Comparison of sparse domain approaches for 4D SPECT dynamic image reconstruction

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Purpose: Dynamic imaging (DI) provides additional diagnostic information in emission tomography in comparison to conventional static imaging at the cost of being computationally more challenging. Dynamic single photon emission computed tomography (SPECT) reconstruction is particularly difficult because of the limitations in the sampling geometry present in most existing scanners. We have developed an algorithm *Spline Initialized Factor Analysis of Dynamic Structures* (SIFADS) that is a matrix factorization method for reconstructing the dynamics of tracers in tissues and blood directly from the projections in dynamic cardiac SPECT, without first resorting to any 3D reconstruction.

Methods: SIFADS is different from “pure” factor analysis in dynamic structures (FADS) in that it employs a dedicated spline-based pre-initialization. In this paper, we analyze the convergence properties of SIFADS and FADS using multiple metrics. The performances of the two approaches are evaluated for numerically simulated data and for real dynamic SPECT data from canine and human subjects.

Results: For SIFADS, metrics analyzed for reconstruction algorithm convergence show better features of the metric curves vs iterations. In addition, SIFADS provides better tissue segmentations than that from pure FADS. Measured computational times are also typically better for SIFADS implementations than those with pure FADS.

Conclusion: The analysis supports the utility of the pre-initialization of a factorization algorithm for better dynamic SPECT image reconstruction. © 2018 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.13099>]

Key words: cardiac imaging, convergence measures in optimization, dynamic SPECT reconstruction, matrix factorization

Abbreviations

FADS factor analysis with dynamic structures

SIFADS spline-initialized FADS

TAC time activity curve

LV left ventricle

RV right ventricle

1. INTRODUCTION

In conventional static nuclear imaging, one assumes equilibrium in tracer concentration and reconstructs a three dimensional image of the accumulated tracer distribution. Dynamic imaging extends beyond that and probes dynamic properties of the tracer by measuring the tracer

distribution as it changes with time from the moment of injection. We have shown previously how to obtain direct organ segmentation based on the respective tracer dynamics for both single photon emission computed tomography (SPECT)¹ and positron emission tomography (PET),² by applying a known non-negative matrix factorization technique³ called factor analysis in dynamic structures (FADS).⁴ In these works, our algorithm¹ [Spline Initialized Factor Analysis of Dynamic Structures (SIFADS)] adds an additional modification to FADS by providing a pre-initialization to the FADS algorithm with a spline optimization. In addition, our approach involves reconstructing tracer dynamics directly from projections that we claim provides more accurate tissue time activity curves (TACs) and blood input functions than those obtained in conventional approaches from post-reconstruction region-of-interest (ROI) sampling of three dimensional reconstructed temporal images. Although diagnostic accuracy of a method is determined by its sensitivity and specificity, by analyzing convergence properties of an algorithm and combining this with its performance based upon known cardiac physiology and segmented anatomical regions, one can show that the pre-initialization improves performance by avoiding local minimums to obtain better optimized solutions.

There have been several works published about dynamic cardiac SPECT using various cameras: three headed cameras,⁵ two headed large field of view cameras,^{6–9} two headed large field of view cameras with diagnostic CT,¹⁰ and new dedicated cameras using CZT.^{11–13} With these various cameras, dynamic cardiac SPECT has been performed with various tracers, including: ²⁰¹Tl,¹⁴ ^{99m}Tc-teboroxime,^{5,15–18} ^{99m}Tc-sestamibi,⁸ and ^{99m}Tc-tetrofosmin.^{9,13} Recently, some works have shown that dynamic SPECT has promise for measuring flow and coronary flow reserve (CFR) with rotating large field of view gamma cameras.^{8,9,19–21} However, in all of these works, it is recognized that because of the slow camera rotation, dynamic data must be reconstructed directly from the projections themselves, that is, performing 4D reconstruction^{1,6,7,9,10,20–22} with appropriate corrections for attenuation, partial volume, and scatter.^{23–25}

Algorithms have advanced,²⁶ including modeling of cardiac motion in dynamic 5D reconstruction,^{27,28} modeling of cardiac and respiratory motion in dynamic 6D reconstruction,²⁹ and directly fitting compartment models.³⁰ Our SIFADS method^{1,31} is a 4D reconstruction approach that directly estimates time activity curves (TACs) from projections of dynamic data acquired from slowly rotating gamma cameras and differs from these previous methods where first dynamic image frames are reconstructed, and then, from which TACs can be generated. Our method first uses splines to obtain an initial solution for a FADS algorithm that estimates the desired TACs. The method involves segmenting the tissues based on their dynamics and involves a similar approach as proposed by Zan et al.³² via reduction in spatial and temporal dimensions. Zan et al. used a fixed prior from static reconstruction and changed time-basis function manually with a spline-based method (where basis function remains

constant over iterations) rather than FADS. The SIFADS method can be further extended to address cardiac motion.

Dynamic SPECT imaging with slow gantry rotation involves camera heads rotating while the tracer concentration is temporally changing due to tracer kinetics. Direct reconstruction from the projection data is the only way to describe tracer dynamics immediately following the injection, since a dynamic sequence of static 3D reconstructions is not feasible^{9,10,20–22} because of data inconsistencies. The FADS approach⁴ is a way to address this problem. However, such matrix factorization techniques are known to be dependent on optimization initialization. SIFADS addresses that using a spline-based initialization technique. This approach of initialization acts also as a generic method for estimation of tracer dynamics without being sensitive to which tracer is actually being used in the experiment. This leads to better quantitative and qualitative results in the reconstruction of TACs as evidenced from our results.

Our method provides accurate TACs that can be used for kinetic modeling.^{26,33–35} We segment the tissues based on their dynamics. The curve dynamics can then be used to study the diffusion of the radioactive tracer between blood and tissue types using compartment models. In this work, we concentrate on the accuracy of the TACs not on the actual compartment model parameters. Accuracy measures presented in this work are similar to those of Jin et al.²⁸ SIFADS differs from that work in factor initialization⁵ and regularization.³⁶ Our work does not address cardiac or any motion at this stage.^{28,29,37}

The paper is organized as follows. In Section 2, we present the algorithm and some measures that we use in the current work to evaluate the algorithm's performance. We also describe in this section methods used to generate simulated data and to acquire canine and human SPECT projection data. The results of our work and a conclusion are provided in Sections 3 and 4, respectively.

2. MATERIALS AND METHODS

2.A. Algorithm

The forward problem in our dynamic reconstruction is:

$$P_n = \sum_k S_{nk} V_k(t), \quad (1)$$

where P_n are the projection data that depend on time (one projection view angle per time instance), S_{nk} are the elements of the (sparse) system matrix, $V_k(t)$ are the time-dependent voxel intensities to be determined, n is the index for the detector bins, and k is the index for the image voxels. To solve this problem, the time-dependent volume is factorized:

$$V_{k,t} = \sum_j C_{kj} f_{j,t}, \quad (2)$$

with t the index of discretized time, $j \in [1, J]$ the index of the factor f from a set of J one-dimensional time series acting as expansion basis functions for factorization (typically $J \sim 3-5$), and C the spatially discretized distribution of factor

expansion coefficients. Each estimated C is thresholded using Otsu's method.³⁸ Thresholded coefficients represent segmentation of the tissues based on the respective temporal dynamics, and the corresponding factors f represent estimated temporal dynamics. Note that the index t addresses both time points and equivalently, the subset of projection bin indices n corresponding to the gantry rotation angle for the SPECT camera. SPECT system matrices in our work were generated by us from the acquisition parameters and collimator specification modeled as a Gaussian point spread function. Attenuation coefficients were used for real data, but not in the case of simulated data. No scatter correction was used in this work.

In a pure spline-based method,³⁹ f is a fixed set of b-splines. The optimization procedure estimates only the coefficients C [Fig. 1(a)]. In pure FADS,^{4,5,40} both C and f arrays are estimated from P and S , with the optimization algorithm iteratively searching alternately for C and for f [Fig. 1(b)]. For this pure FADS, initialization of f vectors is with quadratic b-splines but initialization of C matrix may be with arbitrary values, and we initialize with all ones. The primary limitations of these methods are reliance on the correct choice of initial temporal basis functions for the pure spline-based approach, and high sensitivity to factor initialization and high likelihood of converging to a local minimum for FADS. These methods are types of a *non-negative matrix factorization* approach³ that is known to be very sensitive to initialization. FADS method is also similar to *dictionary learning* in image processing.^{41,42}

We show the spline-based method in Fig. 1(a) as we use it for the pre-initialization process within SIFADS, and the pure FADS in Fig. 1(b), which constitutes the primary component of SIFADS. The purpose of developing SIFADS is to find a way to initialize FADS better with the spline-based method. Figure 1(c) shows how these two algorithms are used within SIFADS. The top right side of Fig. 1(c) is where the spline-based method produces initial values for the subsequent FADS algorithm [the bottom three steps Fig. 1(c)]. SIFADS mitigates the problem of both the pure spline-based method and the arbitrarily initialized FADS method by first using a few iterations of the spline-based method (typically, 3–5 iterations) to initialize C and corresponding f arrays and, subsequently, performs FADS. The result is a robust and more reliable method as described in Ref. [1].

To quantitate the performance differences between SIFADS and its predecessors, we apply the algorithm to three dynamic cardiac SPECT datasets: simulated data using an XCAT phantom, data from a canine dynamic imaging study, and data from a human dynamic imaging study. To have a fair comparison, we initialize all algorithms with the same b-splines. In pure FADS, the number of TACs may differ from the number of initial b-splines based on how many regions for which we want to estimate TACs. The final estimated TAC for each segment is the average over all the TACs of the voxels in that segment. Each segment is obtained by segmentation of the 3D image reconstructed from later projections (usually projections are almost consistent 4.5 to 30 min after

FIG. 1. Flow diagram for the three approaches. (a) Spline-based method. (b) FADS method. (c) SIFADS method. [Color figure can be viewed at wileyonlinelibrary.com]

tracer injection) of the same SPECT data acquisition. Maximum likelihood expectation maximization (MLEM) algorithm, or rather its regularized version, *maximum a-posteriori* (MAP) algorithm⁴³ with *anisotropic total variation*,⁴⁴ is used for this static reconstruction. The earlier tomographic rotations are used for the dynamic reconstruction (inconsistent projections from 0 to 4.5 min after tracer injection).

2.B. Performance measures

The following measures are used to evaluate the performance of the algorithm as a function of the iteration: projection error, an objective function, convergence estimate, and TAC curve error. All of these measures (except CPU time) are dimensionless. Our primary objective in designing these measures is to analyze the algorithms' behavior over iterations. In the absence of ground truth, we also relied significantly on our understanding of the physiology (for example: relative time of the peak of the curves in the right ventricle, lung, and left ventricle) and anatomical segmented regions or coefficient maps (C) in evaluating the performance of the algorithms.

2.B.1. The mean square projection distance

The *mean square projection distance* computes how close the estimated projections are to the measured projections. In the absence of the ground truth, this quantity serves as the most direct estimate of the validity. This distance would never become zero except for noise-free simulated projections of a smooth distribution, as the projection/backprojection generally reduces noise and smooths the signal noise:

$$\text{Error Distance} = \frac{1}{N} \sum_{n=1}^N (\text{sinogram}_{\text{True},n} - \text{sinogram}_{\text{est},n})^2. \quad (3)$$

2.B.2. The objective function

The objective function in the MAP reconstruction⁴³ is the log of likelihood of the reconstructed image taking into account the acquired projections and the prior information:

$$\begin{aligned} L(C, f) = & \sum_{n,t} \left(- \left(\sum_k S_{nk} \sum_j C_{kj} f_{j,t} \right) \right. \\ & + P_{n,t} \ln \left(\sum_k S_{nk} \sum_j C_{kj} f_{j,t} \right) \\ & \left. + \ln(P_{n,t}!) \right) - U(C, f), \end{aligned} \quad (4)$$

where $U(C, f) = \Omega(C) + \Theta(C) + \Theta(f)$ is a prior function that describes the available *a priori* knowledge about C and f . We use two types of regularizing functions within U , one for *spatial regularization* and one for *temporal regularization*, described in more detail in Abdalah et al.¹ Spatial regularization is applied to the coefficients C and includes two penalty functions. One function for preventing the coefficients from

being mixed together in the same voxel, that is, we prefer each voxel to be of one tissue type. This is managed by minimizing the dot product between coefficients.⁴¹

$$\Omega(C) = \sum_{k,j} \sum_{l \neq j}^J (C_{k,j} \cdot C_{k,l}). \quad (5)$$

For more detail on this penalty function, one may refer to Abdalah et al.^{1,31} The second penalty is an *anisotropic (tissue-specific) total variation* function to enforce spatial smoothness:⁴⁴

$$\Theta(C) = \sum_{k,j} \sum_{n \in \{N_k\}} |C_{k,j} - C_{n,j}|, \quad (6)$$

where $\{N_k\}$ is the set of the k th voxel's immediate neighbors. The temporal regularization function is applied to the estimated factor curves f to enforce their smoothness. We use the L_1 -norm for the smoothness penalty functions that is more robust against outliers:^{44,45}

$$\Theta(f) = \sum_{j=1}^J \sum_{t=2}^T |f_{j,t} - f_{j,t-1}|. \quad (7)$$

Although our results (in subsequent sections) show that SIFADS does not always converges to lower objective function values compared to that of FADS, we still used this measure in the study to have a level playing field. The objective function in both algorithms is the same and this is the only measure that the optimization algorithm attempts to maximize. We discuss the implication of our results later in this paper.

2.B.3. Degree of convergence

To measure the iteration-wise *degree of convergence* of the coefficients $C_{k,j}$ (independent of its accuracy), we use the asymptotic mean ratio of the reconstructed voxel values to the values of the same voxels in the previous iteration of the algorithm:

$$\text{Convergence}_i = \frac{1}{J \times K} \left(\sum_j \sum_{k=1}^K \frac{C_{k,j}^i}{C_{k,j}^{i-1}} \right). \quad (8)$$

At the i th iteration the convergence value is equal to the sum of the current measured coefficient value divided by the coefficient value from the previous iteration, where k is the voxel index and j is the factor index. However, this measure has to be interpreted with care as only non-zero voxels participate in this computation. The number of non-zero voxels, with respect to an arbitrarily assigned low threshold used by us, fluctuates from iteration to iteration. In essence, this measure produces a combined effect of zero elimination and voxel-convergence. Our main objective with this measure is to provide the respective algorithm's overall behavior from iteration to iteration, although varying non-zero values cause some minor fluctuations in its values as may be observed in plots.

2.B.4. Root-mean square

When the ground truth is available, as in the simulated dynamic projection data generated from the XCAT phantom,⁴⁶ we also measure the accuracy of the TACs by

calculating the relative *root-mean square* (RMS) difference between the estimated TACs and the ground truth TACs used to generate the dynamic projections:

$$RMS(TAC_j) = \sqrt{\frac{\sum_t \left[(TAC_j^{est.})_t - (TAC_j^{true})_t \right]^2}{\sum_t (TAC_j^{true})_t^2}}. \quad (9)$$

2.B.5. CPU time

CPU time of the algorithm is also measured as a function of iteration for comparing SIFADS against pure FADS.

2.C. Data description: simulation, canine, and human subject studies

2.C.1. Simulation study

The simulated dynamic datasets were generated from a $64 \times 64 \times 41$ array of voxels of an XCAT phantom with a parameter set characteristic for cardiac scans performed using the GE Millennium VG3 Hawkeye SPECT/CT camera (the camera that has been used to acquire human subject data addressed in this paper). The dynamic projections were generated by forward projecting the phantom with realistic tracer activities of ^{99m}Tc -sestamibi over different three tissue types segmented from the XCAT phantom: left-ventricular blood pool, myocardial tissue, and liver. Figure 2(a) shows the TACs used to model the tracer concentration for these three segments of the phantom, respectively, and the corresponding phantom segments are shown in the same colors in Fig. 2(b) [to produce the dynamic projections, some sample slices shown in Fig. 3(c)]. Background had zero values.

The three curves are based on our expected shape of tracer dynamics as observed in our dynamic SPECT imaging studies⁴ and are represented here with quadratic b-splines. We use only three segments in this study focusing on imaging the heart. During simulation, the heart was presumed stationary. These segments and the three curves were subsequently used as the ground truth for comparisons with the reconstructed

TACs and coefficient images. Projection data were created using a real system matrix of our camera, similar to the one used in the human data acquisition, but without any attenuation. Poisson noise was subsequently applied to the simulated projection data that also added noise to the background. Noise level is determined purely by data values. Acquisition parameters used for the forward projection were: (a) LEHR parallel-hole collimation, (b) single head detector, (c) 64×64 bins per projection angle, (d) 72 projections over 360° rotation, and (e) camera rotating at a speed of 1 s per projection, that is, 72 s for a full rotation.

2.C.2. Canine study

The pre-clinical cardiac data set used in this work came from a canine rest study performed with a GE Millennium VG3 Hawkeye SPECT/CT camera (GE Healthcare, Chicago, IL, USA). The study was approved by the Human and Animal Research Committee (HARC) at Lawrence Berkeley National Laboratory, Berkeley, California. The two detector heads were mounted with LEHR parallel-hole collimators and positioned in H-mode (opposite to each other) for continuous rotation. A bolus injection of 3.7 mCi (1.37×10^8 Bq) of ^{201}Tl tracer was administered at the onset of acquisition that continued for 20 min. For each rotation, two sets of 72 one-second projections over 360° were acquired. First few rotations (results for 72 s of one rotation are shown in all respective figures) of inconsistent data were used for dynamic reconstruction. However, subsequent projections from consistent data set are used for a static reconstruction that is used as an anatomical prior inside the dynamic reconstruction algorithm. Each view contained 64×64 projection bins with 4.42×4.42 mm bin size, close to the intrinsic resolution of the camera.

2.C.3. Human study

Human dynamic cardiac data came from a rest study of a standard clinical rest-stress study using an Infinia Hawkeye 4 SPECT/CT camera (GE Healthcare) configured in H-mode (two detectors oriented 180° to each other. The study was approved by the Committee on Human Research (CHR), the

FIG. 2. Left (a), an example of the ground truth TACs and center (b), segments of XCAT in color, respectively for each curve. Each curve represents how each corresponding segment's intensity is varied while producing the forward projected dynamic data. Right (c), generated dynamic projections with added Poisson noise. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 3. Results of SIFADS and FADS algorithms using simulation data. (a): the spline functions used in both algorithms for initialization. (b): ground truth TACs (gray background curve) along with resulting TACs after 30 iterations using SIFADS, and (c): the same result using FADS. SIFADS produces better TACs. 2nd row: (d): ground truth coefficients, (e): resulting coefficients from SIFADS, and (f): those from FADS (right col.). Activity values on resulting TACs (y-axis) and intensity values on voxels of coefficients are relative. TAC values are relative to that of the input of the initial spline, where the peak value is 1 (for the fourth open spline on (a) and coefficient voxel values are in terms of the counts in the sinogram, such that TACs multiplied with coefficient values of respective voxels [Eq. (2)] produces the respective estimated counts for voxels on the resulting 4D image. [Color figure can be viewed at wileyonlinelibrary.com]

Institutional Review Board (IRB) at University of California San Francisco, California. Dynamic acquisition began immediately prior to the patient receiving an IV bolus injection (10–20 s duration) of approximately 10 mCi of ^{99m}Tc -tetrofosmin. Two views with a 3° increment every second and a total of 120 projection images (60 views from each camera head) per minute were acquired. The rotation speed of each camera head was 2 min per rotation. Projection data were binned into 128×128 detector bins with a bin size of 4.42×4.42 mm. In this work, the projections were cropped to 128×40 pixels (around the heart) to reduce the data size. Projections used in this study are similar to that in the canine study mentioned above — first few rotations for the dynamic study supported by the static reconstruction from later consistent projection data.

3. RESULTS

3.A. Simulation study

Figure 3 shows an example of a comparison of the TACs and the coefficient images obtained using the two algorithms,

SIFADS and pure FADS, against the ground truth. Time axes in all figures are in seconds. A better recoverability of the TACs using SIFADS is clear. When comparing the FADS part of the SIFADS algorithm against the pure FADS (i.e., using factor analysis with spline-based pre-initialization vs initialization with arbitrary b-splines), the curves illustrate that, with TACs and coefficients estimated with the splines, the subsequent FADS portion of SIFADS algorithm is more accurately initialized and the resulting convergence is faster and more accurate (as observed from resulting coefficient images, TACs, and often with the convergence measures) than the pure FADS.

We ran the SIFADS and FADS algorithms several times with different initializing b-splines; each time both algorithms started with the same set of b-splines. Each column of Fig. 4 corresponds to a set of initializing b-splines in the first row. For each of the three initializing splines the SIFADS algorithm demonstrates faster convergence and better optimization than the pure FADS algorithm. Figure 4 shows measures of convergence for the two algorithms vs iteration for three different initializing b-splines. The figure shows the convergence [Eq. (8)], the estimation error [Eq. (3)], and the

value of the objective function [Eq. (4)] vs iteration in rows Figs. 4(d)–4(f), 4(g)–4(i), and 4(j)–4(l), respectively.

SIFADS has two phases of iterative processes: spline-based optimization and then FADS optimization. We distinguish between these two types of iterations as *pure spline-based iterations* and *FADS-iterations*. The FADS algorithm has only FADS-iterations. We compared the performance of the two algorithms for 35 iterations. Two FADS-iterations take approximately the same time as five pure spline-based iterations used within SIFADS (see Table I below). Hence, we adjust each plot's x-axis by two units of time toward the right to adjust for the overhead of pre-initialization time in SIFADS (blue curve). Note that the pure spline-based optimization algorithm optimizes only for the coefficients of the splines, whereas the FADS algorithm optimizes for both the factors (starting with the splines) and their coefficients,¹ and hence, a FADS iteration takes more time than a spline-based algorithm.

We experimented with several base-factors sets (approximately 20, with different number of factors and shapes) for initialization purposes. However, for brevity, we present only three such representative experiments here. Figure 4 shows that SIFADS and FADS converge to similar values given enough time. However, SIFADS produces better estimation in less time (i.e., with less iterations), even including the extra overhead for the iterations in the spline-based initialization. For example, only five iterations of SIFADS will produce better results than FADS with seven iterations with arbitrary initialization (two FADS iterations take equivalent time to that of five spline-based pre-initialization steps within SIFADS). We chose 35 iterations, because we did not see much change in the updates of the images as our measures of convergence demonstrate. Achieving full convergence is very time consuming.

Figure 5 shows the resulting curves in the respective columns for the same initializing b-splines as in Figs. 4(a)–4(c) first row. Figures 5(a)–5(c) shows the corresponding results for arbitrarily initialized FADS, and Figs. 5(d)–5(f) shows the same with SIFADS.

Table I has the computation times for the FADS and SIFADS algorithms. All algorithms were implemented and evaluated on an Apple Xserve (Early 2009 version) running Mac OS X server. The machine had two dual quad-core 2.93 GHz Xeon processors and 12 GB of RAM. We report the timings for SIFADS in two parts: spline-based pre-initialization and FADS (first row, columns 3 and 4). Timings for pure FADS are in the second row.

3.B. Canine study

Figure 6 shows estimated TACs from the canine SPECT study. Even though the curves exhibit significant mutual contamination between tissues, SIFADS-computed factors describe the expected physiology of the LV blood pool concentration more realistically. Also, the reconstructed coefficient images computed with SIFADS [Figs. 7(a) and 7(c)] demonstrate better separation between different tissue types, whereas the coefficients estimated by FADS with blind

initialization [Figs. 7(b) and 7(d)] crossover more between different tissue types. All relevant results including 3D images are available online for any interested reader to view.⁴⁷

Figure 8 shows comparisons of the SIFADS and pure FADS algorithms in terms of rates of convergence, image quality, and the objective function values vs iteration for the canine data. Note that although the number of initializing spline-curves for SIFADS may differ (in each of our experiments as shown in Figs. 8(a)–8(c)) the number of factors are determined by the number of segments we want to extract from the data. This number is determined by visual inspection of the projection data or by trial and error. Surprisingly, the projection error and the value of the objective function do not differ significantly at large number of iterations, suggesting fewer iterations are sufficient. FADS show better or very similar convergence characteristics for the first two criteria, whereas SIFADS shows better objective function convergence when initial curves are widely different from expected final curves (last two columns of Fig. 8). Fluctuations of the metrics observed for both algorithms are for reasons unknown to us, but they do not affect the overall observations. Possibly, they are related to the removal and reintroduction of zero values on coefficients as iteration progresses. This is because our implementation avoids storing and computing lower than threshold values that we consider as zero's.

Corresponding to the initialized b-splines of Figs. 8(a)–8(c), the resulting TACs for pure FADS and SIFADS are shown in the two rows of Fig. 9, respectively. SIFADS-computed TACs describe more realistically the expected physiological timing of the RV and LV blood pool concentrations, and lung and myocardial tissue concentrations.

Table II shows that SIFADS exhibits only minor reduction in time per iteration compared to pure FADS. We believe the speed up becomes less as the data becomes more complex and noisy. This happens because fewer non-zero values are obtained in the intermediate results as our implementation ignores zero values. There is no ground truth for the TACs for the real data to measure the RMS error value, as was for the simulation data in Table I.

3.C. Human study

Figure 10 shows the same set of comparisons as in the previous studies with the two algorithms used to estimate TACs from data in a human dynamic SPECT study. At a first glance, the TACs from pure FADS in Fig. 10(b) appear to separate RV and LV TACs as can be seen in Fig. 9. However, visually in Fig. 10(a), SIFADS provides better overall tissue separation.

SIFADS estimates the blood tracer concentration as a single curve (blue in Fig. 10). The myocardium seems to be well represented by the green curve (see its coefficients in Fig. 11 below where it shows a clear shape of the heart). On the other hand, FADS (right) estimates two curves for blood (blue for RV and red for LV). However, the RV curve (blue) has a lower signal than the LV (red), which is unrealistic and not

FIG. 4. Results of comparison measures using the simulation data. 1st row of each column (a–c): three different initializing b-splines. 2nd row (d–f): convergence values [Eq. (8)]; 3rd row (g–i): error distance [Eq. (3)]; 4th row (j–l): objective functional values [Eq. (4)] vs number of iterations. The SIFADS curves (blue) are artificially shifted here by 2 iterations on x-axis to compensate for the spline-initialization overhead time. Contrast of convergence between the two algorithms is mostly observed between 5 to 10 iterations. We show results for up to 35 iterations on x-axis. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE I. Computation times for simulation data.

	Convergence value [Eq. (8)]	Computing time of initial coefficients and TACs with spline-method (s)	FADS time (s)	Total time (s)	Error distance of last iteration [Eq. (3)]	RMS of TACs [Eq. (9)]
SIFADS CPU (5 spline-based iterations, and subsequent 30 FADS-iterations)	0.172	44.931 (5 iterations) 8.99/iterations	390.632 13/FADS- iterations	435.563	0.285	0.070
Pure FADS (30 FADS-iterations)	0.179	—	507.031 16.90/FADS- iterations	507.031	0.285	0.292

Computation times for the FADS and SIFADS algorithms in processing the simulated data. The spline-based initialization phase in the SIFADS algorithm can accelerate the conventional FADS algorithm in spite of the fact that it needs more time to prepare the initial TACs and coefficients. These results are from the first initialization in column 1 of Fig. 5.

FIG. 5. TACs comparison in simulation study. TACs estimated by FADS and SIFADS for the three initializations as in Fig. 4. 1st row (a–c): TACs estimated by the FADS algorithm. 2nd row (d–f): TACs estimated by the SIFADS algorithm. Ground truth curves are shown in gray for comparison. Lesser RMS values for each curve show that SIFADS consistently produces better curves. [Color figure can be viewed at wileyonlinelibrary.com]

obvious in the projection data. Also, the myocardium curve (green) seems to have an unrealistically fast uptake and wash-out (50 s). Furthermore, liver and kidney TACs are mixed together in the FADS results. Each frame in Fig. 11 consists of an overlay of the corresponding four color-coded slices from the four 3D coefficient images, where the colors are the same as that for the corresponding curves of factors in Fig. 10. It is evident by the coefficients of SIFADS that the tissue types are better distinguishable (each color represents a tissue type, i.e., blood, heart, liver, or kidneys). This is in contrast to the fact that the coefficients estimated by FADS are not well separated.

We believe that the FADS curves are less accurate because: (a) LV actually has a stronger signal than the RV (as seen in the projections) as opposed to what the pure FADS curve is showing. (b) Coefficients from pure FADS visually do not show the clear segmentation observable in the SIFADS coefficient images. Visual inspection of the coefficients obtained from pure FADS does not allow clear correspondence of the blue and red curves to specific ventricular regions, whereas in SIFADS the unseparated blue curve clearly corresponds to a single ventricular region. (c) Liver is not clearly segmented with pure FADS despite being well defined in the projections.

FIG. 6. Estimated TACs for the canine SPECT study by: (a) SIFADS and (b) FADS. The arrows on the x-axis show the time at which the tracer uptake arrives to a peak: RV first (blue), then myocardium (green) followed by (or simultaneously with) LV (red). Lungs (purple) peak appears at relatively different times for the two algorithms. Initializing b-splines are shown on Fig. 8(a). [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 7. Estimated tissue coefficient images for the canine SPECT study by: (a and c) SIFADS, and (b and d) FADS. The upper row (a and b) shows some slices of respective coefficients and the lower row (c and d) shows the same images in 3D from SIFADS and FADS, respectively.

FIG. 8. Measures of comparison on canine study for three different initializing b-splines (a–c, 1st row for each column). 2nd row (d–f): convergence values [Eq. (8)]; 3rd row (g–i): error distance [Eq. (3)]; 4th row (j–l): objective functional value [Eq. (4)] all vs number of iterations. The resulting SIFADS curves (blue) are shifted by 1 iteration to compensate for the overhead time in the spline initialization (see Table II below). [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 9. Estimated TACs by FADS and SIFADS for the three initializations in Fig. 8. 1st row (a–c): TACs estimated by the FADS algorithm. 2nd row (d–f): TACs estimated by the SIFADS algorithm. Blue curves for RV, red curves for LV, green curves for myocardium and purple curves for lungs. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

TABLE II. Computation times on canine data.

	Convergence value [Eq. (8)]	Computing time of initial coefficients and TACs with spline-method (s)	FADS time (s)	Total time (s)	Error distance on last iteration [Eq. (3)]
SIFADS CPU (5 spline-based iterations, and 30 subsequent FADS-iterations)	1.674566	56.293 (5 iterations) 11.25/iterations	486.794 16.06/FADS- iterations	543.087	2.5043
Pure FADS (30 FADS-iterations)	1.793	—	488.049 16.27/FADS- iterations	488.049	2.852

Computation times for the FADS and SIFADS algorithms in processing the canine data. Convergence value and running time for the two methods in estimating TACs from the canine data with 30 iterations. These results are from the first initialization in column 1 of Fig. 8.

Figures 12(a)–12(c) show three sets of initial b-splines, and the subsequent rows display the algorithm performance measures corresponding to these sets. All three performance measures for SIFADS (blue curves) are notably similar across the three initialization sets, demonstrating the stability and reproducibility of the algorithm. Convergence plots in Figs. 12(d)–12(f) show that in two cases [first and third columns, Figs. 12(d) and 12(f)] SIFADS achieves better convergence than pure FADS after a few iterations. The third row Figs. 12(g)–12(i) present error distances [Eq. (3)] between the estimated and the actual projections that indicates pure FADS better estimates the projections. The human scan data were extremely noisy, and SIFADS actually removed more noise than did FADS, thus, the

solution deviated further from the input data. The objective function values in the fourth row of Figs. 12(j)–12(l) suggest that FADS outperforms SIFADS after 6 to 12 iterations. This is an anomalous result since the optimization in both algorithms is performed with the same objective function, and we clearly see better segmentation in the coefficient images produced by SIFADS after thirty iterations (see Fig. 11 and the data available on the provided link⁴⁷). This may mean that SIFADS and FADS are converging to two different local minima and the local minimum attained by SIFADS is better suited for tissue segmentation based on tracer kinetics.

TACs computed from two algorithms corresponding to different initializations (Fig. 12, first row) are shown in the

FIG. 10. Estimated TACs for the human study after 30 iterations by: (a) SIFADS and (b) FADS. X-axis is in seconds. Blue curves for RV, red curves for LV, green curves for myocardium and purple curves for lungs. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 11. Coefficient images. Frames from color-coded superimposed coefficient images after 30 iterations of SIFADS (a) and pure FADS (b). Colors are assigned based on the corresponding TACs' colors in Fig. 10: Blue for RV, red for LV, green for myocardium and purple for lungs.

two rows of Fig. 13, respectively. SIFADS-computed TACs describe the expected physiology more realistically.

Table III shows that the pure FADS algorithm surprisingly takes slightly less time per iteration on average for the human data although its convergence is slower (Figs. 12(d)–12(f), and Table III-column 1).

4. DISCUSSION

The focus of this paper was to compare accuracy and convergence properties of SIFADS and FADS reconstruction algorithms. SIFADS clearly performs better on all three performance measures for simulated data, reconstructing dynamic noise-added data generated from the XCAT phantom (Figs. 3–5). This was true for any number of iterations.

In the canine study (Fig. 8), although FADS attains better values for the objective function after around ten iterations, the physiological features estimated by SIFADS is more realistic (Fig. 7). For the human study (Fig. 12), the objective function values for the two algorithms cross-over between 8 to 15 iterations, depending on the initialization. The other two measures of convergence and error distance seem to follow fairly similar trends after a few iterations, again depending on the initialization. Overall, SIFADS seems to provide better estimates of the expected physiological aspects of the tracer kinetics with fewer iterations (only 5) than FADS. Note that the curves estimated by SIFADS are already adjusted for the overhead time to determine the initial spline coefficients.

We believe that SIFADS and FADS are converging to different local minima because of different initializations.

FIG. 12. Measures of comparison using the human data for three different initializing b-splines (1st row for each column, a–c). 2nd row (d–f): convergence values [Eq. (8)]; 3rd row (g–i): error distance [Eq. (3)]; 4th row (j–l): objective functional values [Eq. (4)] vs number of iterations. The SIFADS curves (blue) are shifted by 1 iteration to compensate for the spline-initialization overhead time (see Table III). Blue curves for RV, red curves for LV, green curves for myocardium and purple curves for lungs. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 13. Estimated TACs by FADS and SIFADS for human study for the three initializations in Fig. 12. 1st row (a–c): TACs estimated by the FADS algorithm. 2nd row (d–f): TACs estimated by the SIFADS algorithm. Blue curves for RV, red curves for LV, green curves for myocardium and purple curves for lungs. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE III. Computation times on human data.

	Convergence value [Eq.(8)]	Computing time of initial coefficients and TACs with spline-method (s)	FADS time (s)	Total time (s)	Error distance at last iteration [Eq. (3)]
SIFADS (5 spline-based iterations, and 30 FADS-iterations)	0.54	2444.21 (5 iterations) 488.84 s/iterations	22961.86 765.40 s/FADS-iterations	25406.07	0.37
FADS (30 iterations)	1.30	–	22633.06 754.44 s/FADS-iterations	22633.06	0.39

Computation times for the FADS and SIFADS algorithms in processing the human data. Convergence values and run times for the three methods in reconstructing the TACs from the human data. These results are from the first initialization in column 1 of Fig. 12.

Although FADS show different values of the objective function than that of SIFADS after 30 iterations (human data, Fig. 9) the estimated TACs and coefficient images with SIFADS appear much more realistic upon visual inspection as shown in Figs. 10–11,⁴⁷ over a range of iterations. This observation leads us to conjecture that the objective function is not the best performance metric for estimating the quality of segmenting tissues based on the tracer dynamics.

In the previous section, we commented that the FADS iterations take less computation time as opposed to those of SIFADS (Table III, third column). This seemingly counter-intuitive effect is explained by the procedure of how zero values are eliminated below a pre-assigned threshold from being processed further in the reconstruction. Some factor values

approach zero after only a few FADS iterations. Potentially, this may compromise the estimation of TACs by pure FADS by providing less realistic TACs in return for slight improvement in efficiency.

One may observe in the plots in Figs. 6, 9 and 13 that many curves are converging to similar values. Thus, one may wonder why then one sees clear segmentations from a static reconstruction with the same tracer. The reason for this is the fact that the intensity values in static and dynamic imaging have a different interpretation. The ^{99m}Tc-sestamibi uptake in the heart begins immediately with the injection and continues with little washout. At the start of the static perfusion phase approximately 60–70 min later, there is excellent contrast between the myocardium and the blood in the left-ventricular

cavity. The plots show that at that time there is very little activity in the blood in the left-ventricular cavity; whereas, the activity in the heart in a typical perfusion imaging is really the integral of the time curve shown here for the heart over the 60–70 min. This integral of activity provides excellent contrast compared with the background blood activity.

5. CONCLUSION

FADS are a powerful method capable of reconstructing tissue TACs and spatial distributions from dynamic SPECT projections; however, it is overly sensitive to the initialization both in terms of performance and the reconstruction accuracy. FADS accuracy and convergence time may be improved using b-spline-based initialization of the factors implemented in our SIFADS algorithm. SIFADS clearly outperforms FADS in reconstruction of simulated phantom study as seen from our results presented here. However, to check its performance further on real data, we have compared SIFADS with FADS on data sets of canine and human studies. When reconstructing these real data, numerical performance comparisons do not give clear advantage to either algorithm; however, the tissue distribution images obtained with SIFADS appear to be more physiologically meaningful. This suggests a few primary directions for future work: (a) Changing the objective function formulation that reflects our goal of tracer-dynamics based segmentation may further improve the quality of the dynamic SPECT reconstruction. (b) Using alternative initialization techniques (other than the spline-based one as in SIFADS) may be explored² to address the non-uniqueness of FADS. (c) Studying how cardiac motion affects the dynamics results²⁹ with respect to our initialization techniques. Results with simulation data depict the algorithms' progress (over iterations), even under Poisson noise. It proves SIFADS' general superiority. However, noise in real data as well as the qualitative nature of our measures contributes to the not-so-perfect representation of the performance of the two algorithms. Although, these results diverge somewhat from those for simulation data, they still point toward our conclusion that it is worth using spline-based initialization before running FADS as we do within SIFADS.

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CONFLICT OF INTEREST

The authors have no conflicts to disclose.

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