Time separation technique with the basis of trigonometric functions as an efficient method for flat detector CT brain perfusion imaging

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Abstract

Dynamic perfusion imaging is routinely used in the diagnostic workup of acute ischemic stroke (AIS). At present, perfusion imaging can also be performed within the angio suite using flat detector computed tomography (FDCT). However, higher noise level, slower rotation speed and lower frame rate need to be considered in FDCT perfusion (FDCTP) data processing algorithms. The Time Separation Technique (TST) is a model-based perfusion data reconstruction method developed to solve these problems. In this contribution, we used TST and dimension reduction, where we approximate the time attenuation curves by a linear combination of trigonometric functions. Our goal was to show that TST with this data reduction does not impair clinical perfusion measurements. We performed a realistic simulation of FDCTP acquisition based on CT perfusion (CTP) data. Using these FDCTP data, we showed that TST provides better results than classical straightforward processing. Moreover we found that TST is robust to additional noise. Furthermore, we achieved a total processing time from reconstruction of FDCTP data to generation of perfusion maps of under 5 minutes. Perfusion maps created using TST with a trigonometric basis from FDCTP data show equivalent perfusion deficits as CT perfusion maps. Therefore, this technique can be considered a fast reliable tool for FDCTP imaging in AIS.

Keywords: CT Perfusion, Stroke Imaging, Perfusion Imaging, Computed Tomography, Algorithm Development

1. Introduction

CT perfusion (CTP) is a technique used to quantify and visualize impaired brain’s hemodynamics in acute ischemic stroke (AIS) due to large vessel occlusion (LVO). Perfusion imaging is used in patient selection for endovascular treatment (EVT) of AIS, see \cite{1,2,3,4,5}. To aid patient selection for EVT in the late time-window after six hours, current American Stroke Association guidelines recommend performing a CTP, see \cite{6}.

By now, flat detector imaging (FDCT) has been described as a promising first-line image modality within the angiosuite, as it speeds-up the AIS workflow, see \cite{7,8,9,10}. Feasibility of FDCT perfusion (FDCTP) in AIS has already been shown in practise, see \cite{11}. However, when compared with CTP, FDCTP suffers from higher noise-level, lower frame rate and slower rotation speed. To overcome these drawbacks, there is an ongoing effort to improve FDCTP processing algorithms, see \cite{12,13,14,15,16,17,18}. Time separation technique (TST) is a

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promising technique to compensate high level of noise, slow rotation speed and produce highly reliable perfusion maps, see [17]. However, studies on real-world perfusion data using TST are still scarce.

We aimed to apply TST using a basis of trigonometric functions, derived from first terms in trigonometric polynomial, on clinical CTP data sets. Our hypothesis was that (i) the basis of trigonometric functions is suitable for the data reduction of CTP data and that (ii) TST can improve FDCPT maps.

This paper is structured as follows. The materials and methods section first describes the dataset and patient group used. Then the algorithms for processing the perfusion data are explained in detail. Next, the creation of realistically simulated FDCTP data based on CTP data is described. Emphasis is placed on describing the differences between the TST and the straightforward method. The basis functions used for dimension reduction are also introduced. For completeness, the procedure for generating perfusion maps and the data visualization procedure are also added. In the results section, the perfusion maps using the proposed dimension reduction of CTP data are first compared with the perfusion maps without dimension reduction. Then, the results based on simulated FDCTP data are presented. Specifically, a comparison of TST with the straightforward method is provided. Then, results involving data with additional noise are shown. The results section presents both quantitative results in the form of Pearson correlation coefficient comparisons for each method and qualitative results in the form of perfusion maps for a selected patient. Finally, in the Discussion and Conclusion sections, the results are summarized and an optimal trigonometric basis for TST is proposed that can be used to process FDCTP data with results comparable to CTP.

2. Materials and methods

A total of 7 patients were included. All patients had symptoms of AIS due to suspected LVO and underwent multimodal CT. Four patients with AIS due to LVO and 3 patients without LVO between December 2019 and July 2020 were randomly selected. Table 1 summarizes the basic characteristics of the patient cohort, including age, ischemia location and stroke severity scoring.

CT was performed using a 128-section scanner (Somatom Definition AS+; Siemens Healthcare GmbH, Forchheim, Germany). CTP was performed in caudocranial direction. Coverage in the z-axis was 96 mm, centered in the basal ganglia (80 kV, 80 mAs). Acquisition of one scan every 1.5 s over a period of 67.98 s was initiated with a delay of 2 s after contrast injection. At a rate of 5 mL s⁻¹, 30 mL contrast agent (Imeron® 400, Bracco Imaging, Konstanz, Germany) were injected through an 18-gauge cubital-vein-cannula followed by 50 mL of saline flush. During each CTP scan, a total of 35 volumes were created with dimensions (nₓ, nᵧ, nₗ) = (512, 512, 31) with voxel sizes (Δₓ, Δᵧ, Δₗ), where Δₓ = Δᵧ = 0.39 mm and Δₗ = 3.0 mm.

In all subjects, the arterial input function (AIF) was located in the internal carotid artery (ICA) near the skull base. In LVO patients, the ICA opposite to the occlusion side was used. In control subjects, the AIF was located in the left ICA.

Informed consent was gathered by the patients or legal representatives according to local law and regulations. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.
Table 1: Characteristics of the patient cohort. NIHSS refers to National Institutes of Health Stroke Scale, which is a 42 points scale of the severity of the stroke based on physical examination, see [19]. The modified Rankin scale (mRS), see [20], was used to evaluate the degree of disability of the patients at show up and after 90 days. The scale has range 0 meaning no disability to 6 meaning death of the patient. Columns Location and Side describe location and side of the ischemic blockade. AIF location describes the site where we select arterial input function for perfusion imaging. ICA stands for internal carotid artery and M1 and M2 stands for respective segments of middle cerebral artery.

| PtsID | Age | LVO | NIHSS | mRS initial | mRS day 90 | Onset to CT [min] | Location | Side | AIF location |
|-------|-----|-----|-------|-------------|------------|------------------|----------|------|--------------|
| 1A    | 81  | ✓   | 17    | 3           | 3          | 144              | M1       | R    | ICA L        |
| 2A    | 73  | ✓   | 7     | 2           | 6          | 205              | M2       | L    | ICA R        |
| 3A    | 87  | ✓   | 7     | 1           | 1          | 117              | M2       | L    | ICA R        |
| 4A    | 85  | ✓   | 15    | 0           | 5          | 90               | ICA      | R    | ICA R        |
| 1B    | 79  | x   | -     | -           | -          | -                | ICA      | L    | ICA L        |
| 2B    | 35  | x   | -     | -           | -          | -                | ICA      | L    | ICA L        |
| 3B    | 87  | x   | -     | -           | -          | -                | ICA      | L    | ICA L        |

2.1. Algorithms

Analysis of the brain perfusion involves complex processing of the CTP or FDCTP data. Precise algorithms to process perfusion data vary from vendor to vendor, see [21, 22, 23]. Therefore, reproducibility of results is an important issue, see [24, 25]. For the sake of unambiguity and accuracy, we describe extensively the perfusion imaging algorithms we use in this paper. We have developed and implemented the entire CTP and FDCTP data processing pipeline from scratch. This low level universal pipeline is able to process variety of perfusion data sets and was extensively tested using data from various devices, see [26, 27].

The processing of perfusion data consists of three major steps. First, the scanned volume is discretized using voxels. Each voxel is associated with a scalar function of time that corresponds to the dynamics of the contrast agent during the scan, called the time attenuation curve (TAC). In the straightforward approach, the TACs are modeled as an interpolation of the individual reconstructed volumes. In model based approaches, such as TST, the TACs are approximated by a mathematical model and are often from some low-dimensional space of temporal functions. In the second step of perfusion processing, the arterial input function (AIF) has to be determined. This is a single TAC that represents the dynamics of the contrast agent at the arterial input site. The selection of the AIF is a critical step because the value of perfusion parameters throughout the volume depends on it. The last step is to compute the perfusion parameters and produce perfusion maps. We use the deconvolution based model described in [28], where we regularize deconvolution operator using Tikhonov regularization.

2.2. Time attenuation curves estimation for CTP

Let $\mathcal{I} = [0, T]$ be the time interval of the CTP scan, then the TAC $x_i(t)$, $t \in \mathcal{I}$ is sought for $i$-th voxel. We assume that the CT speed is sufficiently high that a single slice of the reconstructed volume captures one time
Figure 1: FDCTP reprojected data, a single view of the 212-th angle of the first sweep using the flat panel detector with dimensions $616 \times 480$ and patient 1A. The original discretization of the CTP reconstructions causes step-like patterns in the reprojected data. The FDCT field of view is larger compared with the CT acquisition.

instant of the contrast agent dynamics. For a given voxel $i$, the input data contain a series of measurement times $t^i_j$, $j \in \{1 \ldots 35\}$ with corresponding values of the attenuation $x_i(t^i_j)$. Because of the moving table during the acquisition, the times depend on the $z$ index of the particular voxel. To obtain the function $x_i(t)$ over the entire interval $I$, the values $x_i(t^i_j)$ have to be interpolated. We use spline interpolation using Akima splines, see [29]. Spline interpolation was performed using Intel(R) Math Kernel Library 2020 for Linux.

2.3. Simulated FDCTP data

We compare CTP data with the matched data of simulated FDCTP acquisition. During FDCTP acquisition, the C-arm of the FDCT scanner performs 5 consecutive pairs of back and forth rotations to capture the dynamics of the contrast agent. Each unidirectional rotation is called a sweep. One sweep takes 4.1 s and the table is static during the whole process. The time gap between two consecutive sweeps is 2.5 s. The acquired projection data for each sweep contains 248 views of the size $616 \times 480$.

To realistically simulate FDCTP acquisition, we use CTP data with the temporal dynamic model described in section 2.2. We use TT projector, see [30], to create projections of the interpolated CTP volumes. Using this reprojection technique we obtain the projection data that are qualitatively similar and have the same dimensions as the actual FDCTP data, see fig. [1].
The original CTP data contain noise because the perfusion protocol operates under low dose conditions. Reprojection may contribute to additional noise in the simulated FDCTP data. However, depending on the protocol used, the noise level in real FDCTP acquisition may be even higher. Therefore, we simulated the data under two different noise conditions. In the moderate noise scenario, Poisson noise was added to the projection data corresponding to the acquisition of a blank image with $6 \times 10^5$ photons per mm$^2$. The same level of simulated noise was used in [15]. The high noise scenario considers $2.1 \times 10^5$ photons per mm$^2$, which corresponds to the setting used in [14].

2.4. Time attenuation curves estimation for FDCTP data

We compare two approaches to TACs approximation. The first technique corresponds to classical CTP data processing, see section 2.2 and is referred here as the straightforward approach. It uses static reconstructions of FDCT projection data from individual sweeps. The second method, Time Separation Technique is an advanced model-based approach to FDCTP reconstruction, see [17].

The input are projections obtained during the FDCTP scan or simulated FDCTP projections as described in the previous section. Let voxel discretization be introduced and $x_i(t)$, $t \in I$ is the TAC that belongs to the i-th voxel. For all reconstructions in this paper, an algebraic CT reconstruction technique, namely the CGLS method, implemented in an open source package at [https://github.com/kulvait/kct_cbct/](https://github.com/kulvait/kct_cbct/) was used, see [31]. Perfusion processing with algebraic reconstruction generates less noisy results compared to analytical reconstruction, see [17]. CGLS provides fast convergence properties, so we achieve acceptable reconstruction times for given problem.

A step-like pattern appears in the simulated FDCTP data, see fig. 1. This problem is caused by the original discretization of CTP volumes, where the distance between z-slices is $\Delta z = 3.0$ mm. To compensate for this and to avoid introducing additional artifacts, we use the same volume discretization in the reconstruction of the FDCTP data as is the discretization of the original CTP data.

2.4.1. Straightforward approach

Suppose the flat detector has $m = m_1 \cdot m_2$ pixels. During the FDCTP scan interval $I = [0, T]$, $R$ one-way rotations called sweeps are performed. During one sweep, projection data corresponding to $Q$ different angular configurations of the source and detector are acquired. Using the temporal function $p_q(t) : I \rightarrow \mathbb{R}^m$, the time course of the projection data for a given configuration $q \in \{1 \ldots Q\}$ can be described. For each rotation $r \in \{1 \ldots R\}$ and acquisition configuration $q$ we have an incomplete set of projection data $p^r_q \in \mathbb{R}^m$, where $p^r_q = p_q(t^r_q)$. Here $t^r_q$ corresponds to the time of acquisition of the projection $q$ in sweep $r$.

Let the volume be discretized by $N = N_1 \cdot N_2 \cdot N_3$ voxels. The time-dependent vector $x(t) : I \rightarrow \mathbb{R}^N$ represents the scanned volume at time $t$ to be reconstructed. We assume that for each configuration $q$ there is a projection operator $A_q \in \mathbb{R}^{m \times N}$ that projects the volume $x$ onto the projection data $p_q$ such that

$$A_q x(t) = p_q(t), \quad t \in I. \quad (1)$$

We can assemble all operators $A_q$ and all projection vectors $p_q(t)$ to get the global operator $A \in \mathbb{R}^{M \times N}$ and the

\[5\]
The equation (2) cannot be used to reconstruct the TAC because it is valid only for a given time instant and the projections \( p^r_q \), \( q \in \{1 \ldots Q\} \) were obtained during the time interval of the corresponding rotation \( I^r = [a^r, b^r] \). In the straightforward approach, we neglect this fact and assume that the projections \( p^r_q \) were obtained at time \( t^r = (b^r - a^r)/2 \). Then the equation (2) can be used to statically reconstruct the volumes \( x^r = x(t^r) \) corresponding to the rotations \( r \in \{1 \ldots R\} \). To approximate the contrast agent dynamics based on static volumes, we use the same spline approximation approach as for CTP data, see section 2.2.

### 2.4.2. Time separation technique and trigonometric basis

The straightforward approach violates the model (2) when performing reconstructions. Model based approaches, see [12, 13, 17], assume that TACs can be modeled as a linear combination of a set of \( K \) temporal functions. Under this assumption, the model (2) can be applied to the resulting data without further approximations. Time separation technique, see [17], additionally exploits the linearity of the projection operator and performs the data reduction in the projection space. Let’s suppose that

\[
B = \{\Psi_1, \ldots, \Psi_K\}
\]

is the set of temporal profiles \( \Psi_i = \Psi_i(t), t \in I, i \in \{1 \ldots K\} \). We assume that the functions \( \Psi_i \) are from the vector space \( V \) with a scalar product \( \langle ., . \rangle \) and that they are mutually orthogonal, so \( \langle \Psi_i, \Psi_j \rangle = 0 \) for \( i \neq j \). Therefore, the set \( B \) forms an orthogonal basis that generates the subspace \( V^B \subset V \) of dimension \( K \).

TST is based on the assumption that the time dynamics of each voxel can be expressed as a linear combination of basis functions

\[
x(t)(x_1, x_2, x_3) = \sum_{k=1}^{K} w^k(t) \Psi_k(t),
\]

and that the projection data can also be decomposed as

\[
p_q(t)(m_1, m_2) = \sum_{k=1}^{K} c^k_q(t) \Psi_k(t).
\]

We can reformulate the equation (2) by means of (3) and (4) into the form

\[
A \sum_{k=1}^{K} w^k \Psi_k(t) = \sum_{l=1}^{K} c^l(t) \Psi(t), \quad t \in I = [0, T].
\]

TST was introduced to decouple contrast agent dynamics over time from volume reconstruction. Equation (5) implies that the temporal dynamics is given by the basis functions from \( B \) and the spatial information is encoded by the coefficient vectors \( c^l \) and \( w^k \). If we perform the scalar product of the both sides of the equation (5) with any function \( \psi_i, i \in \{1 \ldots K\} \), we obtain

\[
A \sum_{k=1}^{K} w^k(t) \psi_i = \sum_{l=1}^{K} c^l(t) \psi_i,
\]
which can be used for reconstruction in the case of a non-orthogonal basis. The orthogonality of the basis further simplifies the equation to the form
\[ A w^i = c^i, \quad i \in \{1 \ldots K\}. \] (7)
The equation (7) induces the problem of reconstructing \(K\) unknown vectors \(w^i, i \in \{1 \ldots K\}\), in other words \(K\) standard static reconstruction problems. Thus, under the TST assumptions, we can recover the full temporal dynamics by solving \(K\) static reconstruction problems.

In order to use (7) to compute the coefficients \(w^i\) and recover the volume dynamics (3), we need to estimate the coefficients \(c^i, i \in \{1 \ldots K\}\) describing the dynamics of the projection data (4). To do this, we use standard regression analysis using the given basis functions. For each \(p_q\) we have the number of measurements equal to the number of rotations of the FDCT. Specifically, we have that \(p_q(r_q) = p_r\) for \(r \in \{1 \ldots R\}\) and we can fit these numbers to the equation (4) to obtain the vectors \(c^l, l \in \{1 \ldots K\}\) as the least squares solution.

In this work, we have chosen a basis consisting of mutually orthogonal trigonometric functions \(\Psi_0 = 1, \Psi_1 = \sin\left(\frac{2\pi t}{T}\right), \Psi_2 = \cos\left(\frac{2\pi t}{T}\right), \Psi_3 = \sin\left(\frac{4\pi t}{T}\right), \Psi_4 = \cos\left(\frac{4\pi t}{T}\right), \Psi_5 = \sin\left(\frac{6\pi t}{T}\right), \Psi_6 = \cos\left(\frac{6\pi t}{T}\right)\). (8)

We use either the basis \(\mathcal{T}_4 = \{\Psi_0, \Psi_1, \Psi_2, \Psi_3, \Psi_4\}\) or \(\mathcal{T}_6 = \{\Psi_0, \Psi_1, \Psi_2, \Psi_3, \Psi_4, \Psi_5, \Psi_6\}\). Since \(\Psi_0\) is constant, we refer to \(\mathcal{T}_4\) and \(\mathcal{T}_6\) as to the bases of four and six trigonometric coefficients. Therefore, we represent the data by a low-order trigonometric polynomial with period \(T\).

2.5. Perfusion maps

The perfusion data obtained by the techniques described above consist of TACs \(x_i(t), t \in I\), where \(i\) is the voxel index. The perfusion parameters, namely cerebral blood flow CBF, cerebral blood volume CBV, mean transit time MTT and time to peak TTP, represent the aggregate information about the perfusion in a given voxel calculated from the perfusion data. Mathematically, these parameters can be formalized using functionals that assign a single real number representing the value of a given perfusion parameter to a particular temporal function \(x(t), t \in I\). Calculating the perfusion parameters for the entire imaged volume yields so-called perfusion maps, which are the diagnostic output of perfusion imaging.

Here we briefly outline the method of computing perfusion parameters based on the indicator dilution theory as described in [28]. To use this theory, we need to discretize time attenuation functions \(x(t), t \in I\) by the vector \(x \in \mathbb{R}^G\), which represents their values in \(G\) equidistant points of the interval \([0, T]\) such that the \(k\)-th component of the vector \(x\) is
\[ x^k = x(\Delta(k - 1)), \quad \Delta = \frac{T}{G - 1}, \quad k \in \{1 \ldots G\}. \] (9)
In this study, the interval granularity was set to \(G = 100\). Calculations of all perfusion parameters except TTP depend on the arterial input function \(x_{AIF} \in \mathbb{R}^G\). Therefore, the selection of \(x_{AIF}\) is essential for the quality of perfusion imaging. Let the discretized TAC for a given voxel be given by the function \(x_v \in \mathbb{R}^G\). It is assumed that there exists a convolution kernel \(k_v \in \mathbb{R}^G\) such that
\[ x_v = x_{AIF} * k_v, \] (10)
where \( \ast \) is a discrete convolution operator for which the following equation holds

\[
\begin{pmatrix}
    x_1^1 \\
    x_2^1 \\
    \vdots \\
    x_G^1
\end{pmatrix}
= \begin{pmatrix}
    x_{AIF}^1 & 0 & 0 & \cdots & 0 \\
    x_{AIF}^2 & x_{AIF}^1 & 0 & \cdots & 0 \\
    \vdots & \vdots & \vdots & \ddots & \vdots \\
    x_{AIF}^G & x_{AIF}^{G-1} & x_{AIF}^{G-2} & \cdots & x_{AIF}^1
\end{pmatrix}
\begin{pmatrix}
    \Delta k_1^1 \\
    \Delta k_2^1 \\
    \vdots \\
    \Delta k_G^1
\end{pmatrix}
\] (11)

The Toeplitz matrix

\[
X_{AIF} = \begin{pmatrix}
    x_{AIF}^1 & 0 & 0 & \cdots & 0 \\
    x_{AIF}^2 & x_{AIF}^1 & 0 & \cdots & 0 \\
    \vdots & \vdots & \vdots & \ddots & \vdots \\
    x_{AIF}^G & x_{AIF}^{G-1} & x_{AIF}^{G-2} & \cdots & x_{AIF}^1
\end{pmatrix}
\] (12)

is a discrete version of convolution operator. Theoretically, by inverting the matrix \( X_{AIF} \), we can obtain the convolution kernel using the equation \( \Delta k_v = X_{AIF}^{-1} x_v \). The matrix \( X_{AIF} \) contains tiny singular values that represent noise, see [28]. Therefore, the computation of the \( X_{AIF}^{-1} \) is an ill-conditioned problem that needs to be stabilized. Our aim is to invert parts of \( X_{AIF} \) corresponding to large singular values and to diminish the influence of extremely small singular values by constructing the matrix \( X_{AIF}^{INV} \approx X_{AIF}^{-1} \). Tikhonov stabilization or truncated SVD are usual techniques to compute the matrix \( X_{AIF}^{INV} \), for details see [28]. Tikhonov stabilization better reduces the solution oscillations and was chosen as a preferable variant based on our data. In this study, we used the parameter \( \lambda_{rel} = 0.2 \).

Let AIF be given by the vector \( x_{AIF} \in \mathbb{R}^G \). We construct the convolution matrix \( X_{AIF} \) and approximate its inverse \( X_{AIF}^{INV} \) using Tikhonov stabilization. The perfusion parameters for a given attenuation curve \( x_v \in \mathbb{R}^G \) are computed as follows.

**Time to peak** is computed as a time when the maximum TAC value is reached. First, we calculate the index of the maximum element of the vector \( x_v \)

\[
i_{\text{TTP}}(x_v) = \min \{ p : x_v^p \geq x_v^i, \text{ for all } i \in \{1 \cdots G\} \}.
\] (13)

Using \( i_{\text{TTP}}(x_v) \) we compute time to peak from the equation

\[
\text{TTP}(x_v) = \Delta (i_{\text{TTP}}(x_v) - 1).
\] (14)

**Cerebral blood flow** according to indicator dilution theory shall be expressed as the first element of the convolution kernel \( k_v^1 \). According to the model [11], we investigate how close a given TAC resembles the shape of the AIF without any delay. In the paper [28, p. 9], the authors noticed that taking the first element of the vector \( k_v \) leads to instabilities, and suggest using its maximum value instead. This choice has apparently been implemented in some perfusion processing software. By mathematical intuition, we now seek the value of \( k_v \) at which the shape of the TAC most closely resembles the AIF, irrespective of the delay. We observe that this makes the dynamics of the CBF very similar to that of the CBV value, making their ratio, MTT, mostly redundant. Since MTT is supposed to be an indicator of collateral flow, the algorithm in [28, p. 9] could undermine the quality of therapeutic decisions. By taking the maximum of \( k_v \) in the CBF calculation, MTT would not accurately capture
the flow delay due to collateral flow reconstitution, and the perfusion deficit could be erroneously assessed as not being accompanied by collateral reconstitution. On the other hand, taking $k_i$ could lead to underestimation and instability of CBF due to noise and the presence of a natural flow delay between the arterial input and the measured parenchymal location. A compromise approach used in this work is to calculate the maximum of the convolution kernel over a short period at the beginning of the acquisition.

In this study, we set the parameter $T_{CBF}^{MAX} = 5$ s and take the maximum of $k_i$ in the interval $[0, T_{CBF}^{MAX}]$. More precisely we set

$$\text{CBF}(x_v) = \max\{k_i^v, \quad i \in \{1 \cdots G\}, \quad (i - 1)\Delta \leq T_{CBF}^{MAX}\}. \quad (15)$$

Setting $T_{CBF}^{MAX} = T$ in Eq. (15) yields the method of calculating CBF according to [28, p. 9], while setting $T_{CBF}^{MAX} = 0$ in (15) leads to the theoretically optimal value from indicator dilution theory.

Cerebral blood volume is related to the amount of blood that flows through a given voxel. We compute it by integration or, in the discrete case, by summing all values of the vector $k_v$.

$$\text{CBV}(x_v) = \sum_{i=1}^{G} k_i^v. \quad (16)$$

Mean transit time refers to the time it takes for a unit of blood with contrast medium to be transferred through a given area. Its elevated values at normal CBV may refer to collateral flow reconstitution. It is calculated as the ratio of CBV to CBF

$$\text{MTT}(x_v) = \frac{\text{CBV}(x_v)}{\text{CBF}(x_v)}. \quad (17)$$

2.6. Segmentation of the soft tissues of the brain for visualization

Brain perfusion is a technique that shows the state of perfusion of the soft tissues of the brain. During visualizations, it is important to exclude any signal that would impair the readability of the resulting perfusion maps. It is important to exclude areas outside the intracranial region and to remove large vessels from the visualization, as high signal from vessels would impair the contrast of perfusion data in the parenchyma.

To create a soft tissue mask, we use thresholding based on a range of Hounsfield units $[20, 100]$ combined with the boundary fill algorithm with the seed inside intracranial area. In the straightforward method, we segment based on the average of the reconstructed volumes and in the case of TST we use a coefficient corresponding to a constant basis function $\Psi_0 = 1$ to guide the segmentation. This choice of volumes reduces noise in both CTP and FDCTP data.

To exclude large blood vessels from the visualization, we can create a mask based on the one percentile of the highest intracranial CBF signal. The CBF signal is an order of magnitude higher in vessels than in soft tissues. It has been shown recently, that a high CBF signal is a robust predictor that can be used in segmenting the cerebral vasculature, see [27]. The drawback of this approach is that segmentation would implicitly depend on the position of the AIF from which the CBF signal is calculated. Therefore, we calculate the CBFGV parameter, which is calculated as the CBF from Eq. (15), based on the artificial AIF given by the Gamma variate function

$$x_{GV}(t) = \frac{t}{t_{max}} \exp \left(1 - \frac{t}{t_{max}}\right), \quad t \in [0, T], \quad (18)$$
where $t_{\text{max}}$ is the peak time, see [32]. In this study, we set $t_{\text{max}} = 9$ s. The high CBFGV values in the perfusion data still correspond to the signal of large vessels and therefore we use the upper percentile of this signal for their segmentation. Because CBFGV can be calculated before localizing the AIF, this parameter can also be a guide to the exact location of the AIF.

2.7. Visualization and additional Gauss blur

For visualization of perfusion maps, we use the color map [33], designed by the Acute Stroke Imaging Standardization Group Japan. To reduce noise in the data and to ensure comparability with the results of the major perfusion packages, we add the Gauss blur with $\sigma = 3.5\text{ px} = 1.365\text{ mm}$ to all slices of perfusion maps regardless the type of map and processing algorithm.

2.8. Correlation of perfusion maps

In addition to the visual comparison of the generated perfusion maps, we implemented a quantitative metric to compare their similarity. We use Pearson’s correlation coefficient to quantitatively study the differences between perfusion maps produced by different approaches. First, we apply a brain soft tissue mask to the two maps being compared, excluding large vessels, see section 2.6. Then, we correlate the pairs of corresponding values in the compared maps in a 48 mm wide region in the middle of the volume. Based on this approach, we create tables with correlations of perfusion parameters CBF, CBV, MTT and TTP for all study subjects, see tables 2 to 4.

3. Results

In this section, first, the differences between ground truth CTP data and the CTP data of reduced dimension will be introduced. Next, results obtained using realistic simulations of FDCTP data will be presented, see section 2.3. To study the different noise levels during FDCTP acquisition, two different scenarios were used, a moderate noise scenario and a high noise scenario, see section 2.3. Using this approach, we obtain two different simulated FDCTP perfusion data for each study subject, which differ in the level of initial noise. From now on, we will simply refer to them as moderate or high noise FDCTP data.

The CTP scans of all study subjects were processed according to section 2 materials and methods. We consider the CTP data processed by the straightforward method, see section 2.2, being ground truth data and therefore compare all other analyses with them, see fig. 3 as an example slice of the ground truth perfusion maps for Patient 1A. Perfusion maps are calculated for all analyses according to section 2.5.

AIF was uniquely determined for each study subject by a single voxel for all analyses to ensure comparability of results. In fig. 2 top, the comparison of the AIF reconstructed from the CTP data with the AIF reconstructed from the FDCTP datasets with different level of the noise for Patient 1A is shown. In fig. 2 bottom there is a comparison of the AIF reconstructed using CTP data with the reduced dimension and using TST on the FDCTP data with the basis of the four trigonometric functions $T_4$ for the Patient 1A.
3.1. Dimension reduction for CTP data

By means of regression analysis and least squares fitting, the dimension of the original CTP data was reduced using the bases $T_4$ and $T_6$ of four and six trigonometric functions, respectively, which are defined in (8). This corresponds to fitting a low-dimensional trigonometric polynomial to the TACs. We obtain the volume coefficients related to the particular basis functions in Eq. (3). Table 2 shows the correlation coefficients between the perfusion maps generated using the ground truth data and the reduced dimension data using the $T_4$ and $T_6$ bases of the four and six trigonometric functions, respectively. By comparing fig. 3A with fig. 3B, the difference between the ground truth CTP maps and the maps generated from the data of reduced dimension using the $T_4$ basis can be seen in the example visualization of Patient 1A.

3.2. Comparison of TST with the straightforward method for FDCTP data

Figure 2: Patient 1A. AIF derived from spline interpolation of CTP data and straightforward processing of FDCTP data (TOP). AIF derived from reduced-dimension CTP data and from FDCTP data processed using TST with $T_4$ basis (BOTTOM).
Figure 3: Perfusion parameters patient 1A, $z = 15$. A: ground truth CTP data, B: CTP data, dimension reduction to 4 trigonometric functions, basis $T_4$, C: CTP data, dimension reduction to 6 trigonometric functions, basis $T_6$, D: FDCTP data, moderate noise, straightforward method, E: FDCTP data, moderate noise, TST with the basis of four trigonometric functions $T_4$. 
To compare the straightforward method with TST, the FDCTP data were processed in two ways. The straightforward approach uses reconstructions of individual FDCT device rotations, see section 2.4.1. The resulting perfusion maps for the FDCTP data with moderate noise and Patient 1A are shown in fig. 3D. TST uses a dimension reduction of the FDCTP data given by the underlying basis functions, see section 2.4.2. The resulting perfusion maps using TST with the basis $T_4$ for the FDCTP data with moderate noise and Patient 1A are shown in fig. 3E.

Based on section 2.8, a quantitative analysis of the FDCTP data processed by the above two approaches was performed. The tables 3 and 4 compare the ground truth CTP data to the FDCTP data processed by the straightforward method (left) and to the same FDCTP data processed by TST with the $T_4$ basis (right). Table 3 shows comparisons under the moderate noise scenario, while table 4 contains analogous comparisons for FDCTP data with high noise.

### Table 2: Pearson correlation coefficients comparing ground truth CTP data with CTP data of reduced dimension using $T_4$ basis (left) and $T_6$ basis (right). Results for individual perfusion maps.

| Patient | Control | Patient | Control |
|---------|---------|---------|---------|
|         | 1A 2A 3A 4A | 1B 2B 3B | 1A 2A 3A 4A | 1B 2B 3B |
| CBF     | 0.96 0.94 0.96 0.97 | 0.97 0.97 0.98 | CBF     | 0.97 0.96 0.96 0.97 |
| CBV     | 0.94 0.90 0.89 0.91 | 0.91 0.94 0.95 | CBV     | 0.94 0.90 0.91 0.94 |
| MTT     | 0.81 0.79 0.79 0.78 | 0.76 0.75 0.75 | MTT     | 0.84 0.82 0.82 0.80 |
| TTP     | 0.54 0.58 0.59 0.57 | 0.54 0.41 0.47 | TTP     | 0.56 0.66 0.65 0.63 |

### Table 3: Pearson correlation coefficients comparing ground truth CTP data with moderate noise FDCTP data processed by the straightforward method (left) and with moderate noise FDCTP data processed by TST with $T_4$ basis (right).

| Patient | Control | Patient | Control |
|---------|---------|---------|---------|
|         | 1A 2A 3A 4A | 1B 2B 3B | 1A 2A 3A 4A | 1B 2B 3B |
| CBF     | 0.69 0.80 0.67 0.69 | 0.74 0.84 0.82 | CBF     | 0.84 0.80 0.81 0.78 |
| CBV     | 0.82 0.79 0.73 0.74 | 0.79 0.82 0.82 | CBV     | 0.86 0.77 0.76 0.77 |
| MTT     | 0.40 0.38 0.43 0.42 | 0.38 0.36 0.36 | MTT     | 0.59 0.48 0.52 0.50 |
| TTP     | 0.42 0.42 0.36 0.44 | 0.35 0.27 0.25 | TTP     | 0.37 0.39 0.38 0.41 |

### 3.3. Running times

The CT reconstruction problems were solved using the OpenCL implementation of the CGLS method, see [31], using five RTX2080 Ti GPUs. Other computations were performed on a machine with four Intel Xeon E7-8890 CPUs. We use SSDs and parallel processing to achieve the highest possible speed. We compare the processing of FDCTP data using TST with the $T_4$ basis, which contains a total of 5 basis functions, with the straightforward method. We report the average running times of the given algorithms.

Data preprocessing took an average of 17 s for both the TST and the straightforward method. Fitting the five basis functions to the data within the TST took 71 s. The reconstruction took 128 s on average for the TST. For
Table 4: Perarson correlation coefficients comparing ground truth CTP data with high noise FDCTP data processed by the straightforward method (left) and with high noise FDCTP data processed by TST with $T_4$ basis (right).

| Patient | Control | Patient | Control |
|---------|---------|---------|---------|
|         |         |         |         |
| CBF     | 0.57    | 0.70    | 0.52    | 0.63    | 0.59 | 0.78 | 0.73 |
| CBV     | 0.75    | 0.72    | 0.62    | 0.69    | 0.72 | 0.77 | 0.76 |
| MTT     | 0.28    | 0.28    | 0.32    | 0.35    | 0.29 | 0.29 | 0.27 |
| TTP     | 0.33    | 0.32    | 0.26    | 0.33    | 0.27 | 0.21 | 0.19 |
|         |         |         |         |         | CBF | 0.77 | 0.75 | 0.72 | 0.74 | 0.80 | 0.83 | 0.84 |
|         |         |         |         |         | CBV | 0.83 | 0.73 | 0.70 | 0.74 | 0.78 | 0.79 | 0.81 |
|         |         |         |         |         | MTT | 0.47 | 0.38 | 0.41 | 0.42 | 0.34 | 0.36 | 0.34 |
|         |         |         |         |         | TTP | 0.31 | 0.31 | 0.30 | 0.33 | 0.26 | 0.20 | 0.22 |

the straightforward method it was 275 s. The generation of perfusion maps from the reconstructed data using the deconvolution method took 81 s for the TST and 55 s for the straightforward method. We achieved a total time of 4 min 57 s for TST processing and 5 min 47 s for the straightforward method.

4. Discussion

When comparing the AIF profiles of ground truth CTP data with the AIF profiles of FDCTP data calculated by the straightforward method, see fig. 2 top, it is apparent that the imprecision of the AIF estimation when using the FDCT is relatively small. The attenuation profiles of the arterial input are well preserved even in the high-noise scenario. In the case of TST, see fig. 2 below, the situation is similar. Again, the AIF profile for the FDCTP data is close to the AIF profile obtained from the CTP data by dimension reduction corresponding to a given basis, regardless of the noise level. This is partly due to the fact that the arterial signal with a dynamic change of more than 200 Hounsfield units is the most pronounced of all the TAC curves. In particular, an important aspect of perfusion imaging is the correct capture of soft tissue dynamics, where the signal can be strongly confounded by the low soft tissue contrast during FDCT acquisition due to the presence of noise. This is particularly apparent when processing FDCTP data by the straightforward method, see e.g. fig. 3D, where noise overlays important diagnostic information even in moderate noise scenario.

The TTP perfusion maps calculated from ground truth perfusion data, see section 2.5, contain more noise than the maps of other perfusion parameters. This is evident, for example, from fig. 3A and is related to the fact that TTP is the only parameter for whose computation the deconvolution operator stabilized by Tikhonov regularization is not used. This problem was already described in [14], where the computation of TTP had to be stabilized using Savitzky-Golay smoothing. In our case, the dimension reduction to the trigonometric basis acts similarly to Savitzky-Golay smoothing to stabilize the TAC shapes. Comparing the perfusion maps fig. 3A with fig. 3B, it is clear that the TTP map in fig. 3B visually preserves important perfusion patterns but appears smoother. Therefore, the lower TTP correlations in tables 2 to 4 when using trigonometric bases are affected by the different levels of smoothness of the compared maps.

Studying the dimension reduction of the original CTP data in (3) using the $T_4$ basis of four trigonometric functions, we see that perfusion maps, which preserve important diagnostic information from the ground truth CTP data, were generated, see fig. 3A, fig. 3B and table 2. An interesting finding was that the quality improvement
when using the \( T_6 \) basis, which contains two extra temporal functions compared with the \( T_4 \) basis, was significant neither in terms of the visual quality of the resulting maps, see fig. 3C, nor in terms of quantitative analysis, see table 2.

The TST is a dimension reduction method where all possible shapes of the TACs are reduced to a superposition of \( K \) profiles, where \( K \) is a number that is smaller than the number of rotations of the FDCT machine due to data fitting. As the number of \( K \) increases, the number of reconstructions according to the equation (7) also increases, and it is therefore important to balance the number of basis functions so that they are able to capture the behavior of the contrast agent and produce accurate perfusion maps, and on the other hand to keep this number small enough to reduce noise and computational complexity. Similar to the previous paragraph, a pattern of only small improvement was observed when we used a TST with a \( T_6 \) basis instead of \( T_4 \) basis to process the FDCTP data, data not shown here due to lack of space. Therefore, \( T_4 \) appears to be optimal choice of the trigonometric basis, so we have focused on presenting results using this basis.

The main sources of error in TST are the dimension reduction associated with the selection of basis and the inaccuracy of fitting the projection data to this basis. The results discussed above show that the dimension reduction using \( T_4 \) basis generates perfusion data of high quality comparable to ground truth data. Therefore, we next focus on how TST behaves compared with the direct method when processing FDCTP data with different noise levels.

When processing the FDCTP data and comparing TST using the \( T_4 \) basis with the straightforward method, we see that the correlations of all perfusion parameters except TTP are consistently better for TST, see tables 3 and 4. According to this quantitative comparison, the CBF, CBV and MTT maps show high similarity to the ground truth data for TST. The TTP correlation coefficients are comparable for both methods. The slightly inferior TTP values may be related to different levels of data smoothing as discussed in the previous section. By visual inspection, it can be concluded that TST captures all important information present in the ground truth CT data with less noise than the straightforward method, see e.g. the comparison of D with E in fig. 3.

At higher noise levels, TST performs much better than the straightforward method, see table 4. When using the high noise scenario, the results of the straightforward method deteriorate quickly as they are contaminated by noise, while on perfusion maps that are based on TST with \( T_4 \) basis, it is still possible to detect the perfusion deficit, the visualizations are not shown here due to lack of space.

Comparing the different AIF function profiles of the 7 subjects, we see that the variability of these functions is quite high, data not shown. Therefore, we chose general bases of trigonometric functions instead of specialized bases. The method could be improved in the future by incorporating a priori knowledge of the shape of important TACs. A possible approach is to prepare an orthogonal basis based on PCA analysis of a multi-patient CTP dataset, see [17]. The problem with this approach is the high variability of attenuation profiles and different contrast agent arrival times due to PCA bases not being shift-invariant. Therefore, when using PCA bases, it will be necessary to determine the peak time of AIF for a given perfusion scan. An interesting option could also be to prepare a PCA basis individually for each patient based on FDCTP projection data. Thus, in future research we will investigate whether it is possible to improve the current TST results with trigonometric bases by using a...
priori knowledge-based information.

In this study, we have shown that the Time separation technique is a robust approach suitable for FDCTP data analysis that outperforms the straightforward approach. Using the basis $T_4$ of four trigonometric functions, noise in the data was noticeably reduced and the resulting perfusion maps were able to properly capture the brain perfusion status of stroke patients and control subjects. We will continue to work on the integration of the a priori information into the model and further refinement of the techniques used.

A limitation of the study is the use of simulated FDCTP data instead of actual FDCTP datasets. Using reprojected CTP data with additional noise to create a realistic approximation of FDCTP data was an option to bridge the gap between purely simulated data and patient safety requirements.

From the run times in section 3.3, it is evident that we have managed to speed up the processing times such that the entire perfusion processing can be performed within 5 min. This was achieved due to the TST with a basis of five functions and the fast implementation of algorithms for CT algebraic reconstruction and computation of perfusion maps based on deconvolution. Since TST with this basis requires half the reconstructions compared to the straightforward approach, it is faster and less computationally intensive even with significant parallelization of the problem.

5. Conclusion

In this study, we have shown that the Time separation technique is a robust approach suitable for FDCTP data analysis that outperforms the straightforward approach. Using the basis $T_4$ of four trigonometric functions, noise in the data was noticeably reduced and the resulting perfusion maps were able to properly capture the brain perfusion status of stroke patients and control subjects.

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