evaluated by application of simulated perfusion data contaminated with white noise. Estimations of $r(t)$ and of blood perfusion were compared.

As deconvolution is an ill-posed problem, different constraints should be applied to the solution of $r(t)$. In particular, difficulties occurred in estimating perfusion due to low excitation power (i.e. data contained little information about the initial part of $r(t)$), located mainly at the upslope of $C_I(t)$. Since this information is located in the high frequency band of the signals where SNR is limited, estimation of perfusion appeared sensitive to noise. As could be expected, the model-based deconvolution techniques had a reasonable accuracy in estimating $r(t)$ for monotonically decaying underlying residue functions (Figure 3A, B and C), but yielded large errors when applied to the gamma variate function (Figure 3D).

The method using B-splines with Tikhonov regularization performed well, although it was sensitive to the number of knots. While a previous study reported an optimum of 15 equally spaced break points$^6$, we obtained better results by reducing the number of break points to 5. However, the optimal number of break points may differ for more complex underlying residue functions than those that were considered in this study. A frequently observed problem of using B-splines, and to lesser extend for Tikhonov regularization, are the border effects at the beginning and final parts of the solution of $r(t)$. These effects increased by further reducing the number of break points. The final border effects were resolved by removing the last 10 s of $r(t)$ - this part is not of special interest. However, the border effects at the beginning of $r(t)$ are a limiting factor in the accuracy of estimated perfusion.

<table>
<thead>
<tr>
<th>Methods</th>
<th>No oscillations in $r(t)$</th>
<th>Unbiased perfusion</th>
<th>Random errors perfusion</th>
<th>Accuracy $r(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fermi$^*$</td>
<td>++</td>
<td>--</td>
<td>++</td>
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<tr>
<td>Exponential$^*$</td>
<td>++</td>
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<td>++</td>
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<tr>
<td>System identification$^*$</td>
<td>++</td>
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<tr>
<td>Truncated SVD</td>
<td>--</td>
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<td>Tikhonov</td>
<td>++</td>
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<tr>
<td>B-splines + Tikhonov</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
</tr>
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</table>

$^*$ Same underlying residue function not considered. For system identification method exponential residue function is not considered. Values are determined by subjective comparison of simulation results obtained for all SNRs and perfusion values.
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The system identification approach with an output error model yielded stable solutions for low model orders only (one or two poles). Since a low order significantly reduces the degrees of freedom, this method is strictly speaking not model-independent. Probably, increasing the order would be more successful by regularization of the solution. This should be further studied. These findings are in contrast to a study of Seethamraju et al.\textsuperscript{9} who reported successful quantification of perfusion using an autoregressive moving average (ARMA) model structure with orders up to 5 poles and zeros. However, ARMA modeling is generally intended for modeling time series and seems not appropriate here.

Finally, we should acknowledge some limitations. All methods were only evaluated on simulated data contaminated with white noise. It is unknown how these methods would perform on experimental data, as model errors cannot be totally excluded, and noise would probably not only be white. A further limitation is that we did not evaluate the effect of a delay on the estimated of $r(t)$ and blood perfusion.

**Conclusions**

All deconvolution methods were evaluated using series of Monte Carlo simulations to test the ability to reproduce different underlying vascular residue functions and blood perfusions at a range of SNRs. The use of model-dependent approaches may lead to large systematic errors, especially at high perfusions, but appeared very robust both at low and high SNR. The model-independent approaches allowed good reproduction of the true, underlying vascular residue function and perfusion at high SNR. Toward lower SNR, the methods differed significantly. The use of B-splines with Tikhonov regularization had a reasonable accuracy in estimation of perfusion and was less biased than using Tikhonov regularization only. However, this technique was sensitive to the number of break points and should be carefully optimized. Application of this technique to experimental data seems promising.

**Acknowledgements**

We thank Mark Lubberink (Department of Nuclear Medicine & PET Research, VU University Medical Center) for assistance.

**Sources of funding**

T. Kind was financially supported by the Netherlands Organisation for Scientific Research (NWO), Toptalent grant, project number 021.001.120.
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