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SLIC robust (SLICR) processing for fast, robust CT myocardial blood flow quantification

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Abstract

There are several computational methods for estimating myocardial blood flow (MBF) using CT myocardial perfusion imaging (CT-MPI). Previous work has shown that model-based deconvolution methods are more accurate and precise than model-independent methods such as singular value decomposition and max-upslope. However, iterative optimization is computationally expensive and models are sensitive to image noise, thus limiting the utility of low x-ray dose acquisitions. We propose a new processing method, SLICR, which segments the myocardium into super-voxels using a modified simple linear iterative clustering (SLIC) algorithm and quantifies MBF via a robust physiologic model (RPM). We compared SLICR against voxel-wise SVD and voxel-wise model-based deconvolution methods (RPM, single-compartment and Johnson-Wilson). We used image data from a digital CT-MPI phantom to evaluate robustness of processing methods to noise at reduced x-ray dose. We validate SLICR in a porcine model with and without partial occlusion of the LAD coronary artery with known pressure-wire fractional flow reserve. SLICR was ~50 times faster than voxel-wise RPM and other model-based methods while retaining sufficient resolution to show all clinically interesting features (e.g., a flow deficit in the endocardial wall). SLICR showed much better precision and accuracy than the other methods. For example, at simulated MBF=100 mL/min/100g and 100 mAs exposure (50% of nominal dose) in the digital simulator, MBF estimates were 101 ± 12 mL/min/100g, 160 ± 54 mL/min/100g, and 122 ± 99 mL/min/100g for SLICR, SVD, and Johnson-Wilson, respectively. SLICR even gave excellent results (103 ± 23 mL/min/100g) at 50 mAs, corresponding to 25% nominal dose.

Keywords

Dynamic CT perfusion; myocardial blood flow; super-voxel; dose reduction

1. Introduction

CT myocardial perfusion imaging (CT-MPI) can provide physiologic information for noninvasive diagnosis of cardiovascular disease. Myocardial blood flow (MBF) is one of the most useful functional measurements. MBF can be quantified from dynamic contrast-enhanced scans data with different mathematical techniques¹. Previous work in CT-MPI² has shown that model-based deconvolution methods are more accurate and precise than model-independent methods such as singular value decomposition. Although model-based MBF quantification may be most preferred, computation time can be a limiting factor. It is time consuming to calculate MBF for each voxel on each slice for the JW model where 5 parameters need to be optimized for each voxel. In typical dynamic CT-MPI data with FOV=150mm × 150mm and 512 × 512 voxels, the area of myocardium region is 15,000 to 30,000 voxels per slice. Then, for each slice, we need 15,000 to 30,000 MBF computations. Although the resolution of flow maps is high if we compute the MBF for each voxel and a high resolution MBF map could provide useful information such as transmural perfusion gradient, the computation time is prohibitively long and single-voxel resolution is not necessary for diagnosis. Another challenge in model-based MBF quantification in CT-MPI is that perfusion models are sensitive to noise which requires high radiation exposure for voxel-wise perfusion analysis. The noise sensitivity in perfusion models is due to the ill-conditioned deconvolution problem³, thus requiring robust computational techniques and/or high SNR data.

To address the problems of dose reduction (giving increased noise) and computation speed, we introduce the idea of super-voxel clustering implemented by simple linear iterative clustering (SLIC) algorithm⁴ into MBF estimation in CT-MPI. The idea of using super-voxel or k-means clustering has previously been applied to perfusion imaging. By applying k-means clustering guided bilateral filter for CT cerebral perfusion noise-reduction⁵, signal quality was successfully improved but MBF computation on each voxel was required. A k-means clustering based on measurements from CT cerebral CT perfusion data has been used to classify ischemic tissue and normal tissue⁶. SLIC super-voxel was also used for tumor segmentation on DCE-MRI data⁷. A similar idea⁸ by using a model based clustering to reduce noise prior to kinetic analysis of PET data. However, this model based clustering method does not incorporate spatial information of the data and can group voxels that are spatially and physiologically unrelated. In this work, by clustering voxels with similar physiologic properties and spatial information into one super-voxel by SLIC, the signal quality for MBF quantification is improved and regions can be shaped according to physiologic properties rather than fixed grid or in unrelated myocardial territories. After voxel clustering, a robust physiologic model is used which can reduce the uncertainty in parameter estimation.

In this work, we present a SLIC robust (SLICR) processing method for myocardial blood flow quantification in CT-MPI. We identify features for super-voxel clustering according to hemodynamic properties. After super-voxel clustering on the myocardium, TACs are estimated from super-voxel regions. MBF is quantified for each super-voxel using a robust physiologic model. The final results are MBF maps that capture the physiologic spatial distribution of MBF with robust quantitative measurements.

2. Methods

The SLICR algorithm consists of super-voxel feature selection, SLIC⁴ super-voxel generation, super-voxel time-attenuation curve generation and quantification of blood flow by a robust physiologic model.

2.1 SLIC super-voxel generation

For one slice of image data with N voxels and feature set with M temporal features, $f(x, y, l) = [f_{x,y}^1, f_{x,y}^2, \dots, f_{x,y}^l]$, $f_{x,y}^1, f_{x,y}^2, \dots, f_{x,y}^l$ correspond to the time course features from the at position (x, y) , with feature index $l = 1, 2, \dots, M$. The approximate size of a super-voxel is N/k voxels, where k is an input parameter to determine the number of super-voxels to be generated. The cluster center $c_k = [f_{x,y}^1, f_{x,y}^2, \dots, f_{x,y}^M, x_k, y_k]^T$ can be initialized by sampling k regularly grids with approximate interval $S = \sqrt{N/k}$. The search area for each cluster center is $2S \times 2S$. The distance measure D_S is:

$$d_{temporal} = \sqrt{\sum_{l=1}^M (f_c^l + f_i^l)^2}, \quad (1)$$

$$d_{spatial} = \sqrt{(x_c - x_i)^2 + (y_c - y_i)^2}, \quad (2)$$

$$D_S = \sqrt{d_{temporal}^2 + \left(\frac{d_{spatial}}{S}\right)^2 m^2}, \quad (3)$$

where $d_{temporal}$ and $d_{spatial}$ are corresponding to temporal feature distance and spatial distance between one cluster center c and a voxel i . The input parameter m allowing us to weight the relative importance between temporal and spatial distance. When m is large, super-voxels are more regular and compact. When m small, super-voxels is show less regular size and shape, but voxels in each region share more similar hemodynamic properties.

2.2 Candidate features

We analyze different temporal features for grouping different types of tissue (ischemic tissue, healthy tissue). We calculate the bolus arrival time (BAT) point which is defined as the time point when arterial input function (AIF) begins to rise and peak time of AIF as two references for feature selection. Candidate features are listed below and measured for each individual:

1. mean HU over all scans,
2. mean HU from the first scan to BAT,
3. mean HU from BAT to peak time of AIF,
4. mean HU from peak time of AIF to the last scan,
5. standard deviation over all scans,

6. standard deviation from the first scan to BAT,
7. standard deviation from BAT to peak time of AIF,
8. standard deviation from peak time of AIF to the last scan.

2.3 Feature selection with Maximum-Relevance-Minimum-Redundancy (mRMR) feature selection method

Features were ranked by using Maximum-Relevance-Minimum-Redundancy (mRMR) feature selection method⁹ to identify a set of features for optimal grouping ischemic tissue and normal tissue. This feature selection process was performed in order to find out features that are best able to discriminate between different tissue types but provide unique information from other features therefore reduce the measurement and computing time in SLICR. The mRMR method ranks features based on two terms: 1) maximum relevance to target variable and 2) minimum redundancy within the features. For one feature, mutual information(MI) is used to measure the relevance to target variable and redundancy with other features in this filter based feature selection method. Let Ω_x be the selected feature set which contains x features and Ω be the whole feature set. To obtain feature f_i in $\Omega - \Omega_x$ with maximum relevance and minimum redundancy, the mRMR is defined as:

$$\max_i [D_i - R_i], \quad (4)$$

$$D_i = MI(f_i, l), \quad (5)$$

$$R_i = \frac{1}{x} \sum_{f_j \in \Omega_x} MI(f_i, f_j), \quad (6)$$

where i is the index of feature in $\Omega - \Omega_x$, D_i is the relevance of f_i to the label l alone and R_i is the mean redundancy of f_i to each of the feature f_j in Ω_x . Finally, mRMR objective function can be rewrote by substituting equation (5) and (6) into

$$\max_{f_i \in \Omega - \Omega_x} [MI(f_i, l) - \frac{1}{x} \sum_{f_j \in \Omega_x} MI(f_i, f_j)]. \quad (7)$$

At each round, the mRMR selects a feature with the biggest difference between relevance and produces a ranked list which indicates the discriminating ability of each feature.

2.4 Noise reduction for time-attenuation curve in super-voxel regions

In this work, we use the 10% trimmed mean of each time point (the lowest 10% and the highest 10% are discarded) of voxels in one super-voxel region to construct a tissue attenuation curve for such super-voxel region. This 10% trimmed mean helps to eliminate outliers but still preserve enough data samples for denoising.

2.5 Flow estimation with Robust physiologic model (RPM)

The robust physiologic model is based on the Johnson-Wilson model¹⁰. In the Johnson-Wilson model, the observation region is composed of spatially distributed intravascular and extravascular spaces. Contrast agent enters in the intravascular space (e.g. capillary) and, assuming plug flow, passes through the length of the vessel while exchanging with the extravascular space. In the adiabatic approximation to the Johnson-Wilson model, the extravascular space is approximated by a lumped compartment and exchange between the intravascular space and extravascular space is approximated by a single, fast intravascular-extravascular contrast agent described by extraction fraction. This adiabatic approximation to the Johnson-Wilson model has five free parameters: t_d (s), MBF (mL/min/100g), ITT (s), E (unitless), and u (1/s). The corresponding IRF is given by:

$$R_{MBF}(t) = MBF \cdot \begin{cases} 0, & t < t_d \\ 1, & t_d \leq t < t_d + ITT \\ E \cdot \exp(-u(t - (t_d + ITT))), & t_d + ITT \leq t \end{cases}. \quad (8)$$

In the robust physiologic model, we incorporate prior knowledge of extraction fraction (E) and intravascular transit time (ITT). This model is a reduced form of AATH with parameters fixed to $E=0.6$ and $ITT=2s$. These values were selected when considering CT contrast agent extraction from the literature, which can range from $E=0.3$ to $E=0.8$ ¹¹, CT voxel size and capillary flow velocity¹², goodness-of-fit to preclinical data, and parameter estimability across imaging conditions. The RPM model is defined with three free parameters: t_d , MBF, and u .

3. Experimental Methods

3.1 Testing image data set

- 1) Dynamic perfusion scan sequences in healthy and ischemic conditions are generated from a digital cardiac porcine phantom. We generated contrast agent dynamics in the image based on the same left ventricle AIF and myocardium kinetics based on a physiologic simulator adopted¹³. This physiologic driving model was modified¹⁴ and includes multiple large blood pools with delay and dispersion effects, as well as heterogeneous small vessel flow paths and post-capillary venules within the observation region. Time-attenuation curves include dispersive effects and time delays. The CT simulation software models a realistic CT scanner (Brilliance 64, Philips), with cone beam source, finite width detector grid, x-ray prefiltration, and x-ray spectrum. In this work, we used only 70keV photons for a true mono-energetic CT-MPI data set in order to remove any possible confounding effects from beam hardening artifact. The simulation computes line integrals based on analytic object geometries with defined mass-attenuation spectra from NIST¹⁵ and accounts for Poisson noise in the projections but does not include x-ray scatter or electronic noise. We reconstructed both physiologic condition on 4 different dose levels: a) noise-

free, b) 200mAs which can be considered as nominal dose, c) 50% nominal dose, and d) 25% nominal dose.

- 2) Dynamic perfusion scan sequences from an animal model (4 pigs, weight: 40 – 50 kg) with adjustable levels of introduced myocardial ischemia guided by fractional flow reserve (FFR) for dynamic CT myocardial perfusion acquisition¹⁶. We acquire 3 different physiologic conditions FFR=1.0, FFR=0.7 and FFR=0.3. We used SDCT with tube potential of 120kVp and 100mA tube current. The 70KeV projection-based monoE images were generated in the projection domain. MonoE images greatly reduce beam hardening artifacts which can cause under-estimation of MBF in the LAD region. Images were reconstructed with 2mm slice-thickness at 2mm increment.

3.2 Super-voxel generation

For feature selection, ROIs of healthy and ischemic myocardium are manually selected from animal data. We randomly chose 10,000 time attenuation curve (TACs) with healthy labels and 10,000 TACs with ischemic labels as the feature selection dataset from 2 pigs. Different candidate features described previously are extracted. We chose top 3 features from mRMR ranking. They are 1). mean HU from BAT to peak time of AIF, (2). standard deviation over all scans and 3). mean HU from peak time of AIF to the last scan.

In SLIC, there are two parameters, number of super-voxel k and shape penalty m . The number of super-voxels, k , varies with FOV of data. In our study, we test CNR of MBF results with $k = 1000$. We expect voxels on each super-voxel share the same time course property and still constrain by spatial location of voxels. We fixed $m = 0.1$.

3.3 MBF analysis

We used a 3D elastic registration approach based on 3D cubic B-splines and normalized mutual information to align the 3D volumes from different time points. To these ends, we have used the multi-processor implementation of the registration software, NiftyReg¹⁷.

To compare our method to other conventional MBF estimation methods on digital phantom data and animal data, MBF is estimated by 6 different methods. **a)** L-curve criterion SVD deconvolution based method (LccSVD)³, **b)** Tikhonov regularization SVD deconvolution based method (ThSVD)³, **c)** Johnson-Wilson 5 parameters model (JW)¹⁸, **d)** single-compartment exponential model (EXP)¹⁹, **e)** proposed Robust physiologic model (RPM), **f)** proposed SLICR(SLIC+RPM) method. Computation time of each method is recorded. Based the MBF maps from different algorithms, we compute and flow-CNR in ROIs in the ischemic LAD and remote LCX territories. Flow-SNR measures the amount of noise in the image relative to the mean flow, and flow-CNR measures the ability to discriminate an ischemic region from healthy tissue. For digital phantom, MBF maps are assessed for precision, bias, and visual quality. We compute flow-SNR for all hemodynamic conditions and flow-CNR for ischemic (FFR<0.7) conditions. The flow-CNR (CNR_f) and flow-SNR (SNR_f) were defined as:

$$CNR_f = \frac{\mu_{healthy} - \mu_{ischemia}}{\sqrt{\frac{1}{2}(\sigma_{healthy}^2 + \sigma_{ischemia}^2)}} \quad (9)$$

$$SNR_f = \frac{\mu_{healthy}}{\sigma_{healthy}} \quad (10)$$

where $\mu_{healthy}$ and $\mu_{ischemia}$ are the mean MBF inside the healthy ROI and mean MBF inside the ischemic ROI, $\sigma_{healthy}$ and $\sigma_{ischemia}$ are the standard deviation of MBF inside the healthy ROI and ischemic ROI. Healthy and ischemic ROIs are manually selected.

4. Results

4.1 Comparison of super-voxel with different shape.

To compare the difference between fixed super-voxel, SLIC super-voxel with regular and irregular shape. Figure 1 shows the results of approximately the same number of fixed super-voxel and different types (regular/irregular) of SLIC super-voxel overlaid on a slice of data.

4.2 Dose reduction with SLICR in digital CT-MPI phantom.

The results of applying RPM with and without SLIC super-voxel in the digital CT-MPI phantom at 3 different dose levels reconstructed with conventional FBP are shown in figure 2. Figure 2 simulates baseline (FFR = 1.0, MBF = 100 mL/100g/min). From the first column to the third column dose of simulation and SNR of data are from high to low. Some small inhomogeneous regionals in noise-free columns are caused by partial volume artifact of the ventricle with the tissue. Results of RPM and SLICR in different rows. We measure the quality of flow maps by calculating SNR_f .

4.3 Accuracy and precision of quantitative MBF methods on phantom data.

We analyze accuracy and precision of different MBF estimation methods based on our digital CT-MPI phantom. Accuracy is defined as the difference of mean MBF value of one method to the preset MBF value. Precision is defined as the standard deviation of MBF of one method. From healthy tissue, the preset MBF is 100 ml/100g/min. We use the preset MBF as ground truth. We select ROI from results of different methods and calculate mean and standard deviation from ROI and compare to the preset MBF value. From figure 3, the thick black line is the preset MBF value, result of 5 voxel-wise MBF estimation methods (ThSVD, LccSVD, JW, EXP and RPM) and SLICR on 4 different dose levels (Noise-free, 200 mAs, 100mAs and 50 mAs.) are shown. For all methods, standard deviation increase as dose level reduced indicating worse precision at lower dose. Compared to all voxel-wise methods in different dose level, SLICR shows a closer mean value to ground truth (more accurate) and smaller standard deviation (more precise).

4.4 Complete LV assessment.

To check if the SLICR can show continuity in flow estimates in z direction, we apply SLICR to multiple slices of pig CT-MPI data at different hemodynamic conditions (FFR=1,

FFR=0.7, FFR=0.3) in Figure 4. The MBF maps at FFR=1 indicate homogeneous MBF values and spatial distributions across slices. From moderate occlusion (FFR = 0.7) and full occlusion (FFR = 0.3), the ischemic LAD myocardial region can be detected and the flow value from one slice to another is visually continuous.

4.5 Computation time assessment.

All work in this study was performed using our in-house software implemented in MATLAB. All MBF estimations are ran with parallelization with 12-cores CPU. Table 1 records the performance of each method with and without SLIC super-voxel on preclinical data. Model independent methods, ThSVD and LccSVD, are faster than model based methods for one voxel (one TAC) since they do not require parameter optimization (LccSVD requires optimization of the Tikhonov regularization factor by the L-curve, but computation time can be neglected compare to model based methods). RPM is faster than JW 5parameter model since it has three free parameters as opposed to five free parameters. SLIC accelerates the computation significantly because it reduces the number of TACs for MBF estimation. The computation time for generating SLIC super-voxels is about 2 seconds.

5. Discussion

Our previous paper ² suggests model based deconvolution method is more accurate and precise than model independent deconvolution method for MBF estimation. However, a high order model, such as Johnson-Wilson with 5 free parameters, simultaneously estimates parameters which interplay with the MBF value and can create large uncertainty in MBF. The reduced 3 parameter model which includes prior information about intravascular transit time and extraction fraction, robust physiologic model (RPM), appears to be more robust and accurate in MBF estimation. The other reason for choosing a low order model is the computation time for parameter optimization.

For CT-MPI, obtaining a high resolution MBF map acquisition using voxel-wise model-based or model-independent deconvolution is time consuming. Furthermore, voxel-wise MBF maps have low contrast to noise ratio and non-precision due to image noise. Applying a fixed large averaging/median kernel before MBF estimation can reduce image noise and improve MBF estimation accuracy and precision. However, large kernels can blur potentially important distributions in perfusion, such as the transmural gradient perfusion, an indicator of disease. The k-means clustering guided bilateral filter developed by ⁵ can reduce noise and preserve boundaries. However, it still requires MBF estimation on each voxel, which slows the computation time. Model based clustering ⁸ method does not incorporate spatial information therefore voxels grouped together are spatially unrelated. This model based method also requires parameters to be computed before clustering therefore also slows the computation time. In the proposed SLICR method, super-voxels are generated by grouping voxels with similar temporal features together. By representing the super-voxel by a single, low-noise TAC, MBF estimation computation time is greatly accelerated by >97%. Since each super-voxel only groups region with similar hemodynamic condition, spatial distributions in MBF, such as transmural gradient perfusion gradient, are preserved.

The number of super-voxels on myocardium is depended on the voxel size of myocardium. In this work, we chose the number of super-voxels by assessing the SNR of the MBF map at different numbers of super-voxels. Some region merging algorithm such as ^{20–22} can be applied to determine an optimal number of super-voxels after an initial SLIC super-voxel oversegmentation.

In conclusion, the proposed SLIC super-voxel idea for CT-MPI flow estimation serves two purposes. First, SLIC super-voxels generate deformable kernels for which allows for denoising over voxels which share similar hemodynamic properties. Second, MBF is estimated in a super-voxel only once based on the denoised TAC, significantly accelerate computation. The reduced, 3-parameter model, Robust physiologic model, is applied to improve precision and accuracy of MBF quantification as compared SVD and the 5-parameter Johnson-Wilson model. The combination of SLIC and RPM, SLICR, shows high CNR, MBF accuracy and fast computation time compare to other conventional MBF flow estimation method on different noise levels and different hemodynamic conditions. In preclinical 3D data, our method also shows continuity slice by slice and detects ischemia under different hemodynamic conditions.

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Figure 1. MBF map based on RPM by and RPM with different super-voxel shape. a) voxel-wise RPM, b) RPM with fixed super-voxel, c) RPM with regular shape SLIC super-voxels and d) RPM with SLIC super-voxels $m = 0.1$, $k = 1000$. Different shapes of super-voxel are overlaid on original data are showed in b), c) and d).

Figure 2.

Flow estimation with SLICR as a function of simulated x-ray dose in healthy myocardium. Results are from baseline (MBF = 100 mL/100g/min) simulated phantom. Rows show MBF estimated at 3 different dose levels, Noise-free, 200 mAs and 50 mAs. The first column shows voxel-wise RPM results. The second column shows SLICR results.

Figure 3.

Bar plot shows accuracy and precision of different method on phantom data. Black line shows the ground truth. Results from 6 different methods (ThSVD, LccSVD, JW, EXP, RPM and SLICR) at 4 different dose levels are shown. Error bars are standard deviation. At 100 mAs exposure, average and standard deviation MBF value of ThSVD is 160 ± 54 mL/min/100g, LccSVD is 105 ± 31 mL/min/100g, EXP is 101 ± 103 mL/min/100g, Johnson-Wilson is 122 ± 99 mL/min/100g, RPM is 115 ± 81 mL/min/100g and SLICR is 101 ± 12 mL/min/100g. At 50 mAs (25% nominal dose), average of MBF value of voxel-wise methods >140 mL/min/100g and standard deviation of MBF value > 80 mL/min/100g. Average and standard deviation MBF value of SLICR at 50 mAs is 103 ± 23 mL/min/100g.

Figure 4.

Complete LV assessment. This figure shows flow maps of one pig experiment from $\text{FFR} = 1$ to $\text{FFR} = 0.3$ which are estimated by SLICR. From the first row $\text{FFR} = 1$, flow map of each slice is homogeneous and flow value from one slice to another is similar. From the second and the third row, ischemic region can be detected and the flow value from one slice to another is visually continuous.

Table 1.

Computation time for different MBF estimation methods. The first column shows method names. The second column shows voxel-wise result of the data. The third column shows results of methods applied using SLIC super-voxel.

Estimation Method	voxel-wise	SLIC
ThSVD	117 sec	3.5 sec
LccSVD	137 sec	3.7 sec
Johnson-Wilson	805 sec	13.1 sec
EXP	273 sec	3.8 sec
RPM	392 sec	7.1 sec