Parametric Myocardial Perfusion PET Imaging using Physiological Clustering

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ABSTRACT

We propose a novel framework of robust kinetic parameter estimation applied to absolute flow quantification in dynamic PET imaging. Kinetic parameter estimation is formulated as a nonlinear least squares with spatial constraints problem (NLLS-SC) where the spatial constraints are computed from a physiologically driven clustering of dynamic images, and used to reduce noise contamination. An ideal clustering of dynamic images depends on the underlying physiology of functional regions, and in turn, physiological processes are quantified by kinetic parameter estimation.

Physiologically driven clustering of dynamic images is performed using a clustering algorithm (e.g. *K*-means, Spectral Clustering etc) with Kinetic modeling in an iterative handshaking fashion. This gives a map of labels where each functionally homogenous cluster is represented by mean kinetics (cluster centroid). Parametric images are acquired by solving the NLLS-SC problem for each voxel which penalizes spatial variations from its mean kinetics. This substantially reduces noise in the estimation process for each voxel by utilizing kinetic information from physiologically similar voxels (cluster members). Resolution degradation is also substantially minimized as no spatial smoothing between heterogeneous functional regions is performed.

The proposed framework is shown to improve the quantitative accuracy of Myocardial Perfusion (MP) PET imaging, and in turn, has the long-term potential to enhance capabilities of MP PET in the detection, staging and management of coronary artery disease.

Keywords: myocardial perfusion, coronary flow reserve, coronary artery stenosis, coronary artery disease, PET, *K*-means clustering, spectral clustering, physiological clustering, penalized least squares

1. INTRODUCTION

Several studies worldwide have attributed a high “morbidity” and “mortality” rate to cardiovascular diseases.^{1–5} The World Health Organization has predicted that by 2030 approximately 23.6 million people will die due to Coronary Artery Diseases (CAD). This is a staggering increase of $\sim 36.4\%$ since 2008.⁶ The importance of this matter can also be gauged from the fact that the 2013 issue of “Atlas of Nuclear Cardiology” is fully devoted to the instrumentation, experimentation, assessment, and analysis of biomarkers for the early detection, staging and management of CAD.⁷

Absolute quantification of myocardial blood flow (MBF) and coronary flow reserve ($CFR = \frac{MBF \text{ at peak-stress}}{MBF \text{ at peak-rest}}$) has provided new insights over conventional myocardial perfusion imaging (MPI) by allowing early detection of preclinical atherosclerosis and providing an opportunity to modify risk factors or initiate treatment.^{5,8,9} CFR has been shown to be related to the degree of coronary artery stenosis (CAS).¹⁰ It thus allows for noninvasive assessment of the functional importance of CAS and may aid identification of patients with either diffuse, nonocclusive luminal coronary artery narrowing or a balanced reduction in coronary artery blood flow (extensive multi-vessel coronary disease).¹¹

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Positron Emission Tomography (PET) is a powerful imaging modality that enables noninvasive and accurate quantification of MBF and CFR by administration of a radio-pharmaceutical tagged with positron emitter.^{7, 12–14} PET, as compared to SPECT, has high sensitivity, superior spatio-temporal resolution, and accurate attenuation correction.^{8, 15–19}

Despite all these pearls, absolute quantification of MBF and CFR has hardly translated into clinical practice and, thus far, remains a research adventure. A major impediment is the production and delivery of short-lived radio-tracers at the clinical site. ⁸²Rb is one of the most commonly used radio-tracer for absolute quantification of MBF and CFR.^{20–22} It does not require on-site cyclotron for production and has a short half-life of 76 secs enabling fast serial imaging (~ 15 min²³) and high patient throughput. ⁸²Rb dynamic PET images suffer from high noise-levels which adversely impacts accurate quantification of MBF and CFR especially at the voxel-level (parametric images).

One way to address the issue of increased noise-levels (poor SNR) is to perform heavy post-smoothing ($FWHM = 5 - 12$ mm) on reconstructed dynamic images before extracting parametric images by kinetic modeling.²⁴ This comes at a cost of resolution degradation (blurring) due to smoothing operator. Another approach is to perform ROI quantification of MBF and CFR where the voxel intensities are averaged over each region-of-interest (ROI).²⁵ This also comes at a cost of loss of spatial information and underlying tissue heterogeneity.

We propose a novel framework of robust kinetic parameter estimation at the individual voxel level that substantially reduces noise using “Physiological Clustering”. Physiological clustering is an approach of clustering a PET image driven by the underlying physiology. The resulting label map (image) is a union of disjoint clusters each represented by its mean kinetics. The parameter estimation problem is then formulated as a nonlinear least squares with spatial constraints (NLLS-SC) where the spatial constraints are derived from the physiologically clustered image. Figure 1 shows a flowchart of the proposed approach.

Figure 1. Flowchart of the proposed approach.

2. THEORY

2.1 Pharmacokinetic Model for ^{82}Rb radio-tracer

^{82}Rb radio-tracer kinetics can be described by a one-tissue compartment model^{26,27} as shown in Figure 2. The myocardial activity concentration, $C_{myo}(t)$, is defined as the convolution of arterial blood concentration, $C_a(t)$, and model impulse response, $h(t)$:

$$C_{myo}(t) = C_a(t) \otimes h(t) \quad (1)$$

where $h(t)$ is a function of the transport rate constants K_1 (uptake rate in units of mL/min/g) and k_2 (washout rate in units of 1/min) and density of myocardial tissue ρ (1.04 g/mL):²⁸

$$h(t) = \rho K_1 e^{-k_2 t} \quad (2)$$

Due to partial volume effects (PVE), caused by the limited resolution of PET scanners, the measured myocardial tissue concentration, $C_{meas}(t)$, is contaminated by “spill-over” of activity from arterial blood:

$$C_{meas}(t) = f_a C_a(t) + (1 - f_a) C_{myo}(t) \quad (3)$$

$$= f_a C_a(t) + (1 - f_a) C_a(t) \otimes \rho K_1 e^{-k_2 t} \quad (4)$$

where f_a is the fractional blood volume spillover that accounts for contribution of blood activity in the measured myocardial concentration curve and $(1 - f_a)$ corrects for partial volume loss in the myocardium.^{27,29}

Figure 2. One-tissue Compartment Model for ^{82}Rb radio-tracer where activity concentration in the myocardial ROI is a convex mixture of concentration curves from arterial blood and myocardial tissue (reproduced from Klein 2010²⁸).

Unlike ^{13}N -ammonia radio-tracer, where the uptake rate is proportional to MBF, K_1 estimates from a ^{82}Rb study needs to be corrected for extraction fraction, EF , which is analytically described by the Renkin-Crone model:^{30,31}

$$K_1 = EF \times MBF = (1 - a e^{-b/MBF}) \times MBF \quad (5)$$

The extraction fraction, EF , is a nonlinear function of MBF and decreases with increase in MBF due to tracer extraction from blood via diffusion and active transport.^{26,27,30,31} Many studies have reported the Renkin-Crone model parameters (a , and b) for various radio-tracers and a comprehensive table can be found in Klein et. al. 2010 (Table 4).²⁷ In this study $a = 0.77$ and $b = 0.63$.²⁶

2.2 Image Derived Input Function (IDIF)

Parameter estimation requires knowledge of input function, $C_a(t)$ (Equations 1 and 4). In clinical practice, the input function is measured invasively by arterial cannulation which is a cumbersome procedure, both for the clinician and the patient. This calls for alternative ways to acquire input function. IDIF are extremely promising and feasible methods that extract the input function directly from the acquired dynamic images.³² In cardiac imaging, this approach is readily applicable due to the presence of large blood pools of Left Ventricle (LV) and Right Atrium (RA) in the PET field of view.⁸

Arterial concentration curve, $C_a(t)$, is extracted from co-registered dynamic PET images by placing an elliptical ROI (50 mm²) in the LV blood pool. These curves are generated from 4 mid-ventricular imaging planes and then averaged to reduce noise.³³

Other approaches use Factor Analysis (FA)³⁴ or Non-negative Matrix Factorization (NMF)^{35,36} to extract concentration curves from the LV, RV, and myocardial tissue. The basic essence underlying FA and NMF is the same: the dynamic data set (A) is factorized into a product of factor images (W) and coefficient matrix (H):

$$A_{N \times M} = W_{N \times r} H_{r \times M} \quad (6)$$

where r is the number of pre-defined factors, N is the number of voxels, and M is the number of dynamic frames. The rows of H matrix provide the TACs for the r factors. In myocardial perfusion PET imaging, $r = 3$ (RV, LV, and myocardium). A major shortcoming of these splitting techniques is the nonuniqueness of the solution matrices (W and H), upto a rotation matrix Q , as shown below:^{37,38}

$$A = (WQ^{-1})(QH) = \tilde{W}\tilde{H} \quad (7)$$

where W , $\tilde{W}$, H , and $\tilde{H}$ are non-negative matrices. Nonuniqueness in FA is addressed by imposing minimal structure overlap (MSO) constraint as implemented in Generalized Factor Analysis for Dynamic Sequences (GFADs).^{23,39} NMF is preferred over GFADs which uses conjugate gradient algorithm as opposed to simple multiplicative/additive update equation in NMF.⁴⁰

2.3 Physiological Clustering

Clustering techniques for enhanced parameter estimation has been reported before.^{41–45} However, in this work clustering is driven by the underlying physiology of functional regions. Physiological clustering approach for noise-reduction is based on an explicit statement: *accurate kinetic parameter estimation requires a segmentation; ideal segmentation requires knowledge of the underlying physiological parameters*.⁴⁶ This dilemma is easily addressed by an iterative “handshaking” algorithm where kinetics drive clustering and clustering drives kinetics.

Algorithm 1 describes the simplest physiological clustering approach that uses K -means with Kinetic Modeling (KM-KM)⁴⁶ to generate a labeling where each label represents a distinct functional region. K -means clustering uses the Euclidean norm of Time Activity Curves (TACs) to gauge physiological similarity of pair of voxels indexed by (i, j) :

$$S_{K\text{-means}}(i, j) = \|TAC_i - TAC_j\|_2 \quad (8)$$

Algorithm 1 Physiological Clustering: K -means clustering with Kinetic Modeling (KM-KM)

Require: number of clusters, N

- 1: Smooth dynamic images **only** for the generation of label map.
 - 2: Randomly sample the dynamic space to select N representative TACs for the myocardial tissue.
 - 3: Perform kinetic modeling to estimate kinetic parameters from the N representative TACs.
 - 4: Compute noise-free TACs from the estimated kinetic parameters in Step 3. These N TACs form the initial cluster centroids for the clustering algorithm.
 - 5: **repeat**
 - 6: Generate voxel-wise label map using K -means clustering and the N representative TACs from Step 4.
 - 7: Compute representative TACs (noisy centroids) for N clusters using the label map from Step 6.
 - 8: Repeat Step 3 to estimate kinetic parameters for the N representative TACs from Step 7.
 - 9: Repeat Step 4 to generate a new set of N representative, noise-free, TACs (cluster centroids).
 - 10: **until** (no significant change in cluster centroids)
 - 11: Estimate kinetic parameters from the final set of N representative, noise-free, TACs. These kinetic parameters act as spatial constraints for their individual clusters.
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K -means clustering, though extremely simple and straightforward, is sensitive to the initialization of representative TACs due to non-convex objective function, requires apriori specification of number of clusters, and

the similarity metric does not incorporate spatial proximity of voxels. Non-convexity is addressed by convex-relaxation of the K -means objective function:

$$\min_{\mathbf{U}} F_{\eta}(\mathbf{U}) = \frac{1}{2} \sum_{i=1}^p \|\mathbf{x}_i - \mathbf{u}_i\|_2^2 + \eta \sum_{i < j} w_{i,j} \|\mathbf{u}_i - \mathbf{u}_j\| \quad (9)$$

where p is the number of voxels, η is a tuning parameter, $w_{i,j}$ is a non-negative weight, $\mathbf{x}_i$ is the TAC for voxel i , and the i^{th} column of matrix $\mathbf{U}$ (i.e. $\mathbf{u}_i$) is the cluster centroid for voxel i . An interesting aspect of this convexification is that it obviates the need of predefining number of clusters (N) at the cost of fixing the tuning parameter η . This problem can be solved using Alternating Direction Method of Multipliers (ADMM).⁴⁷

The similarity metric in Equation 8 can be easily modified to account for spatial proximity of voxels. Such a similarity metric is commonly observed in Normalized Cuts and Spectral Clustering algorithms.^{48–50}

$$S_{\text{Spec. Clust.}}(i, j) = \exp\left(-\frac{\|TAC_i - TAC_j\|_2^2}{\sigma_{TAC}^2}\right) \exp\left(-\frac{\|X_i - X_j\|_2^2}{\sigma_X^2}\right) \quad (10)$$

for $\|X_i - X_j\|_2 < r$ where X_i is the spatial location of voxel i .

In a nutshell, we have a nice family of clustering algorithms that generate a label map (image) where each functionally homogeneous region is represented by mean kinetics. These mean kinetics form the spatial constraints set for robust parameter estimation.

2.4 Robust Parameter Estimation

Robust estimation of physiologically meaningful parameters (like the uptake rate K_1) is achieved by solving the following nonlinear least squares with spatial constraints (NLLS-SC) optimization problem for each voxel:

$$\min_{\beta} J(\beta) = \|\mathbf{C}_{meas}(\mathbf{t}; \beta) - \mathbf{C}_{PET}(\mathbf{t})\|_2^2 + \gamma \|\beta - \beta_{sc}\|_2^2 \quad (11)$$

where $\beta = [K_1 \ k_2 \ f_a]^T$ is the desired parameter vector, $\mathbf{C}_{meas}(\mathbf{t}; \beta)$ models the measured PET signal (Equation 4), $\mathbf{C}_{PET}(\mathbf{t})$ is the measured TAC, and β_{sc} is the spatial constraint derived from physiological clustering of dynamic images. Each voxel belongs to one of the N clusters and the representative kinetic (physiological) parameter vector for that cluster forms the spatial constraint vector (β_{sc}). γ penalizes large deviations from mean kinetics. Equation 11 is solved using a trust-region-reflective nonlinear least-squares algorithm. MBF is estimated from K_1 by solving Equation 5 using a fixed-point iteration approach.⁵¹ CFR is computed as the ratio of MBF at peak-stress and peak-rest.

Table 1. Kinetic parameters used in the simulation of cardiac PET images for ⁸²Rb radio-tracer.

Tissue	K_1 (mL/min/g)	k_2 (1/min)
Liver	0.57	0.97
Lung	0.18	0.98
Muscle	0.06	0.21
Myocardium (rest)	0.70	0.16
Myocardium (stress)	1.48	0.32
Myocardium Defect	0.74	0.25

3. SIMULATION

We simulated a set of dynamic cardiac PET images acquired in 2-D mode (with septa) using XCAT phantom ($128 \times 128 \times 47$ voxels, $3.27 \times 3.27 \times 3.27$ mm³ per voxel). TACs were generated for five tissues (left ventricle (LV), right ventricle (RV), myocardium, liver, lung, and muscle) using realistic kinetic parameters and a one-tissue compartment model. Table 1 lists the kinetic parameters for different tissues. Arterial blood fraction for the

Figure 3. True K_1 image and the TACs generated using a one-tissue compartment model for ^{82}Rb radio-tracer.

myocardial tissue was assumed to be 25%. Figure 3 shows the true K_1 image and the noise-free TACs for LV (input function), normally perfused myocardium and perfusion defect.

The dynamic data set consists of 10 time frames (10×12 secs) spanning a total duration of 2 minutes. Dynamic images were forward projected using a precomputed 2-D projection matrix with 315 angular samples over 180° , and 323 radial bins with 2.26 mm spacing. Positron range blurring, attenuation, normalization, randoms, scatter, and decay were also incorporated. Positron range effect was simulated by blurring the dynamic images with a space-invariant kernel, $h(\mathbf{r}) = e^{-0.56r}$, as previously derived in Rahmim et. al. 2008.⁵² For randoms and scatter, a uniform distribution was assumed in the projection space with the randoms and scatter fractions set to be 20% each. Poisson noise was then added to the dynamic sinograms which resulted in a total number of 10 million events for a 2 minutes study. Noisy sinograms were reconstructed using the OSEM algorithm (2 iterations, and 21 subsets). The input function was extracted using a manually placed elliptical ROI over the LV (Section 2.2). A 2-D Gaussian filter (size 3×3 , standard deviation 0.5) was used to smooth the reconstructed dynamic images for clustering and five clusters were assumed *a priori* ($N = 5$). Physiological clustering was performed on the smoothed reconstructed dynamic images using Algorithm 1 (Section 2.3). Parametric images were generated using the non-smoothed reconstructed dynamic images (Section 2.4) and the IDIF. 50 noise realizations were generated for rest and stress analysis with varying penalty parameter ($\gamma = 0 - 1 \times 10^{-2}$ where $\gamma = 0$ corresponds to no spatial constraint).

Figure 4. K_1 parametric images obtained by varying the penalty parameter, γ , from 0 (no spatial constraint) to 1×10^{-2} .

Figure 4 shows parametric images of K_1 , from rest and stress simulations, for different penalty parameters ($\gamma = 0, 5 \times 10^{-5}, 1 \times 10^{-4}, 3 \times 10^{-4}, 9 \times 10^{-4}, 2 \times 10^{-3}, 4 \times 10^{-3}$, and 8×10^{-3}). We also explored the impact of positron range blurring on parametric image estimation by simulating cardiac PET images with and without positron range blurring. Positron range blurring produced noisier K_1 images in rest and stress simulations. This may be attributed to the loss of counts in the myocardial tissue due to PVE. Qualitative analysis reveal that as spatial constraint is enforced (by increasing γ) noise in K_1 images is reduced thereby enhancing image quality.

Figure 5 shows a bias versus variance tradeoff obtained over 50 noise realizations. Different points on the curves are obtained by varying the penalty parameter ($\gamma \in [0, 1 \times 10^{-2}]$). Quantitative analysis show that as we impose spatial constraints ($\gamma > 0$) on conventional parameter estimation ($\gamma = 0$) noise and bias decrease with increasing γ till a point, γ^* , is reached that gives a minimum $[noise(\gamma^*), bias(\gamma^*)]$ performance. For $0 < \gamma \leq \gamma^*$, physiological clustering reduces noise and noise-induced bias in parametric images by exploiting information from functionally (kinetically) similar voxels. We also observe that, for matched noise performance, positron range blurring enforces a stronger penalty on the spatial constraints producing increased estimation bias. For $\gamma > \gamma^*$, noise is further reduced at the expense of increased bias since the voxel-wise kinetics in each cluster is smoothed to match mean kinetics. Without positron range blurring, K_1 rest images showed a $\sim 12\%$ reduction in noise and a $\sim 40\%$ reduction in bias ($\gamma^* = 6 \times 10^{-4}$), and K_1 stress images showed a $\sim 5\%$ reduction in noise and a $\sim 16\%$ reduction in bias ($\gamma^* = 3 \times 10^{-4}$). With positron range blurring, K_1 rest images showed a $\sim 8\%$ reduction in noise and a $\sim 34\%$ reduction in bias ($\gamma^* = 6 \times 10^{-4}$), and K_1 stress images showed a $\sim 1\%$ reduction in noise and a $\sim 6\%$ reduction in bias ($\gamma^* = 5 \times 10^{-5}$).

Figure 5. Noise-Bias plots for K_1 images. Right-most point corresponds to $\gamma = 0$ and left-most point corresponds to $\gamma = 1 \times 10^{-2}$.

Figure 6 shows MSE of K_1 parametric images for rest and stress simulations with varying γ . We observe that for $0 < \gamma \leq \gamma^*$, MSE decreases monotonically due to reduction in noise and noise-induced bias in the estimation process. γ^* gives the minimum MSE performance. For $\gamma > \gamma^*$, MSE worsens due to substantial increase in bias as compared to modest improvement in noise performance. Without positron range blurring, K_1 rest images showed a $\sim 98\%$ reduction in MSE ($\gamma^* = 6 \times 10^{-4}$), and K_1 stress images showed a $\sim 96\%$ reduction in MSE ($\gamma^* = 3 \times 10^{-4}$). With positron range blurring, K_1 rest images showed a $\sim 98\%$ reduction in MSE ($\gamma^* = 6 \times 10^{-4}$), and K_1 stress images showed a $\sim 5\%$ reduction in MSE ($\gamma^* = 5 \times 10^{-5}$).

Table 2 shows the mean and standard deviation of flow estimates and CFR in normally perfused myocardium and perfusion defect for rest and stress simulations (without positron range blurring). As γ increased, the coefficient of variation ($COV = \frac{\sigma}{\mu}$) for MBF_{rest} decreased by $\sim 3\%$, for MBF_{stress} COV decreased by $\sim 5\%$, and

Figure 6. MSE of K_1 parametric images with varying γ .

for CFR COV decreased by $\sim 3\%$. These results further strengthen the observation that physiological clustering produces MBF and CFR estimates with higher SNR by reducing noise and noise-induced bias in the estimation process.

4. CONCLUSIONS

Parametric imaging based on physiological clustering clearly outperforms conventional parameter estimation techniques by producing images with higher SNR. It substantially reduces noise and noise-induced bias by utilizing kinetic information from physiologically similar voxels. Functionally similar voxels are binned in the same cluster with each cluster represented by mean kinetics. The mean kinetic information for each cluster is enforced as a spatial constraint in the voxel-wise parameter estimation process thereby forcing (by tuning the penalty parameter γ) the estimated parameters to be close to the mean kinetics of its representative cluster. Unlike previous approaches, it avoids resolution degradation as no spatial smoothing of heterogeneous functional regions is performed. This approach is quite promising in clinical applications as the algorithm is extremely fast and no heavy computations is performed. This work reinforced the need of positron range modeling in the reconstruction process for ^{82}Rb radio-tracer to obviate resolution degradation due to PVE and noise propagation in parametric image estimation. Future work involves evaluation on real patient data and extending the concept of physiological clustering in direct 4-D methods.⁵³⁻⁵⁹

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Table 2. MBF and CFR estimates for rest and stress simulations in normally perfused myocardium and perfusion defects.

γ	MBF_{rest}^{myo}	$\text{MBF}_{stress}^{myo}$	$\text{MBF}_{rest}^{defect}$	$\text{MBF}_{stress}^{defect}$	CFR_{myo}	CFR_{defect}
0	2.73 ± 0.29	5.45 ± 0.34	3.36 ± 0.76	3.93 ± 1.01	2.02 ± 0.24	1.20 ± 0.33
5×10^{-5}	2.45 ± 0.27	5.22 ± 0.33	3.14 ± 0.68	3.69 ± 0.93	2.15 ± 0.25	1.21 ± 0.32
8×10^{-5}	2.32 ± 0.25	5.10 ± 0.32	3.03 ± 0.64	3.55 ± 0.90	2.22 ± 0.26	1.20 ± 0.32
1×10^{-4}	2.25 ± 0.24	5.03 ± 0.32	2.96 ± 0.62	3.48 ± 0.88	2.26 ± 0.26	1.20 ± 0.32
3×10^{-4}	1.82 ± 0.19	4.53 ± 0.28	2.52 ± 0.48	3.00 ± 0.71	2.52 ± 0.29	1.22 ± 0.30
6×10^{-4}	1.54 ± 0.16	4.14 ± 0.25	2.20 ± 0.38	2.66 ± 0.58	2.71 ± 0.30	1.24 ± 0.29
9×10^{-4}	1.41 ± 0.14	3.91 ± 0.23	2.02 ± 0.33	2.47 ± 0.51	2.80 ± 0.31	1.25 ± 0.29
1×10^{-3}	1.37 ± 0.14	3.85 ± 0.23	1.97 ± 0.32	2.42 ± 0.49	2.82 ± 0.31	1.25 ± 0.29
3×10^{-3}	1.12 ± 0.11	3.29 ± 0.21	1.60 ± 0.24	2.01 ± 0.37	2.96 ± 0.34	1.29 ± 0.32
8×10^{-3}	1.01 ± 0.10	2.98 ± 0.21	1.41 ± 0.21	1.82 ± 0.34	2.97 ± 0.36	1.33 ± 0.35
1×10^{-2}	1.00 ± 0.10	2.94 ± 0.20	1.38 ± 0.21	1.80 ± 0.34	2.97 ± 0.37	1.34 ± 0.36
True Values	1.36	4.48	1.36	1.50	3.30	1.11

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