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Direct parametric reconstruction in dynamic PET myocardial perfusion imaging: *in-vivo* studies

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Abstract

Dynamic PET myocardial perfusion imaging (MPI) used in conjunction with tracer kinetic modeling enables the quantification of absolute myocardial blood flow (MBF). However, MBF maps computed using the traditional indirect method (i.e. post-reconstruction voxel-wise fitting of kinetic model to PET time-activity-curves -TACs) suffer from poor signal-to-noise ratio (SNR). Direct reconstruction of kinetic parameters from raw PET projection data has been shown to offer parametric images with higher SNR compared to the indirect method. The aim of this study was to extend and evaluate the performance of a direct parametric reconstruction method using *in-vivo* dynamic PET MPI data for the purpose of quantifying MBF. Dynamic PET MPI studies were performed on two healthy pigs using a Siemens Biograph mMR scanner. List-mode PET data for each animal were acquired following a bolus injection of ~7-8 mCi of ¹⁸F-flurpiridaz, a myocardial perfusion agent. Fully-3D dynamic PET sinograms were obtained by sorting the coincidence events into 16 temporal frames covering ~5 min after radiotracer administration. Additionally, eight independent noise realizations of both scans - each containing 1/8th of the total number of events - were generated from the original list-mode data. Dynamic sinograms were then used to compute parametric maps using the conventional indirect method and the proposed direct method. For both methods, a one-tissue compartment model accounting for spillover from the left and right ventricle blood-pools was used to describe the kinetics of ¹⁸F-flurpiridaz. An image-derived arterial input function obtained from a TAC taken in the left ventricle cavity was used for tracer kinetic analysis. For the indirect method, frame-by-frame images were estimated using two fully-3D reconstruction techniques: the standard Ordered Subset Expectation Maximization (OSEM) reconstruction algorithm on one side, and the One-Step Late Maximum a Posteriori (OSL-MAP) algorithm on the other side, which incorporates a quadratic penalty function. The parametric images were then calculated using voxel-wise weighted least-square fitting of the reconstructed myocardial PET TACs. For the direct method, parametric images were estimated directly from the dynamic PET sinograms using a maximum a posteriori (MAP) parametric reconstruction algorithm which optimizes an objective function comprised of the Poisson log-likelihood term, the kinetic model and a quadratic penalty function. Maximization of the objective function with respect to each set of parameters was achieved using a preconditioned conjugate

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gradient algorithm with a specifically developed pre-conditioner. The performance of the direct method was evaluated by comparing voxel- and segment-wise estimates of K_1 , the tracer transport rate ($\text{mL} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$), to those obtained using the indirect method applied to both OSEM and OSL-MAP dynamic reconstructions. The proposed direct reconstruction method produced K_1 maps with visibly lower noise than the indirect method based on OSEM and OSL-MAP reconstructions. At normal count levels, the direct method was shown to outperform the indirect method based on OSL-MAP in the sense that at matched level of bias, reduced regional noise levels were obtained. At lower count levels, the direct method produced K_1 estimates with significantly lower standard deviation across noise realizations than the indirect method based on OSL-MAP at matched bias level. In all cases, the direct method yielded lower noise and standard deviation than the indirect method based on OSEM. Overall, the proposed direct reconstruction offered a better bias-variance tradeoff than the indirect method applied to either OSEM and OSL-MAP. Direct parametric reconstruction as applied to *in-vivo* dynamic PET MPI data is therefore a promising method for producing MBF maps with lower variance.

Keywords

Direct parametric reconstruction; dynamic PET; myocardial perfusion imaging; kinetic modeling; parametric imaging; preconditioned conjugate gradient

1. INTRODUCTION

Myocardial perfusion imaging (MPI) is a powerful technique which allows non-invasive evaluation of the hemodynamic consequences of obstructive coronary artery disease (CAD). In current clinical practice, Single Photon Emission Computed Tomography (SPECT) remains the dominant modality for MPI. However, Positron Emission Tomography (PET) has been increasingly used for MPI in recent years due to its superior spatial resolution and sensitivity and overall better perfusion tracer characteristics in terms of tissue extraction (Lalonde et al., 2009, Klein and Beanlands, 2010). The superiority of PET over SPECT for MPI is further reinforced with the development of the novel ^{18}F -labeled perfusion agent ^{18}F -flurpiridaz (Lantheus Medical Imaging, North Billerica, MA) due to its short positron range, long half-life, and high first-pass extraction fraction (Nekolla et al., 2009). Furthermore, dynamic PET MPI can be used to calculate parametric maps of tracer kinetics, which provides added quantitative information of high clinical value to static (i.e. 'qualitative') SPECT or PET MPI by enabling quantification of absolute Myocardial Blood Flow (MBF) and myocardial flow reserve (stress/rest MBF). The quantification of MBF and MFR, which has been proven to be sensitive for detecting pre-symptomatic abnormalities in coronary arteries function, has in fact allowed extending the scope of MPI from the detection of advanced flow-limiting CAD to early stages of atherosclerosis and micro-vascular dysfunction (Schindler et al., 2010). In addition, MBF quantification has been shown to be particularly useful for detecting multi-vessel CAD that may cause a global reduction in blood flow and lead to false-negative results with qualitative SPECT or PET MPI (Parkash et al., 2004, Yoshinaga and Beanlands, 2007, Gewirtz et al., 1997).

Yet, despite its great clinical value, parametric PET MPI - especially at the voxel level - has been hampered in its infancy by the poor signal-to-noise ratio (SNR) of the estimated parametric images and has thus far remained primarily limited to research applications. The traditional method for calculating parametric images - which we hereinafter refer to as the indirect method - is to reconstruct a time-series of PET images from the dynamic measurements, and then to estimate the kinetic parameters by fitting a compartment model to voxel-wise time-activity curves (TAC), usually by means of weighted non-linear least-square fitting algorithms. This approach assumes that the noise in the TACs is Gaussian distributed. However, the noise distribution of the reconstructed PET images is generally complex - i.e. space-variant and object-dependent (Wilson and Tsui, 1993, Stayman and Fessler, 2000) - and not accurately modeled as Gaussian, especially for low-count dynamic frames, which leads to high variance in the estimated kinetic parameters. One possible approach to tackle the shortcomings of the indirect method is to directly reconstruct the parametric images from the raw PET projection data, by incorporating the kinetic model fitting inside the PET reconstruction itself. This approach, which is commonly referred to as the direct method, was originally proposed by Snyder *et al* (Snyder, 1984) and Carson and Lange (Carson and Lange, 1985). The key advantage of the direct method over the indirect one is that it takes into account the Poisson nature of the measured PET projection data during the estimation of the kinetic parameters. As a result, the variance on the estimated parametric images is greatly reduced as compared to the indirect method, especially for low-count studies (Yan et al., 2012, Karakatsanis et al., 2016, Gravel and Reader, 2015). Direct parametric reconstruction may thus prove particularly beneficial to dynamic PET MPI, where the rapid kinetics of perfusion radiotracers require using short and low-count frames data.

Several direct parametric reconstruction methods have been proposed in the literature for dynamic PET MPI (Rahmim et al., 2014, Germino et al., 2014, Su et al., 2013, Rakvongthai et al., 2013). Comprehensive reviews of direct reconstruction techniques are also available (Rahmim et al., 2009, Tsoumpas et al., 2008b, Wang and Qi, 2013, Reader and Verhaeghe, 2014). Rahmin *et al* (Rahmim et al., 2014) applied the concept of optimization transfer and surrogate functions - originally proposed by Wang and Qi (Wang and Qi, 2009) - for improving the optimization of a Poisson log-likelihood objective function comprising the dynamic PET data and the kinetic model parameters. Su *et al* (Su et al., 2013) modified the expectation maximization (EM) approach proposed by Matthews *et al* and Yan *et al* (Matthews et al., 1997, Yan et al., 2012) to perform direct reconstruction of the linear kinetic parameters of a one-tissue compartment model. They separated the parameters to estimate into several terms, one of them containing the non-linear kinetic parameter k_2 and the others the linear kinetic parameters, and used a list of pre-computed k_2 values to derive the M-step of their algorithm and update the non-linear term at each EM iteration. Germino *et al* (Germino et al., 2014) likewise extended a previously proposed EM-based direct parametric reconstruction method (Yan et al., 2012) to dynamic PET MPI, by incorporating blood spillover terms into the one-tissue compartment model. Their simulation results demonstrated that the direct method yielded lower variance in the estimated kinetic parameters than the indirect method. When tested on a human ^{82}Rb dataset, they found that

the direct method yielded lower K_1 values (-18%) across the myocardium compared to the indirect method.

We have previously developed a maximum a posteriori (MAP) framework for direct reconstruction of parametric images in dynamic PET MPI, and used a novel preconditioned conjugate gradient (PCG) algorithm for optimizing a penalized Poisson log-likelihood objective function (Rakvongthai et al., 2013). Using simulated NCAT phantom data, we have demonstrated that PCG substantially increases the convergence rate of direct parametric reconstruction as compared to the conjugate gradient algorithm. Furthermore, at the same level of bias in K_1 values, the direct method outperformed the indirect method in terms of variance, particularly in lower count studies and myocardium defect regions. However, we used a simple one-tissue compartment model without spillover terms from the blood chambers, which may not accurately model *in-vivo* PET MPI TACs and may in turn lead to an overestimation of K_1 . Furthermore, we neglected scattered and random coincidences and evaluated our method only using simulated data. In fact, to the best of our knowledge, only Germino *et al* (Germino et al., 2014) have applied direct parametric reconstruction to *in-vivo* dynamic PET MPI data.

In this work, we extend our previously proposed method (Rakvongthai et al., 2013) by modeling spillover terms in the one-tissue compartment model as well as scatter and random coincidence distributions so that it can be applied to *in-vivo* dynamic MPI studies for direct reconstruction of MBF maps. We investigated the applicability and performance of our approach using two dynamic PET MPI studies performed on healthy pigs. We compared the performance of the proposed method to the traditional post-reconstruction indirect kinetic parameter estimation method. For the indirect method, we used two different fully-3D reconstruction techniques for estimating the dynamic PET images: the standard Ordered Subset Expectation Maximization (OSEM) reconstruction algorithm on one side, and the One-Step Late Maximum a Posteriori (OSL-MAP) algorithm on the other side, which incorporates a quadratic penalty function.

2. MATERIALS AND METHODS

2.A. Imaging data acquisition

Data presented in this work were acquired on a Biograph mMR, a whole-body integrated PET-MR scanner manufactured by Siemens (Siemens Medical Solutions, Malvern, PA, USA). The PET camera, which is installed between the MR gradient coils and the radiofrequency body coil and operates in fully-3D mode, is composed of 8 rings of 56 blocks of detectors, each made of 8×8 lutetium oxyorthosilicate (LSO) crystals (crystal size: 4×4×20 mm³). A 3×3 array of avalanche photodiodes is used for the readout of each block of detectors. The imaging field of view of the PET scanner in the transaxial and axial directions is 59.4 cm and 25.8 cm, respectively. The mMR fully-3D PET sinograms consist of 837 projection planes (for span = 1 and maximum ring difference = 60), each containing 252 view angles with 344 projection bins per view.

Two healthy domestic pigs (weights: 29–30kgs) underwent dynamic PET MPI studies on the mMR using ¹⁸F-flurpiridaz, a novel ¹⁸F-labeled myocardial perfusion agent currently being

evaluated in a phase-III clinical trial (Bateman et al., 2016). For each animal, anesthesia was induced with telazol and a catheter was placed in the ear vein for injection of the radiotracer. During each of the scans, anesthesia was maintained by means of a continuous infusion of isoflurane through an intubation tube. Physiological signals (pulse, end-tidal CO₂ and breathing rate) were monitored continuously throughout the experiment. Animals were positioned feet-first supine on the scanner's bed and a flexible MR surface coil was placed on the chest. No pharmacological stress was induced during these experiments. First, an attenuation map was acquired using the vendor's supplied Magnetic Resonance based Attenuation Correction (MRAC) protocol. MRAC uses a 2-point Dixon sequence to obtain water and fat volumes, which are in turn processed to obtain a segmented 4-tissue classes (air, lungs, fat and other tissues) attenuation map for PET (Martinez-Moller et al., 2008). PET list-mode data acquisition started simultaneously with MRAC. A bolus injection of ~7-8.0 mCi of ¹⁸F-fluripiridaz was made shortly after starting the list-mode acquisition, followed by a saline flush. The procedures complied with the regulations of the Subcommittee on Research Animal Care at Massachusetts General Hospital. The first ~5 minutes list-mode data after the tracer administration were grouped temporally into a series of 16 frames (10×10s, 6×30s) and rebinned into fully-3D sinograms. Voxel-wise estimation of kinetic parameters was then carried out using the methods described in the next section.

2.B. Estimation of parametric images

This section provides an overview of the methods which were used to estimate parametric images from the acquired dynamic PET MPI data. We first present the compartmental model used to model the kinetics of the perfusion radiotracer in the myocardium (section 2.B.1) and then describe the formalism for the dynamic PET measurements (section 2.B.2). Next, we present the indirect method used for parametric image estimation (section 2.B.3) as well as the proposed direct parametric reconstruction method (section 2.B.4).

2.B.1. Kinetic model—In this study, we used a one-tissue compartment model to describe the kinetics of ¹⁸F-fluripiridaz in the myocardium for ~5 minutes after radiotracer injection. Under this assumption, the time-variation of the tracer concentration in myocardial tissue for a given voxel $j \in [1 \dots J]$, noted $C_M^j(t)$, is governed by the following differential equation:

$$\frac{dC_M^j(t)}{dt} = K_1^j C_p(t) - k_2^j C_M^j(t) \quad (1)$$

where $C_p(t)$ is the concentration of tracer in arterial plasma, K_1^j is the tracer transport rate in mL.min⁻¹.mL⁻¹ and k_2 is the washout rate in min⁻¹. MBF is directly related to the transport rate parameter K_1^j through: $MBF^j = K_1^j / (E * (1 - HCT))$ where HCT is the hematocrit and E is the first-pass extraction fraction, which is assumed to be voxel independent. Since, the first-pass extraction fraction of ¹⁸F-fluripiridaz is very high ($E = 0.94$ (Huisman et al., 2008)) and almost unchanged at high flow rates, there is no need for a flow-dependent extraction fraction to calculate MBF from K_1 (Nekolla et al., 2009). Validation of MBF measured with ¹⁸F-fluripiridaz has been performed by Nekolla *et al* (Nekolla et al., 2009) in

pigs by comparison to microsphere perfusion studies. The input function $C_p(t)$ can be measured using arterial blood sampling or directly derived from the reconstructed dynamic PET volumes using a region of interest drawn within the left-ventricle (LV), as used in this work. The solution to Eq. (1) is given by:

$$C_M^j(t) = K_1^j C_p(t) \otimes e^{-k_2^j t} \quad (2)$$

where symbol $\otimes$ denotes the convolution operator. Due to finite resolution effects, the measured myocardial tissue tracer concentration is affected by spill-in and spill-out activity from the LV and the right-ventricle (RV) blood pools. Therefore, the PET time activity curve (TAC) measured in a given voxel of the myocardium, noted $C_T^j(t)$, is commonly modeled as a combination of 3 contributions: the contribution from the myocardial tissue, modeled with the one-tissue compartment model given in Eq. (1) and (2), and the contributions from the LV and RV cavities, modeled as fractions of measured LV and RV TACs:

$$C_T(t, \mathbf{k}^j) = f_{LV}^j C_{LV}(t) + f_{RV}^j C_{RV}(t) + (1 - f_{LV}^j - f_{RV}^j) C_M^j(t) \quad (3)$$

where $\mathbf{k}^j = [K_1^j, k_2^j, f_{LV}^j, f_{RV}^j]^T$ is the vector of parameters for voxel j , and $f_{LV}^j(f_{RV}^j)$ is the fractional spillover value from the LV (RV) in voxel j .

Replacing $C_M^j(t)$ above, by its expression in Eq. (2) yields:

$$C_T(t, \mathbf{k}^j) = f_{LV}^j C_{LV}(t) + f_{RV}^j C_{RV}(t) + (1 - f_{LV}^j - f_{RV}^j) [K_1^j C_p(t) \otimes e^{-k_2^j t}]. \quad (4)$$

The terms $C_{LV}(t)$, $C_{RV}(t)$ and $C_p(t)$ in Eq. (4) were calculated directly from the dynamic PET images reconstructed using the methods described in section 2.B.3. First, the ‘whole-blood’ terms $C_{LV}(t)$ and $C_{RV}(t)$ were calculated by extracting two TACs in cylindrical volumes of interest (VOIs) of size $\sim 1 \times 1 \times 2 \text{ cm}^3$ centered in the basal portions of the LV and RV blood-pools, respectively. The VOIs were located approximately $\sim 1.5 \text{ cm}$ away from the endocardium surface. Then, the image-derived arterial plasma input function $C_p(t)$ was obtained by transforming the whole-blood TAC $C_{LV}(t)$ to a plasma TAC, using a whole-blood to plasma tracer concentration coefficient calculated from arterial blood measurements performed in 12 pigs (Guehl et al., 2015). No correction for metabolites was performed.

2.B.2 Model for dynamic PET measurements—Let y_{im} denote the number of coincidence events detected in sinogram bin $i \in [1 \dots I]$ and dynamic frame $m \in [1 \dots M]$. The measured dynamic PET sinogram data $\mathbf{y}_m = [y_{1m}, \dots, y_{Im}]^T \in \mathbb{R}^I$ for a given frame m are modeled as a set of independent Poisson variables such that:

$$\mathbf{y}_m \sim \left[\text{Poisson}(\bar{y}_{1m}), \dots, \text{Poisson}(\bar{y}_{Im}) \right]^T, \quad m=1 \dots M \quad (5)$$

where $\bar{y}_{im}$ is the expected number of coincidence events in the i^{th} sinogram bin and m^{th} dynamic frame. The expected PET coincidence data in the frame are then related to the underlying activity distribution $\boldsymbol{\rho}_m$ using:

$$\bar{\mathbf{y}}_m = \Delta t_m \mathbf{P} \boldsymbol{\rho}_m + \bar{\mathbf{s}}_m + \bar{\mathbf{r}}_m, \quad m=1 \dots M \quad (6)$$

where Δt_m is the duration of time frame m , $\boldsymbol{\rho}_m = \{\rho_{jm}\} \in \mathbb{R}^J$ contains the activity values to estimate (average number of decays per unit of time in time frame m) for all voxels,

$\bar{\mathbf{s}}_m = \{\bar{s}_{im}\}$ and $\bar{\mathbf{r}}_m = \{\bar{r}_{im}\} \in \mathbb{R}^I$ are respectively the estimated sinograms of scattered and random coincidences contributing to the expected prompts sinogram PET data, and $\mathbf{P} = \{p_{ij}\} \in \mathbb{R}^{I \times J}$ is the PET system matrix whose elements are the probability for a positron emission occurring in voxel j to be detected in sinogram bin i . The PET system matrix $\mathbf{P}$, which makes the link between the sinogram and image domains, is defined as the following product of matrices:

$$\mathbf{P} = \mathbf{S} \mathbf{A} \mathbf{G} \quad (7)$$

where $\mathbf{G} \in \mathbb{R}^{I \times J}$ is the discrete forward-projection operator - implemented in this work using Siddon's ray-tracing algorithm (Siddon, 1985), $\mathbf{S} = \text{diag}(s_i) \in \mathbb{R}^{I \times I}$ is a diagonal matrix which contains the detectors sensitivity coefficients for each sinogram bin and $\mathbf{A} = \text{diag}(a_i) \in \mathbb{R}^{I \times I}$ is a diagonal matrix which contains the linear attenuation coefficients for each sinogram bin calculated based on the forward-projected attenuation map. In this study, the final attenuation map used for the reconstructions was obtained by incorporating the static hardware attenuation components (e.g. scanner table, MR body coil) to the measured MRAC tissue attenuation map. The attenuating effects of the flexible MR surface coil were however neglected.

2.B.3 Conventional indirect method

Image reconstruction: For the indirect method, the coincidence events detected in each dynamic frame are first reconstructed separately to obtain a time-series of PET images. In this study, we used two different approaches to reconstruct the PET data for each dynamic frame, as detailed hereinafter. For the first approach, the PET image for each dynamic frame was estimated using a maximum likelihood (ML) estimation framework:

$$\hat{\boldsymbol{\rho}}_m = \underset{\boldsymbol{\rho}}{\text{argmax}} [L(\mathbf{y}_m | \boldsymbol{\rho}_m)] \quad m=1 \dots M \quad (8)$$

where $L(\mathbf{y}_m | \boldsymbol{\rho}_m)$ is the Poisson log-likelihood function, which can be written as (after dropping the terms that are constant with respect to the unknown activity distribution):

$$L(\mathbf{y}_m | \boldsymbol{\rho}_m) = \sum_{i=1}^I [y_{im} \log(\bar{y}_{im}) - \bar{y}_{im}]$$

$$L(\mathbf{y}_m | \boldsymbol{\rho}_m) = \sum_{i=1}^I [y_{im} \log(\Delta t_m(\mathbf{P}\boldsymbol{\rho}_m)_i + \bar{s}_{im} + \bar{r}_{im}) - (\Delta t_m(\mathbf{P}\boldsymbol{\rho}_m)_i + \bar{s}_{im} + \bar{r}_{im})], \quad m=1 \dots M$$

(9)

Replacing $\mathbf{P}$ by its expression given in Eq. (7), the image updating loop of the maximum likelihood expectation maximization PET reconstruction algorithm that maximizes Eq. (8) is given by:

$$\hat{\boldsymbol{\rho}}_m^{(it+1)} = \frac{\hat{\boldsymbol{\rho}}_m^{(it)}}{\mathbf{G}^T \mathbf{A} \mathbf{S} \mathbf{1}_I} \left[\mathbf{G}^T \frac{\mathbf{y}_m}{\Delta t_m \mathbf{G} \hat{\boldsymbol{\rho}}_m^{(it)} + (\mathbf{A} \mathbf{S})^{-1} (\bar{\mathbf{s}}_m + \bar{\mathbf{r}}_m)} \right], \quad m=1 \dots M \quad (10)$$

where $\mathbf{1}_I$ is a column-vector of size I with all ones and $\hat{\boldsymbol{\rho}}_m^{(it)}$ is the activity distribution estimated at iteration ' it '. In this study, the sinograms of scattered coincidence events $\bar{s}_m$ were estimated for each frame using a three-dimensional version of the single scatter simulation method (Watson, 2000). The sinograms of random coincidence events $\bar{r}_m$ were estimated on a frame-by-frame basis by rebinning the events detected in the delayed coincidence window saved in the original list-mode file into fully-3D sinograms, followed by Gaussian smoothing to reduce noise. All reconstructions were performed on a $2 \times 2 \times 2$ mm³ voxel grid. Also, to accelerate the convergence of the reconstruction, we used the OSEM (ordered subsets expectation maximization) algorithm with non-overlapping azimuthal angular subsets (Hudson and Larkin, 1994). A total of 10 iterations each with 8 angular subsets were used for all OSEM reconstructions to ensure convergence of activity in all dynamic frames and reduce quantitative biases due to under-convergence of OSEM. No post-reconstruction filtering was performed.

Maximum likelihood (ML) based estimators such as OSEM have attractive properties as they provide unbiased and minimum variance estimates as the number of projections increases towards infinity (Qi and Leahy, 2006). Yet, even the least noisy unbiased estimates may contain unacceptably high levels of noise. It is indeed well-known that ML-based reconstruction algorithms tend to considerably amplify image noise as the iterations proceed, due to the inherent noise in the PET measurements as well as the ill-posed nature of the reconstruction problem. This can in turn increase the variance of the kinetic parameters estimated using noisy dynamic PET reconstructions. A possible solution to the noise issue consists in incorporating spatial smoothness constraints inside the reconstruction process itself to regularize the solution as the iterations proceed (Geman and McClure, 1985, Hebert

and Leahy, 1989, Green, 1990, Bettinardi et al., 2002, Lange, 1990). This is usually achieved by maximizing the posterior probability function defined as

$$P(\rho|y) = P(y|\rho) \cdot P(\rho) / P(y) \quad (11)$$

where $P(y|\rho)$ is the Poisson likelihood term and $P(\rho)$ is the prior probability distribution. The prior probability function $P(\rho)$ is commonly chosen to follow a Gibbs distribution of the form $P(\rho) = e^{-\gamma V(\rho)}$, where $V(\rho)$ is a Gibbs energy function imposing the spatial smoothness of the reconstructed activity distribution and γ is a positive regularization parameter. Taking the logarithm of Eq. (11), the image estimation task for each dynamic frame can be formulated as the following optimization problem:

$$\hat{\rho}_m = \underset{\rho}{\operatorname{argmax}} [L(y_m|\rho_m) - \gamma V(\rho_m)], \quad m=1 \dots M \quad (12)$$

where $L(y_m|\rho_m)$ is the Poisson log-likelihood function defined in Eq. (9) and $V(\rho_m)$ is typically chosen to penalize large differences in the estimated activity values between adjacent voxels. Several methods can be used to perform image reconstruction based on Eq. (12). In this study, we used the well-known one-step late maximum a posteriori (OSL-MAP) reconstruction method (Green, 1990), which builds on the expectation maximization algorithm to optimize Eq. (12). Given the system matrix definition given in Eq. (7) and the Poisson log-likelihood function defined in Eq. (9), the image updating loop for OSL-MAP reconstruction is given by:

$$\hat{\rho}_m^{(it+1)} = \frac{\hat{\rho}_m^{(it)}}{\mathbf{G}^T \mathbf{A} \mathbf{S} \mathbf{1}_I + \gamma \frac{\partial}{\partial \rho} V(\rho) \big|_{\rho=\hat{\rho}_m^{(it)}}} \left[\mathbf{G}^T \frac{y_m}{\Delta t_m \mathbf{G} \hat{\rho}_m^{(it)} + (\mathbf{A} \mathbf{S})^{-1} (\bar{s}_m + \bar{r}_m)} \right], \quad m=1 \dots M \quad (13)$$

Note that setting $\gamma = 0$ in Eq. (13) amounts to performing standard EM reconstruction as shown in Eq. (10). In this study, $V(\rho)$ was chosen to be a uniform quadratic penalty function defined as the scaled sum of the squared differences among neighboring voxels:

$$V(\rho_m) = \sum_{j=1}^J \sum_{p \in N(j), p > j} \frac{1}{2(\Delta t_m)^2} (\tilde{\rho}_{jm} - \tilde{\rho}_{pm})^2 \quad (14)$$

where $\tilde{\rho}_{jm}$ is the number of counts estimated in voxel j and frame m and $N(j)$ denotes the local neighborhood of voxel j , formed based on a 6-point neighborhood system. The scattered and random coincidence sinogram estimates $\bar{s}_m$ and $\bar{r}_m$ in Eq. (13) were obtained using the methods described earlier. Non-overlapping azimuthal angular subsets were used to accelerate the convergence of the OSL-MAP reconstruction algorithm. A total of 10

iterations each with 8 angular subsets were used for all OSL-MAP reconstructions to ensure convergence of activity in all the dynamic frames. All reconstructions were performed on a $2 \times 2 \times 2$ mm³ voxel grid. No post-reconstruction filtering was performed.

Kinetic parameter estimation: The kinetic model parameters for every myocardial voxel were estimated by fitting the PET TACs reconstructed using both OSEM and OSL-MAP algorithms to the model given in Eq. (4), using nonlinear weighted least-square fitting:

$$\hat{\mathbf{k}}_{\text{INDIRECT}}^j = \underset{\mathbf{k}}{\text{argmin}} \left[\sum_{m=1}^M w_m \left(\hat{\rho}_{jm} - \frac{\Delta v}{\Delta t_m} \int_{t_m} \lambda C_T(\tau, \mathbf{k}^j) e^{-\lambda \tau} d\tau \right)^2 \right] \quad (15)$$

where w_m is the weight for each frame m , which was chosen to be the squared frame duration divided by the total number of counts detected in that frame (Gunn et al., 1997), λ in min^{-1} is the decay rate of the radioisotope and v is the volume of one voxel. The Levenberg-Marquardt algorithm was used to minimize Eq. (15). Figure 1 depicts examples of OSEM PET TACs extracted in the LV chamber (red dotted line) and a mid inferior wall segment (black dots), along with the corresponding model fit (black solid line).

2.B.4. Direct parametric reconstruction method

Formalism for direct parametric reconstruction: We used a maximum a posteriori (MAP) algorithm to estimate the parametric images from the dynamic PET sinograms. To formulate the direct parametric reconstruction framework, we first link the activity in a given myocardial voxel j accumulated in a particular dynamic frame m , to the kinetic model, using:

$$\rho_{jm}(\mathbf{k}^j) = \frac{\Delta v}{\Delta t_m} \int_{t_m} \lambda C_T(\tau, \mathbf{k}^j) e^{-\lambda \tau} d\tau \quad (16)$$

The expected dynamic PET sinogram data in each frame can then be directly related to the set of unknown kinetic parameters $\mathbf{k} = \{\mathbf{k}^j\}$ using:

$$\bar{y}_m(\mathbf{k}) = \Delta t_m \mathbf{P} \boldsymbol{\rho}_m(\mathbf{k}) + \bar{s}_m + \bar{r}_m, \quad m=1 \dots M \quad (17)$$

where $\boldsymbol{\rho}_m(\mathbf{k}) = \frac{\Delta v}{\Delta t_m} \left[\int_{t_m} \lambda C_T(\tau, \mathbf{k}^1) e^{-\lambda \tau} d\tau, \dots, \int_{t_m} \lambda C_T(\tau, \mathbf{k}^J) e^{-\lambda \tau} d\tau \right]^T$ is evaluated using the kinetic model given in Eq. (4) and the kinetic parameter estimates at each voxel. The direct MAP parametric image reconstruction framework is formulated as the following optimization problem:

$$\hat{\mathbf{k}}_{\text{DIRECT}} = \underset{\mathbf{k}}{\text{argmax}} [f(\mathbf{y}, \mathbf{k})], \quad (18)$$

where $\hat{\mathbf{k}}_{\text{DIRECT}}$ are the estimated parametric images, $\mathbf{y} = [\mathbf{y}_1, \dots, \mathbf{y}_M]^T$ contains the measured dynamic PET sinograms and $f(\mathbf{y}, \mathbf{k})$ is the objective function to be maximized. We used a penalized likelihood objective function, given by:

$$f(\mathbf{y}, \mathbf{k}) = L(\mathbf{y}|\mathbf{k}) - \beta U(\mathbf{k}) \quad (19)$$

where $L(\mathbf{y}|\mathbf{k})$ is the '4D' log-likelihood function which relates the dynamic PET data to the kinetic parameters, $U(\mathbf{k})$ is a quadratic regularization function defined afterwards, and β is a scalar which controls the strength of the regularization. Dropping the term which does not depend on the unknown kinetic model parameters, the log-likelihood function $L(\mathbf{y}|\mathbf{k})$ is defined as:

$$L(\mathbf{y}|\mathbf{k}) = \sum_{m=1}^M \sum_{i=1}^I [y_{im} \log(\bar{y}_{im}(\mathbf{k})) - \bar{y}_{im}(\mathbf{k})]$$

$$L(\mathbf{y}|\mathbf{k}) = \sum_{m=1}^M \sum_{i=1}^I [y_{im} \log(\Delta t_m (\mathbf{P}\boldsymbol{\rho}_m(\mathbf{k}))_{i+\bar{s}_{im}+\bar{r}_{im}} - (\Delta t_m (\mathbf{P}\boldsymbol{\rho}_m(\mathbf{k}))_{i+\bar{s}_{im}+\bar{r}_{im}}))] \quad (20)$$

The scattered and random coincidence sinogram estimates used in Eq. (20) were obtained with the methods described in section 2.B.3.

The penalty function $U(\cdot)$, which helps stabilizing the estimation of the kinetic model parameters, can be designed to act either on the kinetic parameters or on the image intensity values. One drawback of the former approach however, is that it in principle requires as many regularization parameters as kinetic model parameters. In contrast, the image domain penalty function only requires one regularization parameter. In this study, we used an image domain penalty which was chosen to be a uniform quadratic function defined as the scaled sum of the squared differences among neighboring voxels in the image domain:

$$U(\mathbf{k}) = \sum_{m=1}^M \sum_{j=1}^J \sum_{p \in N(j), p > j} \frac{1}{2(\Delta t_m)^2} \left(\tilde{\rho}_{jm}(\mathbf{k}^j) - \tilde{\rho}_{pm}(\mathbf{k}^p) \right)^2 \quad (21)$$

where $\tilde{\rho}_{jm}$ is the number of counts estimated in voxel j and frame m and $N(j)$ denotes the local neighborhood of voxel j , formed using a 6-point neighborhood system.

Objective function optimization: A preconditioned conjugate gradient (PCG) algorithm with an Armijo-type line search (Bertsekas, 1999) was used to iteratively maximize $f(\mathbf{y}, \mathbf{k})$ and reconstruct the parametric images from the measured dynamic PET sinograms. Starting with an initial estimate of kinetic model parameters $\mathbf{k}^{(0)}$, the PCG algorithm first computes the search direction vector $\mathbf{d}^{(n)}$ given by:

$$\mathbf{d}^{(n)} = \mathbf{Q}^{(n)} \mathbf{g}^{(n)} \quad (22)$$

where $\mathbf{g}^{(n)} = \{g_{jl}^{(n)}\} = \left\{ \frac{\partial f(\mathbf{y}, \mathbf{k})}{\partial k_l^j} \right\}_{\mathbf{k}^j = \mathbf{k}^{j(n)}}$ is the gradient vector, $l = [1 \dots 4]$ is an index for the 4 parameters to be estimated for each voxel, and $\mathbf{Q}^{(n)} = \text{diag}(q_l^{j(n)})$ is the preconditionner, defined as a diagonal matrix whose entries are the ratios between the kinetic model parameters and the sensitivity of the expected detected counts due to the parameters. The preconditionner entries may be written as (Rakvongthai et al., 2013):

$$q_l^{j(n)} = \frac{k_l^{j(n)}}{s_j \left| \sum_{m=1}^M \Delta t_m \frac{\partial \rho_{jm}}{\partial k_l^j} \right|_{\mathbf{k}^j = \mathbf{k}^{j(n)}}} \quad (23)$$

where $s_j = \sum_{i=1}^I p_{ij}$ is the sensitivity of voxel j . Once the search direction vector $\mathbf{d}^{(n)}$ is calculated, the conjugate direction $\mathbf{a}^{(n)}$, initialized as $\mathbf{a}^{(0)} = \mathbf{d}^{(0)}$, is calculated:

$$\mathbf{a}^{(n)} = \mathbf{d}^{(n)} + \gamma^{(n-1)} \mathbf{a}^{(n-1)} \quad (24)$$

where $\gamma^{(n-1)}$ is chosen here using Polak-Ribiere's formula $\gamma^{(n-1)} = \frac{(\mathbf{g}^{(n)} - \mathbf{g}^{(n-1)})^T \mathbf{d}^{(n)}}{(\mathbf{g}^{(n-1)})^T \mathbf{d}^{(n-1)}}$. Finally, the new parameter estimates are computed using:

$$\mathbf{k}^{(n+1)} = \mathbf{k}^{(n)} + \hat{\alpha}^{(n)} \mathbf{a}^{(n)} \quad (25)$$

where $\hat{\alpha}^{(n)}$ is the 'step-size' determined using an inexact Armijo line search:

$$\hat{\alpha}^{(n)} = \arg \max_{l^{(n)} \leq \alpha \leq u^{(n)}} L(\mathbf{y} | \mathbf{k} + \alpha \mathbf{a}^{(n)}) \quad (26)$$

where $l^{(n)}$ ($u^{(n)}$) is the lower (upper) bound for α . As detailed in (Rakvongthai et al., 2013), two line searches are performed for calculation of the optimal step-size. The upper bounds for kinetic parameters were set to be $K_1^{max} = 5.0 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$, $k_2^{max} = 0.3 \text{ min}^{-1}$ (due to ^{18}F -flurpiridaz's high degree of myocardial retention), $f_{LV}^{max} = 1$ and $f_{RV}^{max} = 1$. We initialized the PCG algorithm using the parametric images obtained from the indirect method, i.e. $\mathbf{k}_{\text{DIRECT}}^{(0)} = \hat{\mathbf{k}}_{\text{INDIRECT}}$. The parametric images used for the initialization of the direct method were the ones obtained based on the OSEM dynamic reconstructions. PCG optimization was stopped when the relative change of the objective function between

consecutive iterations was less than 10^{-6} . Furthermore, to reduce computation times, we defined a three-dimensional mask containing the LV myocardium ($\sim 10,800$ voxels), noted J_{mask} , and applied the direct reconstruction method only to this volume of interest within which the validity of the kinetic model is guaranteed (i.e. we only updated voxels located within J_{mask}). The mask was calculated semi-automatically for each animal by applying an intensity threshold to the summed dynamic PET image. The mask for each animal was then forward projected in order to obtain a mask of the myocardium in the sinogram domain, noted I_{mask} . This procedure allowed to only select the LORs going through the myocardium during the optimization of the objective function in order to reduce the computational demand of the direct reconstruction method. Furthermore, the activity values for the voxels located outside the myocardium but positioned along LORs going through the myocardium were obtained from the OSEM reconstructed images. This ROI targeted direct reconstruction approach was implemented by replacing the projection operation in Eq. (20) by its ROI-based version, mathematically formulated as (Rakvongthai et al., 2013):

$$\bar{y}_{im}(\mathbf{k}) = \Delta t_m \left(\sum_{j \in J_{mask}} p_{ij} \rho_{jm}(\mathbf{k}^j) + \sum_{j \notin J_{mask}} p_{ij} \hat{\rho}_{jm} \right) + \bar{s}_{im} + \bar{r}_{im}, \forall i \in I_{mask} \quad (27)$$

where p_{ij} is an element of the PET system matrix, $\rho_{jm}(\mathbf{k}^j)$, $\forall j \in J_{mask}$ is evaluated using the kinetic model given in Eq. (4) and the voxel-wise kinetic parameter estimates within the LV mask, and $\hat{\rho}_{jm}$ is the reconstructed activity value obtained using Eq. (10) for all the voxels that are located outside the LV mask but positioned along the LORs going through the myocardium. All the parametric reconstructions were performed on a $2 \times 2 \times 2$ mm³ voxel grid.

2.C. Data processing and figures of merit

For both animals, parametric images were calculated for the direct method and the indirect method applied to the OSEM and OSL-MAP dynamic reconstructions using all the events acquired in each dynamic MPI scan. Additionally, eight independent noise realizations - each containing $1/8^{\text{th}}$ of the total number of events in each experiment - were created from the original list-mode files by randomly assigning every eighth coincidence event in each dynamic frame to a given noise realization. Parametric images were then calculated for each noise realization using both the direct and indirect methods. The estimated K_1 maps were re-oriented manually into short and long axes orientation, and the myocardium was divided into 17 segments based on the American Heart Association model (Cerqueira et al., 2002).

Since the true K_1 values are not known in this study, the bias of each method could not be evaluated. Instead, we compared the standard deviation performance of the direct and indirect methods, given similarly obtained K_1 values.

For the parametric images calculated using the data with full statistics (for which no multiple realizations are available), we quantified $\overline{K_1^{F,s}}$ versus $SD_{K_1}^{F,s}$, where $SD_{K_1}^{F,s}$ was defined as the standard deviation of K_1 values within heart segment $s \in [1 \dots 17]$:

$$SD_{K_1}^{F,s} = \sqrt{\frac{1}{J_s - 1} \sum_{j \in s} \left(K_1^j - \overline{K_1^{F,s}} \right)^2} \quad (28)$$

where J_s is the number of voxels in segment s and $\overline{K_1^{F,s}} = \frac{1}{J_s} \sum_{j \in s} K_1^j$ is the mean K_1 value in segment s .

For parametric reconstructions comprising multiple noise realizations, we quantified $\overline{K_1^{N_r,j}}$ versus $SD_{K_1}^{N_r,j}$, where $SD_{K_1}^{N_r,j}$ was defined as the standard deviation of K_1 values across all noise realizations in each voxel j :

$$SD_{K_1}^{N_r,j} = \sqrt{\frac{1}{N_r - 1} \sum_{r=1}^{N_r} \left(K_1^{r,j} - \overline{K_1^{N_r,j}} \right)^2} \quad (29)$$

where $K_1^{r,j}$ is the parameter estimated in voxel j for noise realization r , N_r is the total number of noise realizations ($N_r = 8$ in this study), and $\overline{K_1^{N_r,j}} = \frac{1}{N_r} \sum_{r=1}^{N_r} K_1^{r,j}$ is the average K_1 value across all noise realizations for voxel j . The values of the regularization parameters β and γ used for the direct method and the OSL-MAP reconstructions respectively, were chosen empirically so that to obtain matching mean K_1 values across the myocardium. This allowed studying the noise performance of the direct and indirect methods at a given level of bias. In addition, we varied the values of the regularization parameters β and γ in order to study the tradeoff between average $\overline{K_1^{F,s}}$ and $SD_{K_1}^{F,s}$ (resp. average $\overline{K_1^{N_r,j}}$ and $SD_{K_1}^{N_r,j}$) across the myocardium for the direct and indirect methods.

3. RESULTS

Figure 2 shows sample short and long-axis K_1 maps estimated with the direct method and the indirect method applied to the OSEM and OSL-MAP dynamic reconstructions using the data with full statistics (i.e. all the events detected in each scan) for the two animal studies. The regularization parameter for OSL-MAP reconstructions was chosen to be the same for the two studies ($\gamma = 250$). Likewise, the regularization parameter for the direct method was chosen to be the same for both studies ($\beta = 100$). These values for the regularization parameters were selected to obtain equivalent mean K_1 values across the myocardium for the two methods (see Table 1 and Figure 4). As can be seen, a good agreement was found between the K_1 maps produced by the direct and indirect methods for each animal. However, the direct reconstruction visibly reduced the noise (i.e. voxel-wise variability) in the estimated K_1 maps compared to the indirect method applied to OSEM and OSL-MAP data. The K_1 maps calculated using the OSL-MAP reconstructions also exhibited visibly lower noise than the ones obtained using standard OSEM dynamic reconstructions.

Figure 3 depicts Polar maps of $\overline{K_1^{F,s}}$ and $SD_{K_1}^{F,s}$ calculated in the parametric images obtained with the direct method ($\beta = 100$) and the indirect method applied to OSEM and OSL-MAP reconstructions ($\gamma = 250$) using the data with full statistics. Table 1 lists the corresponding average $\overline{K_1^{F,s}}$ and $SD_{K_1}^{F,s}$ values for the whole myocardium in each animal. As can be seen, the direct method and the indirect method applied to the OSL-MAP reconstructions yielded equivalent K_1 values across the myocardium, indicating similar bias. Indeed, there were no statistically significant differences between the mean K_1 estimated using the direct method and the indirect method applied to OSL-MAP reconstructions (all $P > 0.50$) in both studies. For animal 1 (resp. animal 2), the mean K_1 in the myocardium was $0.79 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$ ($0.77 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$) for the direct method, which was lower by 5.9% (9.4%) than that obtained using the indirect method based on OSEM (all $P < 0.01$). The direct method reduced $SD_{K_1}^{F,s}$ by 23.3% and 34.4% for animal 1 and animal 2 respectively, all $P = 0.50$.

The indirect method applied to OSL-MAP reconstructions also reduced $SD_{K_1}^{F,s}$ relative to the indirect method based on OSEM, by 16.6% for animal 1 and by 21.9% for animal 2, all $P < 0.01$.

The direct method did not uniformly reduce $SD_{K_1}^{F,s}$ everywhere in the myocardium. The reduction was indeed more pronounced in segments of the inferior and inferolateral walls (e.g. segments #10 and 11) than in other regions of the myocardium. As expected, the segments that exhibited the highest reduction in $SD_{K_1}^{F,s}$ by the direct method were often the ones that had the largest $SD_{K_1}^{F,s}$ values in the indirect methods.

To further compare the different kinetic parameter estimation techniques, the curves plotted in Figure 4 illustrate the tradeoff between the average $\overline{K_1^{F,s}}$ and $SD_{K_1}^{F,s}$ values across the whole myocardium for the direct and indirect methods using the data with full statistics. The curve obtained for the direct method (blue circle curve) is a function of the regularization parameter β . Likewise, the curve obtained for the indirect method applied to OSL-MAP reconstructions (black triangle curve) is a function of the regularization parameter γ . There is only one data point in the graph for the indirect method based on OSEM (red cross), since there is no regularization parameter for this method. As can be seen, the direct method yields much lower $SD_{K_1}^{F,s}$ than the indirect method based on OSEM. Also, at a similar level of bias (i.e. similar mean $\overline{K_1^{F,s}}$ across the myocardium), the direct method yields substantially lower $SD_{K_1}^{F,s}$ compared to the indirect method applied to OSL-MAP reconstructions. The indirect method applied to OSL-MAP data also yields lower $SD_{K_1}^{F,s}$ compared to the indirect method based on OSEM, but not to that of the direct method.

Figure 5 shows sample short and long-axis images taken in the k_2 , f_{LV} and f_{RV} maps estimated with the direct method and the indirect method applied to the OSEM and OSL-MAP dynamic reconstructions using the data with full statistics for animal 1. A good agreement was found between the f_{LV} and f_{RV} maps obtained with the direct and indirect

methods. Overall, the direct method yielded slightly lower k_2 values than the indirect methods.

Figure 6 shows short and long-axis K_1 maps estimated with the direct method and the indirect method applied to the OSEM and OSL-MAP reconstructions for one noise realization comprising 1/8th of the total number of events acquired during the scans. The regularization parameter used for the direct method was chosen to be $\beta = 1000$ for animal 1 and $\beta = 500$ for animal 2. For the OSL-MAP reconstructions, the regularization parameter was chosen to be $\gamma = 500$ for animal 1 and $\gamma = 1000$ for animal 2. These values for the regularization parameters were selected to obtain matching mean K_1 values across the myocardium for the two methods (see Table 2 and Figure 10). As can be seen, the direct method substantially reduced the noise in the K_1 maps compared to the indirect method applied to either OSEM or OSL-MAP reconstructions.

The mean and standard deviation K_1 images across all eight noise realizations (i.e. $\overline{K_1^{N_r, J}}$ and $SD_{K_1}^{N_r, j}$ images) for the reconstructions corresponding to Figure 6 are shown in Figure 7.

As can be seen, the direct method substantially decreased $SD_{K_1}^{N_r}$ compared to the indirect method based on either OSEM or OSL-MAP reconstructions, indicating superior noise performance. The indirect method applied to OSL-MAP data also decreased $SD_{K_1}^{N_r}$ as compared to the indirect method applied to OSEM. Example of line profiles taken through the myocardium in the basal $\overline{K_1^{N_r, J}}$ and $SD_{K_1}^{N_r}$ short-axis images displayed in Figure 7 are shown in Figure 8 for animal 2. The similarity between the $\overline{K_1^{N_r}}$ profiles indicates that the direct method and the indirect method applied to OSL-MAP yielded close level of bias. However, the standard deviation of the direct reconstruction is in general lower than that of OSL-MAP, especially in the anterior wall, which corresponds to areas where K_1 was relatively lower. The standard deviation of the direct reconstruction is everywhere lower than that of the indirect method applied to OSEM reconstructions.

We calculated the average $\overline{K_1^{N_r, J}}$ and $SD_{K_1}^{N_r, j}$ in each segment of the myocardium for the direct and indirect methods. The corresponding polar maps are shown in Figure 9. Table 2 lists the associated average $\overline{K_1^{N_r}}$ and $SD_{K_1}^{N_r}$ values across the myocardium. As can be seen, the direct method and the indirect method applied to the OSL-MAP reconstructions yielded overall similar mean $\overline{K_1^{N_r, J}}$ values, indicating equivalent level of bias. For animal 1 (resp. animal 2), the mean $\overline{K_1^{N_r, J}}$ in the myocardium was 0.83 mL.min⁻¹.mL⁻¹ (0.82 mL.min⁻¹.mL⁻¹) for the direct method, which was lower by 4.0% (6.7%) than that obtained using the indirect method based on OSEM. The direct method yielded significantly lower standard deviation everywhere in the myocardium as compared to the indirect method applied to OSEM data: for animal 1 (resp. animal 2), mean reduction in segment-wise $SD_{K_1}^{N_r, j}$ was 32.2% (resp. 22.7%), all $P < 0.01$. Compared to the indirect method based on OSL-MAP reconstructions, the direct method reduced $SD_{K_1}^{F, s}$ by 16.6% and 10.5% for animal 1 and animal 2 respectively, all $P < 0.05$. The indirect method applied to OSL-MAP

reconstructions also reduced $SD_{K_1}^{N_r}$ relative to the indirect method based on OSEM, but to a lesser extent than the direct method, by 18.6% for animal 1 and by 13.6% for animal 2, all $P < 0.01$.

In animal 1, the direct method yielded the strongest reduction in $SD_{K_1}^{N_r,j}$ in the anterior and anterolateral walls (e.g. segments #1, 6, 7, 13), which corresponds to regions where $\overline{K_1^{N_r,j}}$ was comparatively lower. Likewise, in animal 2, the direct method yielded a more pronounced reduction in $SD_{K_1}^{N_r,j}$ in the anterior and anteroseptal walls (e.g. segments #1, 2, 8, 13), which had relatively lower $\overline{K_1^{N_r,j}}$. This can also be seen in the line profiles shown in Figure 8 for animal 2 where the direct method yielded a higher reduction in $SD_{K_1}^{N_r,j}$ in the anterior wall than in the inferior wall comparing with OSL-MAP. This observation is consistent with the results of our previous simulation study (Rakvongthai et al., 2013) in which we found that the highest improvement in $SD_{K_1}^{N_r,j}$ afforded by the direct reconstruction method was obtained in segments that had the lowest number of counts (e.g. myocardial defects). This likely results from the fact that the noise is better modeled in the direct approach than in the indirect one.

It can be noted that in general, lower K_1 values were estimated in the apex compared to the rest of the myocardium for all methods (e.g. see Figures 3 and 9). These differences are likely due to partial volume effects, as the tip of the apex in these young animals was merely a few voxels thick, leading to underestimation of both the activity concentration and K_1 in this region of the heart.

Finally, the curves in Figure 10 illustrate the tradeoff between the average $\overline{K_1^{N_r,j}}$ and $SD_{K_1}^{N_r,j}$ across the whole myocardium for the direct method and the indirect method applied to OSEM and OSL-MAP dynamic data. The curve obtained for the direct method is a function of the regularization parameter β . Likewise, the curve obtained for the indirect method based on OSL-MAP is a function of the regularization parameter γ . There is only one data point in the graph for the indirect method based on OSEM since there is no regularization parameter for this reconstruction technique. As can be seen, the direct method yields substantially lower $SD_{K_1}^{N_r}$ than the indirect method based on OSEM. Also, at a similar level of bias (i.e. similar average $\overline{K_1^{N_r}}$ values), the direct method results in lower standard deviation compared to the indirect method applied to OSL-MAP reconstructions, indicating superior noise performance. The indirect method based on OSL-MAP reconstructions also markedly reduces the standard deviation of the estimated K_1 parameters relative to the indirect method based on OSEM. For large values of the regularization parameters, the direct and indirect methods appear to offer similar performance in terms of standard deviation.

4. DISCUSSION

In this work, we have developed and evaluated a method for direct reconstruction of parametric images in dynamic PET MPI. We performed two dynamic ^{18}F -flurpiridaz PET studies on healthy pigs in order to compare the performance of the proposed direct method against the traditional indirect method applied to dynamic PET reconstructions obtained using both OSEM and OSL-MAP algorithms. Our experimental results indicate that the direct method leads to a significant reduction in the standard deviation of the estimated K_1 parameters as compared to the indirect method applied to both OSEM and OSL-MAP data, producing K_1 maps with superior SNR. The use of the indirect method in conjunction with dynamic PET data reconstructed with a smoothness constraint - implemented here using the well-known OSL-MAP algorithm with a quadratic penalty function - also leads to a decrease in the standard deviation of the estimated K_1 parameters compared to OSEM, but inferior to that offered by the direct method. To the best of our knowledge, this is one of the first studies to evaluate direct parametric reconstruction using *in-vivo* dynamic PET MPI data.

One critical challenge of direct parametric reconstruction with nonlinear kinetic models - such as the one used in this work-, is the fact that the optimization algorithm can only guarantee convergence to a local optimum - as opposed to a global optimum - because of the nonlinear relationship between the dynamic PET data and the kinetic parameters. In this study, to cope with the local optima issue inherent to the direct reconstruction method, we initialized the PCG algorithm with the parametric images estimated with the indirect method as explained in section 2.B.4. This choice is based on the assumption that the solution obtained with the indirect method is in the same concave neighborhood than the true parametric images. The results obtained indicate that the direct and indirect methods yielded similar average K_1 values across the myocardium, allowing us to assess the noise performance of each method at a given level of bias.

In this study, we decided to apply our direct parametric reconstruction algorithm to a region of interest comprising the left-ventricular myocardium (which is the organ of interest in MPI), as opposed to the entire PET field of view. Hence, kinetic modeling was performed only in this region of interest. There are at least two reasons that justify this choice. First of all, the optimization of the objective function for the direct method is a computationally intensive task due to the burden of operations mapping the estimated parametric images to the dynamic, fully-3D sinogram domain for every iteration of the optimization algorithm. Hence, restriction of the direct reconstruction to a targeted region of interest allows an important reduction in terms of computation times, while reducing the number of parameters to optimize. Second, including the entire PET field of view during direct parametric reconstruction is adequate only if the chosen kinetic model is valid for all tissues present in the field of view, assumption which may not prove to be entirely true for MPI. Also, if the model is inaccurate outside the region of interest, errors may still propagate to the region when using direct reconstruction methods (Kotasidis et al., 2011, Rahmim et al., 2014), unlike the indirect method for which fitting is performed independently for each voxel.

To implement our ROI-based direct reconstruction method, we used the OSEM PET images to obtain the activity values for all the voxels located outside the ROI but positioned along

LORs going through the ROI, as explained in section 2.B.4. A drawback of this approach, however, is that inaccuracies in the OSEM activity values for such voxels may affect the estimated kinetic parameter values in the ROI for the direct method. Furthermore, the direct reconstruction method used scattered coincidence sinograms estimated by applying the single scatter simulation algorithm (Watson, 2000) to the frame-by-frame OSEM reconstructions. It is however well-known that applying the single scatter simulation method and associated tails fitting procedure to low-counts OSEM reconstructions may produce biased scattered coincidence sinograms estimates (Cheng et al., 2010). Nevertheless, since both the indirect and direct methods incorporated the same scattered sinograms estimates, the aforementioned bias is expected to affect all methods equally, which should therefore not affect the noise performance comparison between the direct and indirect methods.

Although a two-tissue compartment model has been traditionally reported for modeling the kinetics of ^{18}F -flurpiridaz (Nekolla et al., 2009, Alpert et al., 2012), in this work, we used a one-tissue compartment model for modeling the kinetics of this tracer. In their study, Nekolla *et al* (Nekolla et al., 2009) showed that the one-tissue compartment model, as applied to a short acquisition window after injection (2 minutes), yields K_1 values which are very close to the ones obtained with a two-tissue compartment model applied to a longer data acquisition window (10 to 20 minutes after injection). The one-tissue compartment model was therefore deemed adequate in our study, in which a short (~5 minutes) data acquisition window after tracer administration was kept for tracer kinetic modeling. However, as reported by Nekolla *et al* (Nekolla et al., 2009), the one-tissue model may not be accurate for fitting the data acquired over a longer time period (10 and 20 minutes), as it may fail to capture the high retention of the tracer in the myocardium. Therefore, it should be highlighted that the two-tissue compartment model is expected to provide overall more accurate parametric maps than the one-tissue model, both in the healthy and diseased myocardium, as it better describes the kinetics of the tracer *in-vivo*.

In this study, we used OSEM to perform dynamic reconstructions as part of the traditional indirect kinetic parameter estimation method. Yet, even though OSEM has mostly replaced filtered back projection (FBP) in most clinical applications (e.g. 'static' oncologic imaging), FBP remains commonly used for reconstruction of dynamic PET studies because it is fast, linear and yields reliable quantitative results. Advantages of OSEM over FBP, however, include a more optimal handling of the Poisson nature of the PET projection measurements which leads to improved image resolution and SNR and the elimination of the streak artifacts. Disadvantages of OSEM include the increase in noise as the iterations proceed towards convergence, and the possible presence of quantitative biases when a low number of iterations is used or when the counts in the sinograms to be reconstructed are not Poisson distributed (Hogg et al., 2002). One source of modification of Poisson noise characteristics is the use of on-line subtraction of random coincidences, which introduces negative counts in the sinograms; however, this solution is no longer implemented in state-of-the-art PET scanners. Furthermore, in this study, both the randoms and scatter coincidence estimates were incorporated in the forward PET model and not pre-corrected before the reconstruction, therefore leaving 'intact' the raw PET projection measurements and preserving their Poisson statistical nature. In addition, we used a relatively large number of OSEM iterations (10 iterations and 8 subsets) to ensure convergence of activity in the

dynamic frames and thus minimize bias due to under-convergence. Several studies have compared OSEM to FBP in dynamic cardiac PET imaging using phantom and patient experiments (Boellaard et al., 2001, Sndergaard et al., 2007, Lubberink et al., 2004). Overall, these studies reported that FBP and OSEM have equal quantitative accuracy and yield uptake rate constant values that agree very well with each other, provided that sufficient OSEM iterations are applied. For instance, for MPI specifically, Sndergaard *et al* compared both the input functions and K_1 values calculated using OSEM and FBP dynamic reconstructions of $^{13}\text{NH}_3$ PET data, and found no statistically significant differences between the two methods (Sndergaard et al., 2007). Tsoumpas *et al* have compared OSEM and FBP-based indirect estimation methods to a direct reconstruction method for dynamic FDG PET imaging (Tsoumpas et al., 2008a). They found that OSEM and FBP-based indirect methods have a similar level of bias after matching their resolutions, but that OSEM has smaller standard deviation. Furthermore, the direct reconstruction method outperformed both techniques in terms of standard deviation.

We used a quadratic penalty function to help stabilize the estimation of the kinetic model parameters in the direct reconstruction method. A similar quadratic penalty was used for the OSL-MAP dynamic reconstructions. While such quadratic penalty functions work well in homogenous regions such as the healthy myocardium tissue, it is however well-known that they tend to smooth out the resulting solutions and decrease edge information, leading to effectively reduced spatial resolution. Such loss of resolution could be problematic in cases where regional perfusion defects are present in the myocardium and may also obscure true possible regional variation in perfusion characteristics. In contrast, non-quadratic penalty functions such as the Lange function (Lange, 1990) or the Huber function (Huber, 2011) tend to better preserve edges by less severely penalizing large differences between neighboring voxels than the quadratic function, while maintaining the same level of penalty for small differences. However, an area of caution with such non-quadratic penalty functions is that the reconstructed solutions are often very sensitive to the hyper-parameter δ upon which they rely on, and there is currently no practical method to select the optimal δ value (Wang and Qi, 2012). While our initial validation work on simulated data with perfusion defects (Rakvongthai et al., 2013) did not reveal any particularly high bias in K_1 estimated in defect regions using the direct method, additional *in-vivo* studies on infarcted pigs or patients with ischemia are needed to more accurately characterize the limitations of our approach in the presence of perfusion defects.

In this study, the values of the regularization parameters β and γ were set empirically to obtain similar K_1 values for the direct method and the indirect method based on OSL-MAP reconstructions, in order to compare the noise performance of the two approaches at matched level of bias. In general, the ‘optimal’ value for β or γ should depend on the number of counts detected in the study. In fact, we used higher β and γ values to process the data for the noise realizations - which contained only $1/8^{\text{th}}$ of the total number of counts - compared to the data with full statistics. We used approximately same β and γ values for processing the data for each study since approximately the same radiotracer dose was injected to both animals. It is also expected that different β values should be used to reconstruct stress vs. rest scans because more radiotracer would accumulate in the myocardium in stress compared to rest conditions. Further validation studies are however

needed to determine the optimal regularization parameter for various count level scenarios or rest vs. stress conditions.

It is well known that the motion of the heart during the PET data acquisition, caused by both the pumping action of the four cardiac chambers and the respiratory cycle, deteriorates the spatial resolution and quantitative accuracy of cardiac PET images (Klein and Beanlands, 2010, Dinges et al., 2013). Additionally, the partial volume effects (PVE) which are caused by the finite point spread function (PSF) of the PET camera, may further degrade image resolution, SNR and accuracy, particularly when imaging the myocardium because of its complex shape and its small thickness which is often close to the FWHM of the PET PSF (Erlandsson et al., 2012). Altogether, these sources of image degradation may substantially bias the kinetic parameters estimated using both the indirect and direct methods. While several post-reconstruction methods for motion (Dawood et al., 2013) and PVE (Nuyts et al., 1996) correction can be applied to every individually reconstructed PET image prior to kinetic parameter estimation as part of the indirect method, these techniques may not be easily translatable to direct reconstruction methods in which no PET images are actually reconstructed. An alternative “altogether” approach for correcting these factors that can be used with both methods consists in modeling these effects inside the sinogram data formation model *via* the system matrix (Petibon et al., 2013, Petibon et al., 2014b, Petibon et al., 2014a, Ouyang et al., 2014), allowing to reconstruct motion and PSF-corrected images or parametric images. This approach however requires that (1) the PET PSF can be modeled accurately (e.g. based on Monte Carlo simulations (Rahmim et al., 2008) or direct point source measurements (Panin et al., 2006)) and that (2) motion vector fields describing the displacement of individual voxels between all motion phases and a chosen reference one is measured (e.g. using the PET data themselves (Dawood et al., 2013), or MRI in PET-MR (Petibon et al., 2013, Huang et al., 2015)). Alternatively, joint estimation of motion fields and motion-corrected parametric images could be performed, as recently proposed by Jiao *et al* in the case of dynamic brain PET imaging and rigid head motion parameters (Jiao et al., 2014). However, it is unclear whether this type of joint estimation approach can be extended to dynamic MPI due to the complex, nonrigid nature of heart motion and the fact that shorter and hence noisier dynamic frames are needed to capture the rapid kinetics of MPI flow agents. Additional improvements in kinetic parameter estimation could be achieved by modeling time of flight information in the direct method as well as the traditional indirect post-reconstruction method, as was recently demonstrated by Kotasidis *et al* (Kotasidis et al., 2016).

Future work will be dedicated to improve kinetic parameter quantitation by incorporating MR-based motion fields and PSF modeling inside the framework of both indirect and direct estimation, as discussed above. We also plan to implement the kinetic model developed by Alpert *et al* (Alpert et al., 2012) to perform direct estimation of rest and stress K_1 within a single scanning session.

5. CONCLUSION

The aim of this study was to extend and evaluate the performance of a direct parametric reconstruction method for voxel-wise quantification of MBF in dynamic PET MPI. We have

performed two dynamic ^{18}F -flurpiridaz PET MPI studies on healthy pigs to compare the performance of the proposed direct method against the traditional indirect method. Our experimental results indicate that the direct method leads to a significant reduction in the variance of the estimated K_1 parameters as compared to the indirect method, producing K_1 maps with superior SNR. The proposed direct parametric reconstruction method as applied to *in-vivo* dynamic PET MPI data is therefore a promising method for producing MBF maps with lower variance.

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Figure 1.
Example of PET TACs (animal 1) extracted from the LV chamber (red dotted line) and myocardial mid inferior wall (black dots) along with the kinetic model fit (black solid line).

Figure 2.

Short and long axis K_1 images for A: animal 1 and B: animal 2 obtained with the direct and indirect methods using the data with full statistics. The regularization parameter for the OSL-MAP reconstructions was $\gamma = 250$. The regularization parameter for the direct method was $\beta = 100$.

Figure 3.

Polar maps of $\overline{K_1^{F,s}}$ for $SD_{K_1}^{F,s}$ A: animal 1, B: animal 2 obtained with the direct and indirect methods using the data with full statistics. The regularization parameter for the direct method and the OSL-MAP reconstructions was $\beta = 100$ and $\gamma = 250$, respectively.

Figure 4.

Plot of mean $K_1^{F,s}$ vs. $SD_{K_1}^{F,s}$ in the whole myocardium for A: animal 1 and B: animal 2 obtained with the direct and indirect methods using the data with full statistics. The curves obtained for the direct method and the indirect method applied to OSL-MAP reconstructions are functions of the regularization parameter β and γ , respectively.

Figure 5.

Short and long axis k_2 , f_{LV} and f_{RV} images for animal 1 obtained with the direct and indirect methods using the data with full statistics. The regularization parameter for the direct method and the OSL-MAP reconstructions was $\beta = 100$ and $\gamma = 250$, respectively.

Figure 6.

Short and long axis K_1 images for A: animal #1 and B: animal #2 estimated using the direct and indirect methods applied to one noise realization comprising $1/8^{\text{th}}$ of the total number of acquired events. The regularization parameter for the direct method was $\beta = 1000$ for animal 1 and $\beta = 500$ for animal 2. For the OSL-MAP reconstructions, the regularization parameter was $\gamma = 500$ for animal 1 and $\gamma = 1000$ for animal 2.

Figure 7.

Short and long axis slices taken in the $\overline{K_1^{Nr,j}}$ and $SD_{K_1}^{Nr,j}$ images for A: animal 1 and B: animal 2, obtained using the direct and indirect methods. The regularization parameter used for the OSL-MAP reconstructions (resp. direct method) was $\gamma = 500$ (resp. $\beta = 1000$) for animal 1 and $\gamma = 1000$ (resp. $\beta = 500$) for animal 2.

Figure 8.

Line profiles taken in the $\overline{K_1^{Nr}}$ and $SD_{K_1^{Nr}}$ images for the direct and indirect methods (animal 2).

Figure 9.

Polar maps of average $\overline{K_1^{N_r, J}}$ and $SD_{K_1}^{N_r}$ across all noise realizations for A: animal 1, B: animal 2 for the direct and indirect methods. The regularization parameter used for the OSL-MAP reconstructions (resp. direct method) was $\gamma = 500$ (resp. $\beta = 1000$) for animal 1 and $\gamma = 1000$ (resp. $\beta = 500$) for animal 2.

Figure 10.

Plot of average $\overline{K_1^{N_r, j}}$ and $SD_{K_1}^{N_r, j}$ across the whole myocardium for A: animal 1 and B: animal 2 using the direct method and the indirect methods. The curve obtained with the direct method (resp. indirect method based on OSL-MAP reconstructions) is a function of the regularization parameter β (resp. γ).

Average $\overline{K_1^{F,s}}$ and $SD_{K_1^{F,s}}$ values ($\text{mL}\cdot\text{min}^{-1}\cdot\text{mL}^{-1}$) in the whole myocardium for the direct and indirect methods applied to the data with full statistics. The regularization parameter for the direct method and the OSL-MAP reconstructions was $\beta = 100$ and $\gamma = 250$, respectively.

Table 1

	Animal 1			Animal 2		
	Indirect (OSEM)	Indirect (OSL-MAP)	Direct	Indirect (OSEM)	Indirect (OSL-MAP)	Direct
$\overline{K_1^{F,s}}$ Mean	0.84	0.79	0.79	0.85	0.78	0.77
$SD_{K_1^{F,s}}$ Mean	0.36	0.30	0.23	0.41	0.32	0.21

Average $\overline{K_1^{N_{r,j}}}$ and $SD_{K_1}^{N_{r,j}}$ values ($\text{mL} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$) in the whole myocardium for the direct and indirect methods. The regularization parameter for the direct method was $\beta = 1000$ for animal 1 and $\beta = 500$ for animal 2. For the OSL-MAP reconstructions, the regularization parameter was $\gamma = 500$ for animal 1 and $\gamma = 1000$ for animal 2.

Table 2

	Animal 1			Animal 2		
	Indirect (OSEM)	Indirect (OSL-MAP)	Direct	Indirect (OSEM)	Indirect (OSL-MAP)	Direct
Mean $\overline{K_1^{N_{r,j}}}$	0.86	0.83	0.83	0.88	0.82	0.82
Mean $SD_{K_1}^{N_{r,j}}$	0.59	0.48	0.40	0.66	0.57	0.51