Efficient 4D Non-Local Tensor Total-Variation for Low-Dose CT Perfusion Deconvolution

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Abstract. Tensor total variation deconvolution has been recently proposed as a robust framework to accurately estimate the hemodynamic parameters in low-dose CT perfusion by fusing the local anatomical structure correlation and temporal blood flow continuation. However the locality property in the current framework constrains the search for anatomical structure similarities to the local neighborhood, missing the global and long-range correlations in the whole anatomical structure. This limitation has led to noticeable absence or artifact of delicate structures, including the critical indicators for the clinical diagnosis of cerebrovascular diseases. In this paper, we propose an extension of the TTV framework by introducing 4D non-local tensor total variation into the deconvolution to bridge the gap between non-adjacent regions of the same tissue classes. The non-local regularization using tensor total variation term is imposed on the spatio-temporal flow-scaled residue functions. An efficient algorithm and implementation of the non-local tensor total variation (NL-TTV) reduces the time complexity with fast similarity computation, accelerated optimization and parallel operations. Extensive evaluations on the clinical data with cerebrovascular diseases and normal subjects demonstrate the importance of non-local linkage and long-range connections for low-dose CT perfusion deconvolution.

1 Introduction

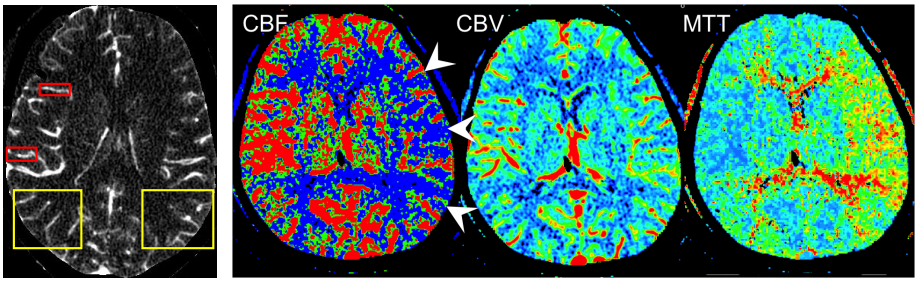
Stroke and cerebrovascular diseases are the leading causes of serious, long-term disability in the United States, with an average occurrence in the population at every 40 seconds. In the world, 15 million people suffer from stroke each year and among these, 5 million die and another 5 million are permanently disabled. The mantra in stroke care is "time is brain". With each passing minute, more brain cells are irretrievably lost and, therefore, timely diagnosis and treatment are essential to increase the chances for recovery. As a critical step in the stroke care, imaging of the brain provides important quantitative measurements for the physicians to "see" what is occurring in the brain. Computed tomography perfusion (CTP), with its rapid imaging speed, high resolution and wide availability, has been one of the most widely accepted imaging modality for stroke care.

Unfortunately, the associated high radiation exposure in CTP have caused adverse biological effects such as hair loss, skin burn, and more seriously, increased cancer risk. Lowering the radiation exposure would reduce the potential health hazard to which the patients are exposed, improve healthcare quality and safety, as well as make CTP modality fully utilized for a wider population. However, low radiation dose in CTP will inevitably lead to noisy and less accurate quantifications. There are various efforts to reduce the necessary radiation dose in CTP, mostly in two classes; noise reduction at the reconstruction stage [1, 2, 3, 4, 5], and stabilization at the deconvolution stage [6, 7, 8, 9].

While the first class of approaches does not solve the inherent instability problem in the quantification (deconvolution) process of CTP, the second class of approaches directly addresses this instability issue. Among these methods, the information redundancy and sparsity is a property that has shed light into the low-dose quantification problems [10, 11, 7, 8], but the sparsity frameworks needs training data for dictionary learning. In another line of work, tensor total variation (TTV) deconvolution [9, 12] has been recently proposed to significantly reduce the radiation dosage in CTP with improved robustness and quantitative accuracy by integrating the anatomical structure correlation and the temporal blood flow model. The anatomical structure of the brain encompasses long-range similarity of the same tissue classes, as shown in Fig. 1(a). However the locality property of the current TTV algorithm limits the search for similar patterns in the 4-connected adjacent neighborhood, neglecting the long-range or global correlations of the entire brain structure. This locality limitation has led to noticeable absence or artifact of the delicate structures, such as the capillary, the insula and the parietal lobe, which are critical indicators for the clinical diagnosis of cerebrovascular diseases. Fig. 1(b) shows the importance of accurate depiction of hemodynamic parameters. The delicate vascular and cerebral structures are critical biomarkers of the existence and severity of the cerebrovascular diseases. Naturally, integrating the long-range and non-local correlation into the estimation process of the hemodynamic parameters would yield more precise depiction of the pathological regions in the brain.

In this paper, we propose a fast non-local tensor total variation (NL-TTV) deconvolution method to improve the clinical value of low-dose CTP. Instead of restricting the regularization of residue functions to the adjoining voxels in the spatial domain and neighboring frames in the temporal domain, the long-range dependency and the global connections in the spatial and temporal dimensions are both considered. While non-local total variation and TTV are not new concepts, the integration of the two methods in a spatio-temporal framework to regularize the flow-scaled residue impulse functions has never been proposed, and can make significant improvement in the perfusion parameter estimation. Furthermore, the efficient algorithm to accelerate the non-local TTV would make the proposed algorithm clinical valuable.

The contribution of this work is two-fold: First, the long-range and global connections are explored to leverage the anatomical symmetry and structural similarity of the same tissue classes in both the spatial and the temporal dimen-



(a) (b)

Fig. 1. (a) The illustration of long-range similarity in the brain. The red and yellow boxes show the non-local regions which have similar patterns. (b) Perfusion parameter maps (CBF - cerebral blood flow, CBV - cerebral blood volume, and MTT - mean transit time) of a 22-year old with severe left middle cerebral artery (MCA) stenosis. Arrows indicate the regions with ischemia. The shape, intensity and coverage of the capillary and vessels are evidence of ischemia in the left hemisphere (right side of the image).

sions. Second, efficient parallel implementation and similarity computation using window offsets reduce the time complexity of the non-local algorithm. The extensive experiments on low-dose CTP clinical data of subjects with cerebrovascular diseases and normal subjects are performed. The experiments demonstrate the superiority of the non-local framework, compared with the local TTV method. The advantages include more accurate preservation of the fine structures and higher spatial resolution for the low-dose data.

2 Efficient Non-local Tensor Total Variation Deconvolution

In this section, we will first briefly review the tensor total variation model for the low-dose CTP and discuss its deficiency in accurate estimation of delicate structure and distinguishing pattern complexities. Based on that, we will introduce the proposed efficient non-local tensor total variation model, followed by experimental results, discussion and conclusion.

2.1 Tensor Total Variation Deconvolution

To reduce the radiation dose in CT perfusion imaging, Tensor total variation (TTV) [9] is recently proposed to efficiently and robustly estimate the hemodynamic parameters. It integrates the anatomical structure correlation and the temporal continuation of the blood flow signal. The TTV algorithm optimizes a cost function with one linear system for the deconvolution and one smoothness

regularization term, as below:

$$K_{TTV} = \underset{K \in \mathbb{R}^{\mathbb{T} \times \mathbb{N}}}{\arg\min} (\frac{1}{2}\|AK - C\|_2^2 + \|K\|_{TTV}^{\gamma}) \tag{1}$$

The first term is the temporal convolution model. In this term, $A \in \mathbb{R}^{\mathbb{T} \times \mathbb{T}}$ is a block-circulant matrix representing the arterial input function (AIF), which is the input signal to the linear time-invariant system of the capillary bed. The block-circulant format makes the deconvolution insensitive to delays in the AIF. $C \in \mathbb{R}^{T \times N}$ is the contrast agent concentration (CAC) curves of all the voxels in the volume of interest (VOI). Both A and C are extracted from the CTP data. $K \in \mathbb{R}^{T \times N}$ is the unknown of this optimization problem - the flow-scaled residue functions of the VOI. Here T is the duration of the signal, and $N = N_1 \times N_2 \times N_3$ is the total number of voxels in the sagittal, coronal and axial directions.

The second term is the tensor total variation regularizer. The TTV regularization is defined as

$$\|K\|_{TTV}^{\gamma} = \sum_{i,j,k,t} \sqrt{\sum_{d=1}^{4} (\gamma_d \nabla_d \tilde{K}_{i,j,k,t})^2} \tag{2}$$

with ∇_d is the forward finite difference operator in the d^{th} dimension, and $\tilde{K} \in \mathbb{R}^{T \times N_1 \times N_2 \times N_3}$ is the 4-dimensional volume reshaped from matrix K with temporal signal for one dimension and spatial signal for three dimensions. t, i, j, k are the indices for the temporal and spatial dimensions. The outside summation means that the square root of the sum of the first order derivative is summed over all the temporal points t and spatial voxels i, j, k of $\tilde{K}$. L_1 norm is used in the forward finite difference operator ∇_d to preserve the edges, and the regularization parameters γ_d designates the regularization strength for each dimension. Cerebral blood flow (CBF) maps can be computed from K as the maximum value at each voxel over time. More details about the TTV framework can be found in [9].

While TTV achieves significant performance improvement on the digital brain phantom and low- and ultra-low dose clinical CTP data at 30, 15 and 10 mAs [9], the locality property of the tensor total variation regularization limits the capability of preserving the small and fine anatomical structures, details and texture in the brain, including the capillary, the insula and the parietal lobe, which are essential indicators of the location and severity of the ischemic or hemorrhagic stroke. It may also create new distortions, such as blurring, staircase effect and wavelet outliers due to the regularization on the adjacent voxels, as shown in Fig. 2. Based on the above observation, we propose a fast non-local tensor total variation (NL-TTV) algorithm to overcome the above limitations of the local TTV method.

2.2 Non-Local Tensor Total Variation Deconvolution

First introduced by [13], non-local total variation has been studied to address the limitations of conventional total variation model, including the blocky effect,

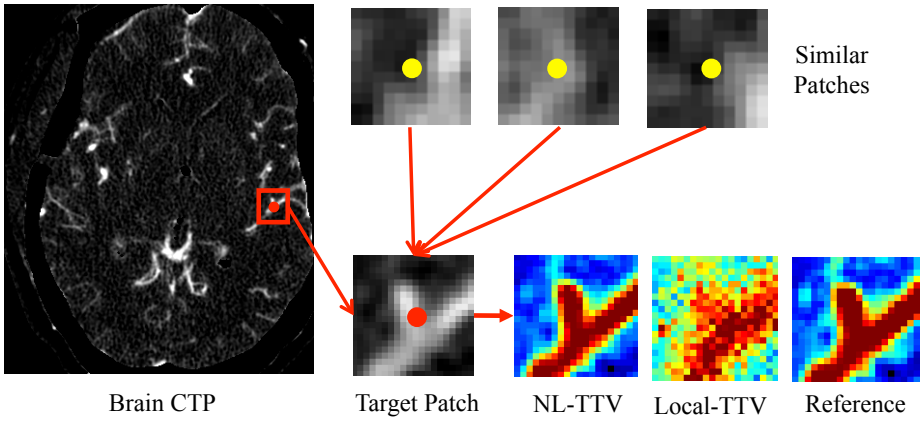


Fig. 2. Illustration of the non-local tensor total variation principle in a 2D image. The NL-TTV regularization term for voxel i (red dot) is a weighted summation of the difference between voxel i and the most similar voxels (yellow dots) in the search window with width W (red box). The weight $w(i,j)$ depends on the patches around the voxels. Compared to local-TTV, which only considers the 4-connected local neighborhood, NL-TTV preserves the accuracy and contrast of the vascular structure with higher fidelity of the reference patch. The actual NL-TTV regularization is imposed on 4D spatio-temporal flow-scaled residue impulse functions across different slices and time points.

the missing of the small edges and the lack of long-range information sharing [14, 15, 16]. It has also been applied to 4D computed tomography [17] and magnetic resonance imaging reconstruction [18]. This work is the first attempt to integrate non-local tensor total variation with the spatio-temporal deconvolution problem in 4D CTP.

The non-local tensor total variation regularizer links each voxel in the volume with the long-range voxels using a weighted function. For every voxel i, instead of computing the forward finite difference on the 4-connected neighbors, we search in a neighborhood window $N(i)$ with window size W, and minimize the weighted differences between the target voxel and voxels in the window. Specifically, the non-local tensor total variation can be formulated as:

$$\|K\|_{NL-TTV} = \sum_i \sqrt{\sum_j (K(i) - K(j))^2 w(i,j)} \tag{3}$$

Here $K(i)$ denotes the value of flow-scaled residue impulse function K at spatio-temporal voxel i, and $w(i,j)$ is a similarity function between the voxel i and j. The higher the similarity between the voxels i and j, the higher the weight function $w(i,j)$. We use an exponential function of the patches surround the two

voxels to model their similarity

$$w(i,j) = \frac{1}{Z(i)} e^{-\frac{\|K(P_i) - K(P_j)\|_2^2}{\sigma^2}} \tag{4}$$

where Z is a normalization factor, with $Z(i) = \sum_j w(i,j)$ and σ is a filter parameter that controls the shape of the similarity function. P_i is a small patch around voxel i with radius d. In this way, when two patches are identical or similar, the weight w will be close to 1; when the two patches are very different, the weight w will approach 0. Non-local total variation has shown superior performance signal reconstruction and denoising [14, 15], and by fusing it with the temporal convolution model, we get

$$K_{NL-TTV} = \underset{K \in \mathbb{R}^{\mathbb{T} \times \mathbb{N}}}{\arg} \min(\frac{1}{2}\|AK - C\|_2^2 + \|K\|_{NL-TTV}) \tag{5}$$

The non-local tensor total variation searches for the similar patches in a larger window instead of the adjacent 4-connected neighbors in the local TTV. In this way, the similar tissue patterns of the same tissue types in the long-range regions of the brain can assist to reduce the artifact and noise in the deconvolution process. This allow the NL-TTV to deconvolve the low-dose CTP volume using long-range and global dependency by removing the noise without distorting the salient structures, as shown in Fig. 2.

It is worthy to note that because the voxel i is any voxel in the spatio-temporal domain of the flow-scaled residue impulse function $K \in \mathbb{R}^{T \times N}$, the NL-TTV is searching the similar patches in the spatio-temporal domain, which includes the multiple slices in the axial direction and the various time points in the temporal sequences.

2.3 Efficient Optimization and Implementation

We implement this algorithm by MATLAB and C++ using mex in MATLAB 2013a environment (MathWorks Inc, Natick, MA) and Windows 8 operating system with 8 Intel Core i5 and 32GB RAM.

Notations: Let's define some parameters first. Let N be the total number of voxels in the entire volume. W be the search window size for the similar voxels around voxel i. d is the radius of the patch around the voxel. N_b is the number of similar voxels chosen to regularize the voxel i in order to speed up the computation. m is the dimension of the spatio-temporal tensor. σ is the Gaussian parameter to control the shape of the similarity function.

In this work, for a 2D slice in the brain CTP data of 512×512 voxels, 120 seconds of scanning duration, $W = 5$ voxels, $d = 4$ voxels, $N_b = 15$, $\sigma = 0.5$. $m = 4$ because the flow-scaled residue impulse functions are spatio-temporal tensor with 4 dimensions.

Brute-Force Search: The non-local tensor total variation has a higher time complexity compared to the local TTV. For each voxel i in the volume, we need to calculate the patch difference between the target voxel and every other voxel

Algorithm 1 The framework of NL-TTV algorithm.

Input: $K^0 = r^1 = 0$, $t^1 = C = 0$, τ
Output: Flow-scaled residue functions $K \in \mathbb{R}^{T \times N_1 \times N_2 \times N_3}$.
for $n = 1, 2, \ldots, N$ **do**
  $C = C + 1$
  (1) Steepest gradient descent $K_g = r^n + s^{n+1} A^T (C - Ar^n)$
  where $s^{n+1} = \frac{vec(Q)^T vec(Q)}{vec(AQ)^T vec(AQ)}$, $Q \equiv A^T(Ar^n - C)$, $vec(\cdot)$ vectorizes a matrix
  (2) Proximal map:
  if $C = \tau$ (*Acceleration Step*) **then**
    $K^n = \text{prox}_\gamma(2\|K\|_{NL-TTV})(fold(K_g))$, $C = 0$
    where $\text{prox}_\rho(g)(x) := \arg\min_u \left\{ g(u) + \frac{1}{2\rho}\|u - x\|^2 \right\}$, and $fold(K_g)$ folds the matrix K_g into a tensor $\tilde{K} \in \mathbb{R}^{T \times N_1 \times N_2 \times N_3}$.
  end if
  (3) Update t, r $t^{n+1} = (1 + \sqrt{1 + 4(t^n)^2})/2$, $r^{n+1} = K^n + ((t^n - 1)/t^{n+1})(K^n - K^{n-1})$
end for

in the search window. Then we rank all the patch differences in voxel i's search window in an ascending order, and pick up the first N_b patches for optimizing the value of i.

The time complexity of the brutal force non-local TTV is $O(N \cdot ((2W+1)(2d+1))^m + N \cdot (2W+1)^m \log(N_b))$. For the parameters above, the computational time reaches up to nearly *10 hours*, which is unrealistic in clinical applications.

Fast Nearest Neighbor Search: An efficient method to compute the intensity difference between two patches is used to accelerate the non-local TTV is needed. Specifically, at each offset $\boldsymbol{w} = (w_x, w_y, w_z, w_t)$ in the search window W, a new matrix D of the same size to the brain volume is created to precompute the patch differences, with $D_{\boldsymbol{w}} = \sum_i (K(i + \boldsymbol{w}) - K(i))^2$. This matrix keeps the sum of the squared differences from the upper left corner to the current voxel. When computing the differences between the two patches at location j and offset w, we only need to compute the value $D(j_x+d, j_y+d) - D(j_x+d, j_y) - D(j_x, j_y+d) + D(j_x, j_y)$. This accelerating method to find the nearest neighbors reduced the time complexity to $O(N \cdot (2W+1)^m + \log(N_b))$. The space complexity is $N \cdot (2W+1)^m$.

Efficient Optimization Algorithm: Due to the relatively slow update in the non-local TTV term, we propose a fast NLTTV algorithm to optimize the objective function in Eq. (5), as outlined in Algorithm 1. In the iterative optimization, K is initialized with zero first, and updated using steepest gradient descent from the temporal convolution model. Then it is further updated using the NL-TTV regularizer with accelerated step. In the accelerated step, instead of alternating between the non-local TTV term and the temporal convolution term once each iteration, we update the non-local TTV term *fewer* times than updating the temporal convolution term, which has shown sufficient accuracy in the experimental results.

Parallel Computing: The intrinsic nature of non-local TTV algorithm allows for multi-threading and parallel computing on the multi-core clusters or grids. We divide the entire brain volume into sub-volumes, with each of them processed by one processor. The patch difference computation for every voxel i and the weight calculation for all the voxels after selecting the top N_b neighbors can be paralleled.

3 Experiments

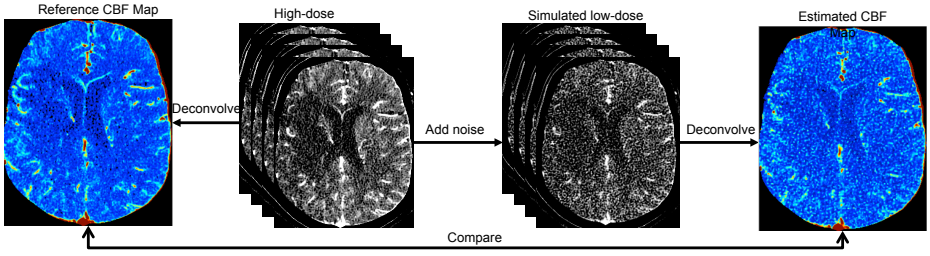


Fig. 3. Simulation of low-dose CTP data from high-dose CTP data and the evaluation framework

Experimental Setting: The goal of our proposed method is to accurately estimate the hemodynamic parameters in low-dose CTP by robust deconvolution (Fig. 3). Due to the ethical issues and potential health risk associated with scanning the same subject twice under different radiation doses, we follow the experimental setting in [9] to simulate low-dose CTP data at 15 mAs by adding correlated Gaussian noise with standard deviation of $\sigma = 25$ [19]. Please note that low-dose simulated is a widely adopted method CT algorithm evaluation in the medical field [20, 21]. The deconvolution methods are evaluated on the simulated low-dose CTP data. The quality of the CBF maps of all methods are evaluated by comparing with the reference maps using peak signal-to-noise ratio (PSNR). While PSNR may not be the best evaluation metric for the clinical dataset, it is an objective reflection of the fidelity between the perfusion maps of the low-dose and the normal dose data.

Our method is evaluated on a clinical dataset of 10 subjects admitted to the Weill Cornell Medical College with mean age (range) of 53 (42-63) years and four of them had brain deficits due to aneurysmal subarachnoid hemorrhage (aSAH) or ischemic stroke, and the rest were normal. CTP images were collected with a standard protocol using GE Lightspeed Pro-16 scanners (General Electric Medical Systems, Milwaukee, WI) with cine 4i scanning mode and 60 second acquisition at 1 rotation per second, 0.5 sec per sample, using 80 kVp and 190 mA. Four 5-mm-thick sections with pixel spacing of 0.43 mm between centers of

columns and rows were assessed at the level of the third ventricle and the basal ganglia, yielding a spatio-temporal tensor of $512 \times 512 \times 4 \times 118$ where there are 4 slices and 119 temporal samples. Approximately 45 mL of nonionic iodinated contrast was administered intravenously at 5 mL/s using a power injector with a 5 second delay.

Results: Fig. 4 shows the representative CBF maps of a subject with brain deficits in the right hemisphere (upper panel) and a normal subject (lower panel). For each subject, from left to right shows the reference map, the low-dose maps of standard singular value decomposition (sSVD) [22], block-circulant singular value decomposition (bSVD) [23], Tikhonov[24], local tensor total variation (TTV) [9], and our proposed non-local TTV (NL-TTV).

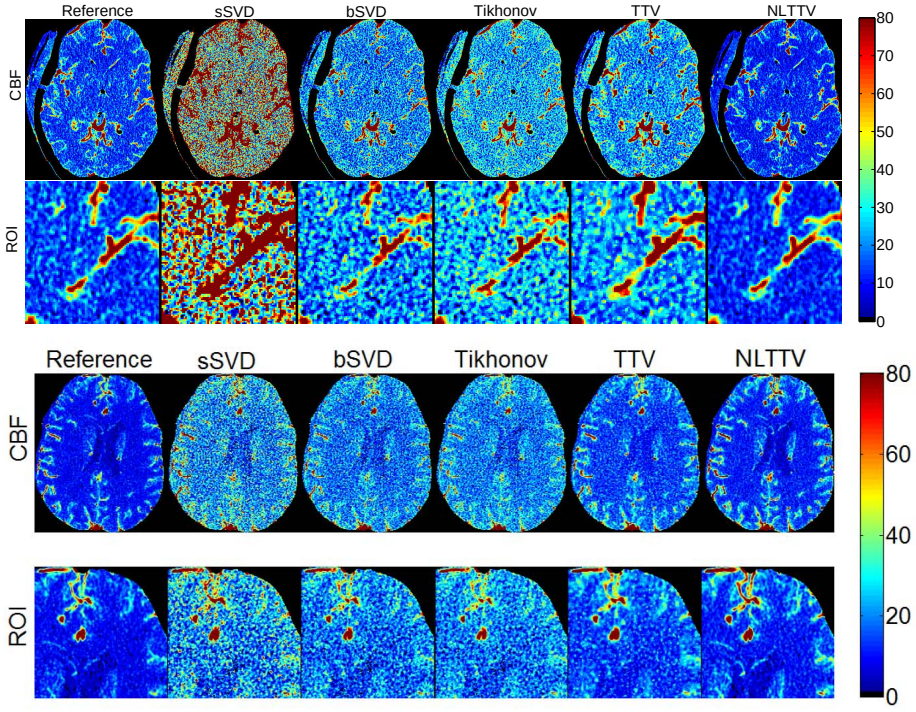


Fig. 4. Results from a subject with right frontoparietal craniotomy due to ischemia in the right anterior cerebral artery (RACA) and right middle cerebral artery (RMCA) territories (upper panel), and a normal subject (lower panel). In each panel, the first row is the entire CBF map and the second row is the closeup view of selected regions.

The entire brain image and the close-up views demonstrate significant improvement in the overall accuracy and preservation of the delicate anatomical

structures using the non-local TTV method for both the deficit and the normal subjects. sSVD tends to severely over-estimate CBF, while SVD-based methods also over-estimate perfusion parameters. TTV performs better than the SVD-based methods in preserving the quantitative accuracy and the contrast resolution between different tissue classes. However, TTV still over-estimates the CBF value, and the capillaries in the close-up view are dilated due to the local smoothing using the tensor total variation regularization. On the contrary, NL-TTV overcomes both issues. The quantitative accuracy of the perfusion maps improve significantly, and more noticeably, the small vessels and capillaries in the brain are precisely preserved without dilation or rupture, as we can observe in the local TTV results.

Quantitative results on the images of 10 subjects are shown in Fig. 5(a). Our proposed method significantly outperforms all other comparison methods ($p < 0.05$). The algorithm converges within 10 iterations (Fig. 5(b)).

The running time of the entire CTP data of one subject is around 30 min, after our accelerated optimization. Since the algorithm is implemented in MATLAB platform and run on a single PC desktop, grid or cluster computing is expected to speed up the experiments.

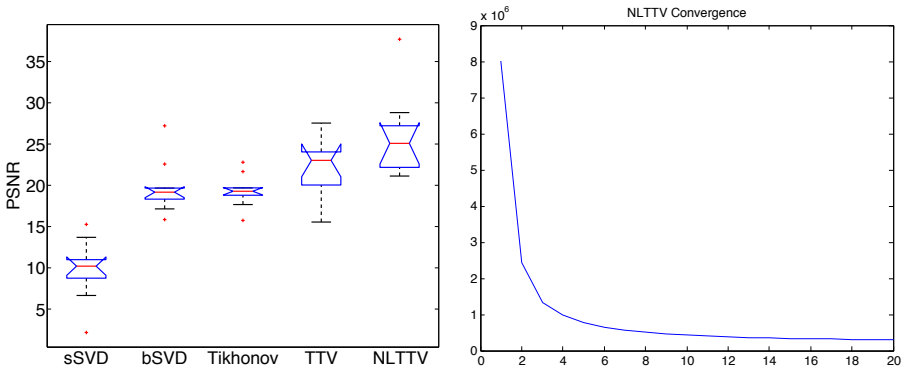


Fig. 5. (a) Boxplot of PSNR and SSIM for the 10 clinical subjects. The proposed NL-TTV method significantly outperforms all other comparison methods ($p < 0.05$). (b) Convergence curve of the cost function for NL-TTV algorithm.

4 Conclusion

In this paper, we proposed an efficient non-local tensor total variation method for low-dose CT perfusion deconvolution. The long-range and global similarities of the same tissue classes in the brain structure are leveraged to stabilize the spatio-temporal residue functions. The overall quantitative accuracy is significantly improved with the delicate anatomical structures such as capillaries

well preserved to assist clinical diagnosis. Fast optimization and implementation schemes are presented to reduce the time complexity and computational cost. Extensive evaluations with comparison to the existing algorithms, including sSVD, bSVD, Tikhonov and local TTV, demonstrate the superior performance of the non-local TTV method in low-dose deconvolution and perfusion parameter estimation.

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