Improved Imaged-derived Input Function for Study of Human Brain FDG-PET

Hongbin Guo, Rosemary A Renaut and Kewei Chen

Abstract

A reliable, semi-automated method for estimation of a minimally-invasive image-derived input function is validated for human [^{18}F]-fluoro deoxyglucose (FDG) positron emission tomography (PET) studies. Two time windows can be recognized in the time activity curve measured from a carotid artery region of interest (CA-ROI). During the first short window of very rapid change, the dominant contamination of the measured activity on the CA-ROI is due to partial volume effects. After this the measured activity is also contaminated by spillover of tracer from tissue to blood. Blood samples acquired at later times, free of both partial volume and spillover effects, avoid the contamination and are used to fit a functional form for the input. Appropriateness of this parameter dependent input is validated using data from 18 healthy subjects and contrasted against measured arterial blood samples, and with previously proposed representations [1]–[3]. Parameters defining the input function and micro parameters of each tissue cluster, (their rate constants K_1 , k_2 and k_3), [4], are estimated simultaneously using the compartmental model for FDG PET [5].

Index Terms

Quantification of FDG PET, Automated Image-derived input function, Neuroimaging.

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I. INTRODUCTION

Positron emission tomography (PET) is a widely used neuroimaging technique that, among others, assists with disease diagnosis, treatment evaluation and study of brain function. In addition to its visual and qualitative assessment, PET images can provide quantitative estimates of physiological or metabolic parameters of interest. For example dynamic [^{18}F]-fluoro deoxyglucose (FDG) PET allows the estimation of the cerebral metabolic rate for glucose (CMRGLc), or even individual kinetic rate constants describing various aspects of the tracer biochemistry/physiology, and has been recommended as the standard for analyses of brain diseases associated with aging, [6]. For such quantification, the input function, the time-varying radiotracer concentration in plasma, is required, whether obtained invasively or using an image-derived technique.

While the invasive gold-standard arterial blood sampling procedure to obtain the input function has long been suggested, its invasive nature has prevented its routine use in basic research, especially in clinical PET studies. Many research groups have proposed alternative methods. These include, not only for FDG but also for other tracers, those using population-based input functions, [3], [7], and others that are based on use of arterialized venous blood sampling, [2]. Alternative techniques are focused on the construction of an image-derived input function, possibly combined with a limited

blood sampling and/or simultaneous estimation of both the input function and the kinetic parameters for a limited number of brain regions, [8]–[15]. Noting the risks and discomfort associated with any kind of blood sampling, the PET Neuroimaging Working Group [6] has recommended that, where possible, FDG-PET studies be accomplished through use of a completely image-derived input function. The work in this paper seeks to make further progress toward this end by extending an existing image-derived approach [10].

We propose and validate a new method for the construction of an input function. The specific form is piecewise linear in the early phase of fast uptake of tracer. The piecewise linear approximation is found by fitting with data from an image-derived blood vessel carotid artery region of interest (CA-ROI). It is corrected for partial volume through continuity at a time point common to both windows. The parameters defining the analytic representation of the input function for the later window, including the partial volume coefficient, the rate constants of two representative tissue activity curves defined by cluster analysis, and spillover from blood to tissue, are estimated by a simultaneously estimated (SIME) nonlinear fitting. For fitting within the SIME three blood samples are still required. The approach accounts for partial volume effects and avoids the tissue-to-blood spillover.

Details of the method are provided in the following sections. Briefly, the method proceeds as follows.

Initially, CA-ROIs are identified via a semi-automated procedure, following that presented already in [10]. The method proposed here differs in that only CA-ROI data from very early time are utilized. While the measurement of the input function from image data is sure to be contaminated at all times by partial volume effects caused by the small size of the carotid artery, relative to the image resolution, spillover from tissue to blood from brain regions surrounding the carotid artery can be ignored during the first very short time window (less than one minute duration) because the initial uptake of the tracer by the tissue is essentially insignificant. For the remaining large time interval, spillover from surrounding tissues will contaminate the measurement of the input derived from any region of interest containing the carotid artery. We thus assume that there are two phases of the input function and treat the initial short window differently from the later time measurements. In particular, because the CA-ROI activity curve on the second window is contaminated by spillover, it is replaced in the SIME technique by an analytic representation of the input for this window, the parameters of which are obtained through the SIME by fitting against three intravenous blood samples, which are free of partial volume effects. Continuity of the input is imposed at the point common to both windows. The SIME approach uses data from dominant tissue time activity curves obtained by a clustering technique applied to the volumetric time course data [16].

In the remainder of the paper the rationale for the new method is presented in Section II. All validation steps are performed with the available data from the clinical data set used in [10], briefly described in Section II-A. Results of the clinical study are given in Section III, with a brief discussion of pertinent implementation details presented in Section IV. Finally our conclusions are summarized

in Section V.

II. RATIONALE AND DEVELOPMENT OF THE PROPOSED METHOD

A. Clinical Data

PET data from 18 healthy subjects who participated in a previous study ([10]) was used to test the proposed technique. Subjects in this study provided their informed consent, and were studied under guidelines approved by Human-Subjects committees at Banner Good Samaritan Regional Medical Center (Phoenix, AZ) and the Mayo Clinic (Scottsdale, AZ.)

The data used are retrospective and the data collection protocol is described precisely elsewhere [10]. Briefly, PET data was collected using a 951/31 ECAT scanner (Siemens, Knoxville, TN) with the identical scanning protocol for each subject. An initial 20 min transmission scan was acquired for attenuation correction and an intravenous bolus of 10 mCi FDG was administered under resting condition. PET images were reconstructed using a filtered back projection algorithm with Hanning filter of 0.40 cycles per voxel. There are 31 transaxial slices of 128×128 voxels, each voxel of size $0.18776 \times 0.18776 \text{ cm}^2$, with a center-to-center slice separation of 3.375 mm and a 10.8 cm axial field of view. The final reconstructed PET images have an in-plane resolution of 9.5 mm full-width at half maximum (FWHM) in the center of the field of view and an axial resolution of 5.0-7.1 mm FWHM. Scanning time durations, given in minutes, for the reconstructed frames are 0.2, 8×0.0333 , 2×0.1667 , 0.2, 0.5, 2×1 , 2×1.5 , 3.5, 2×5 , 10 and 30.

For the purpose of validation arterial blood samples are required. These were drawn every 5 seconds for the first minute, every 10 seconds for the second minute, every 30 seconds for the next 2 minutes, and then at

5, 6, 8, 10, 12, 15, 20, 25, 30, 40, 50 and 60 minutes, yielding a discrete representation of the blood sampled function, denoted by $u_{bs}(t_j)$, for $j = 1, \dots, 34$.

The implementation of the proposed method only requires three blood samples at approximately $t = 10$, 20 and 60 minutes. It has been previously validated, however, that there is good agreement between arterial and venous blood samples, with less than 2.25% mean difference over these time points, [10]. Thus for the purposes of this retrospective study we used data with existing arterial samples. Moreover, to make sure we have high quality blood data in our experiments we were provided with 4 blood samples. In practice bad samples occur either due to the sampling itself or inadequate counting by the well-counter. The quality of the blood samples is checked for consistency with the expected gradual decrease of tracer in blood and for apparent outliers. Thus, we are guaranteed to have at least 3 high quality blood samples. This approach is consistent with the routine use of the procedure [10].

Practically, for new studies in which arterial sampling is not already intended, the use of venous, rather than arterial samples, as described also in [10] is recommended as a less invasive and less painful method of acquiring the necessary data. The use of late venous samples in order to provide additional information for obtaining an image-derived input function has also been validated in [17], in which venous samples at 30 min and 60 min were used.

B. Estimation of the average image-derived blood time activity curve

Details of the method, which involves summing, slice by slice, the initial time frames up to time 2 minutes in order to emphasize those pixels showing the tracer in blood regions including the CA, are given in [10]. An

average blood ROI image-derived input curve, denoted by $v(t)$, is then obtained from all frames in which an individual blood time activity curve can be identified.

C. Evaluation of models for the input function

The curves presented in Figures 3, 4 illustrate the two phases of blood activity seen in the carotid artery. In the initial sub window $W_1 = [0, \tau]$, where typically $\tau < 0.6$, the imaged curve $v(t)$ severely underestimates the tracer activity in the blood, due to partial volume effects. The average imaged blood activity curve $v(t)$ on W_1 provides crucial subject and situation dependent information on the input function, by providing the times at which the tracer reaches the CA-ROI, τ_0 , and then the time at which it peaks in the blood, τ_p . For the window $W_2 = [\tau, T]$, the impact of spillover on $v(t)$ cannot be negligible. It is thus our premise that these two windows on the input function should be treated differently, using the identifiability of the time points τ_0 , τ_p , and τ .

1) *The input function on W_2* : To develop an appropriate formulation for modeling the input function on W_2 , we contrast four different input models. The formulation

$$u_{\text{Phelps}} = A_1 e^{\lambda_1(t-\tau)} + A_2 e^{\lambda_2(t-\tau)} + A_3 e^{\lambda_3(t-\tau)}, \quad (1)$$

was first introduced by [2], and later used by [3] as a population-based input function, dependent on the 6 parameters A_i , λ_i , $i = 1, 2, 3$, and here is modified for decay from time τ . This formulation was modified by [1], [17] for use in a SIME method, and is used here with the data shifted relative to τ_0 in order to obtain the best possible fit:

$$\begin{aligned} u_{\text{Feng}} = & (A_1(t - \tau_0) - A_2 - A_3)e^{\lambda_1(t-\tau_0)} \\ & + A_2 e^{\lambda_2(t-\tau_0)} + A_3 e^{\lambda_3(t-\tau_0)}. \end{aligned} \quad (2)$$

These two formulations are designed so as to provide a fit for the entire window of time activity $W_1 \cup W_2$, and

Fig. 1. Comparison of the arterial blood samples (solid line with cross), un-corrected average blood time activity curve (solid line with open circles) and estimated input function solid line with 3 discrete asterisks. Also illustrated, with the 3 asterisks, is the time at which the average blood tracer activity is initiated in the ROI τ_0 , the time point for the peak value τ_p , the point of continuity τ between windows W_1 and W_2 , and the three blood samples used for the fit. Time is expressed on logarithm scale hence emphasizing the effects for early time.

may therefore be unnecessarily complicated when fitting just for W_2 . We consider a form with a very simple exponential decay after time τ :

$$u_{\text{Exp}} = Ae^{\lambda(t-\tau)}, \quad (3)$$

and a more complicated form

$$u_{\text{new}} = Ae^{\lambda(t-\tau)^\delta}. \quad (4)$$

To validate (4) as sufficient for fitting arterial data on W_2 based on just three measured data points and the point of continuity τ , we do a nonlinear fit for each of (1-4) using data points τ , and blood samples for time greater than 10 minutes. In this way we avoid difficulties in picking points between τ and 10 minutes for which recirculation in the blood input may be evident and may lead to difficulty in the data fitting. Moreover, this comparison is then consistent with our proposed SIME which only uses fitting based on both the value at τ and

the blood samples. We evaluate the sensitivity of the fit relative to the choice of τ for four different choices of τ , the first four time points in each data set after τ_p .

Results of the mean and standard deviation of the root mean square error (RMS) for all formulations, and the different choices of τ , denoted by choice 1 to 4, over all 18 subjects are reported in Table I. Here, and throughout, the notation $x.ye - z$ indicates the number $x.y \times 10^{-z}$.

We observe that there are too few degrees of freedom in (3) to provide a good fit, while (2) is more sensitive to the choice for τ than are (1) and (4). As judged by these results (4) performs slightly less well than (1). On the other hand, we note that (4) requires only three points besides τ whereas (1) requires five, and from the actual fitting illustrated for one subject 5 in Figure 2 it is clear that the fit is better. The fit between time τ and 10 min underestimates the blood samples for (2) and is very sensitive to the choice of τ for (1). This does not contradict the results in Table I where the RMS reported does not use the time interval between τ and 10 min. In summary, (4) is relatively insensitive to the choice for τ in terms of the fit, and provides a good fit to the entire curve between τ and the final time point, even when no points between τ and 10 min are used. Hence (4) provides an appropriate formulation for use in a nonlinear simultaneous estimation of the input.

2) *Determination of time points* (τ_0, τ_p, τ): For W_1 , τ_p is determined automatically as the point at which the highest intensity value $v(\tau_p)$ is achieved. While various methods have been proposed for the estimation of the initiation time of activity, τ_0 , prior to which there is effectively no signal, for example [18], in this work we select τ_0 automatically as the point after which $v(t)$ remains greater than 2% of the peak value $v(\tau_p)$. Although τ can be chosen in a variety of ways, it was noted in Section II-C.1 that the fit is relatively insensitive

TABLE I

THE MEAN AND STANDARD DEVIATION OF THE ROOT MEAN SQUARE ERROR FOR NONLINEAR LEAST SQUARES DATA FITTING FOR FUNCTIONS (1-4) OVER ALL SUBJECTS AND FOR DIFFERENT CHOICES FOR τ .

τ	Analytic Input Function			
	u_{Phelps}	u_{Feng}	u_{Exp}	u_{new}
1	$1.53e-2 \pm 8.0e-3$	$5.23e-2 \pm 1.0e-2$	$3.65e-1 \pm 1.1e-1$	$1.79e-2 \pm 1.1e-2$
2	$1.44e-2 \pm 6.2e-3$	$1.59e-2 \pm 7.3e-3$	$2.75e-1 \pm 9.7e-2$	$1.69e-2 \pm 9.9e-3$
3	$1.48e-2 \pm 7.4e-3$	$1.51e-2 \pm 7.7e-3$	$2.42e-1 \pm 8.3e-2$	$1.67e-2 \pm 1.0e-2$
4	$1.49e-2 \pm 6.5e-3$	$1.44e-2 \pm 7.4e-3$	$2.50e-1 \pm 8.7e-2$	$1.68e-2 \pm 1.0e-2$

Fig. 2. Fitting results for four choices of τ , illustrated for subject 5.

to choice of τ . Therefore, we choose τ automatically as the time point at which $v(t)$ is about 25% of the peak value $v(\tau_p)$.

3) *A parametric model for the input function:* Based on the discussion of the preceding paragraphs, we have developed a formulation for the input function, $u_e(t)$. On W_1 , $v(t)$ is approximated piecewise linearly using the three line segments with nodes $(0, 0)$, $(\tau_0, v(\tau_0))$, $(\tau_p, v(\tau_p))$ and $(\tau, v(\tau))$. Then, to correct for partial volume, $u_e(t)$ on W_1 is obtained from the linearized $v(t)$ scaled by a parameter θ which is inversely proportional to the recovery coefficient of the partial volume coefficient,

see Figure 1. On W_2 we assume decay according to (4) with continuity at τ imposed. Specifically, in terms of all parameters the estimated form of the input function is given by

$$u_e(t, \theta, \lambda, \delta) = \begin{cases} 0 & t \in [0, \tau_0] \\ \theta v(\tau_p) \left(\frac{(t - \tau_0)}{(\tau_p - \tau_0)} \right) & t \in (\tau_0, \tau_p] \\ \theta \left(\frac{v(\tau)(t - \tau_p) + v(\tau_p)(\tau - t)}{(\tau - \tau_p)} \right) & t \in (\tau_p, \tau] \\ \theta v(\tau) e^{-\lambda(t - \tau)^\delta} & t \in (\tau, \infty). \end{cases} \quad (5)$$

In the above model, $v(\tau_p)$ and $v(\tau)$ are known and only the three parameters, θ, λ and δ , need to be determined, and could be obtained simply using the three blood samples for $t > \tau$ along with the value of $v(\tau)$, so as to fit more than 2 parameters. This approach, however, can not compensate or determine the partial volume accurately, which is crucial because of the scaling everywhere due to θ . Instead, while more complicated, simultaneous estimation of the parameters defining the input together with the kinetic parameters of representative tissue TACs provides the necessary additional physical constraints.

D. Clustering the tissue time activity curves (TTACs)

The fast clustering method described in detail in [16] is utilized to find representative tissue TACs for the

whole brain. In this clustering procedure, non-brain, blood vessel and CSF regions are initially excluded by a thresholding step based on the histogram of tracer concentrations at the last time frame. Briefly, the method then uses a hierarchical centroid linkage strategy based on the weighted distance of TACs from the cluster centroid so as to provide average TTACs, $y_i^{\text{TAC}}(t)$, for each cluster i . The advantage of clustering is that it provides an automated way in which to segment the data into tissue groups of similar tracer activity. In particular, as compared to the original method proposed in [10], there is no need to additionally manually determine the tissue region of interest near the CA-ROI. In practice we automatically cluster to 5 groups and pick from these the two largest for the SIME.

E. Simultaneous estimation of the input function and cluster kinetic parameters

In the compartmental model [5] for FDG PET, the output $y(t)$ at a given voxel, or for a specific brain tissue ROI, is given analytically by convolution ($\otimes$) of the instantaneous response function (IRF) with the input $u(t)$

$$y(t) = u(t) \otimes \left(\frac{K_1 k_3}{k_2 + k_3} + \frac{K_1 k_2}{k_2 + k_3} e^{-(k_2 + k_3)t} \right). \quad (6)$$

Here the IRF is the term within the parentheses and is location dependent through the location dependence of the kinetic parameters. K_1 is the transport rate from blood to extra-vascular space, k_2 is the transport rate back from extra-vascular space to blood, and k_3 is the phosphorylation rate of intra-cellular FDG by hexokinase enzymes to FDG-6-phosphate. In this study the scanning duration of 60 minutes is not long enough to provide a reliable estimate of the dephosphorylation rate of intra-cellular FDG-6-phosphate back to FDG, [4], and which is relatively small compared with other three

parameters thus assumed to be 0. Then, if the input $u(t)$ in (6) is known and spillover effects can be ignored, the parameters defining $y(t)$ for a given location may be estimated using nonlinear (NL) fitting of the measured TAC $y^{\text{TAC}}(t)$ to $y(t)$.

Here, we seek to not only find the parameters of the tissue TACs but also recover the input function. Thus, given representative clustered TTACs for p cluster groups, usually $p = 2$, $y_i(t) \approx y_i^{\text{TAC}}(t)$, we obtain a weighted nonlinear least squares (WNLS) cost functional in terms of the unknown parameters θ and $K_1^{(i)}, k_2^{(i)}, k_3^{(i)}$ and α_i ,

$$\Phi(\mathbf{x}, \alpha) = \sum_{i=1}^p \sum_{j=1}^n w_j \left(y_i^{\text{TAC}}(t_j) - \alpha_i \cdot y_i(t_j) - (1 - \alpha_i) \cdot u_e(t_j, \theta) \right)^2. \quad (7)$$

The weight w_j is set to the time duration of each frame, and parameters α_i correct for local spillover from blood to tissue, i.e. α_i is the tissue fraction in y_i^{TAC} . To reduce the complexity of the expressions we introduce the notation $\alpha = (\alpha_1, \dots, \alpha_p)$ and $\mathbf{x} = [\theta, K_1^{(1)}, k_2^{(1)}, k_3^{(1)}, \dots, K_1^{(p)}, k_2^{(p)}, k_3^{(p)}]$. There are in total 11 unknowns which define the SIME.

This expression for the cost functional Φ hides its actual dependence also on the parameters of the input $u_e(t)$. In particular, the evaluation of $u_e(t_j, \theta)$ occurring in $\Phi(\mathbf{x}, \alpha)$ for a given value θ , requires the nonlinear fit of u_e for $t > \tau$ at points $(\tilde{t}_l, u_{\text{bs}}(\tilde{t}_l))$ where blood sampled data, $u_{\text{bs}}(\tilde{t}_l)$, $l = 1, \dots, 3$, are obtained for $\tilde{t}_1 \approx 10$, $\tilde{t}_2 \approx 20$ and $\tilde{t}_3 \approx 60$. The fit is obtained from

$$\min_{\lambda, \delta} \sum_{i=1}^3 \left[\theta v(\tau) e^{-\lambda(\tilde{t}_i - \tau)^\delta} - u_{\text{bs}}(\tilde{t}_i) \right]^2. \quad (8)$$

In other words, λ and δ are implicitly determined by these three blood samples and are not treated as independent variables for the cost functional Φ . As variable θ is adjusted for the cost functional Φ , λ and δ must be

adjusted accordingly. Thus, the actual total number of **independent** unknowns in $\Phi(\mathbf{x}, \alpha)$ is 9.

In order to limit the feasible space of solutions the cost functional Φ is minimized with respect to its independent variables subject to constraints. The bound constraints on the micro parameters are based on experimental results [4] for both gray and white matter from 13 subjects, but with doubling of upper bounds and halving of lower bounds so as to not provide bounds which may be too conservative. Note that in each case the tissue TACs y_i^{TAC} are automatically shifted to match the first peak of $v(t)$ with that of the TTAC. The constrained global fit performed is

$$\begin{aligned} \min_{\mathbf{x}, \alpha} \Phi(\mathbf{x}, \alpha) \quad \text{subject to} \quad (9) \\ 1.2 \leq \theta \leq 4 \quad 0.9 \leq \alpha_i \leq 1 \\ 0.015 \leq K_1^{(i)} \leq 0.3 \quad 0.024 \leq k_2^{(i)} \leq 0.54 \\ 0.01 \leq k_3^{(i)} \leq 0.2. \end{aligned}$$

To solve this minimization we use the Matlab function "fmincon", [19], which uses a sequential quadratic programming (SQP) algorithm. Because of the dependence of Φ on the blood-sampled data the function call for update of Φ at each step of the iteration proceeds as follows:

**Evaluation of objective function $\Phi(\mathbf{x}, \alpha)$
given current updates for α , $\mathbf{x}$ and θ**

1. Update $u_e(t_j, \theta)$ using (5) and (8), in which blood samples are used to provide the fit in (8) leading to update of λ and δ for the current step.
2. Update the estimates for the cluster TACs using (6) for the current micro parameters, to give $y_i(t_j)$, $i = 1$ and 2 .
3. Update the current value of the objective function $\Phi(\mathbf{x}, \alpha)$ using (7).

III. RESULTS

The resulting input functions obtained for the 18 subjects using the described method are compared and validated as follows.

A. Qualitative comparison for the input function

A comparison of the estimated input function u_e with the blood-sampled input u_{bs} is illustrated in Figure 3. The upper figure presents the portion within 1.5 minutes, and the middle figure the curves for the whole time duration, 45 minutes, on the logarithmic scale. Because these two curves come from different sources, namely estimation and actual blood samples, there is a time shift between them. In order to provide better comparison u_{bs} is automatically shifted to match u_e , see the lower graph in Figure 3. As expected the tails of both curves are closer because the tail of the estimated curve is obtained by the fit with the blood samples. For all subjects $u_e(t)$ is smoother for later time because it is evaluated using a functional form. Representative comparisons of u_e with shifted u_{bs} are shown in Figure 4. The heights of the peaks $u_e(\tau_p)$ match well in all cases, with differences in peak always less than 20%.

B. Estimation of the model parameters

The estimates obtained for θ , λ and δ are provided in Table II, along with the average values for each parameter in each case. The spillover from blood to tissue, $1 - \alpha_i$, for the group TACs is remarkably consistent across all subjects and clusters, and well within the range prescribed by the constraints. On the other hand, partial volume coefficients of the blood ROIs, $1/\theta$, vary considerably because of the differences in their location (artery or venous), size and shape between subjects. The consistency of the estimate for δ around the average of 0.248 suggests the robustness of (4) with respect to

Fig. 3. The recovered input function $u_e(t)$ compared with arterial blood samples. Illustrated are the data focused on the initial window (top), the whole time window given on logarithm scale (middle), and the same data with $u_e(t)$ shifted to account for the time delay relative to the arterial blood samples (bottom).

Fig. 4. Comparison of estimated input u_e , continuous line, and arterial blood-sampled input u_{bs} , solid line with crosses, for representative subjects, 1, 2, 3 and 4 from top to bottom.

TABLE II

PARAMETERS OBTAINED IN SIME PROCEDURES.

Subject	θ	λ	δ	α_1	α_2
1	2.049	0.923	0.233	0.930	0.931
2	1.975	0.805	0.226	0.923	0.927
3	2.843	0.691	0.241	0.935	0.935
4	2.730	0.872	0.237	0.958	0.957
5	1.790	0.518	0.318	0.912	0.915
6	2.294	0.828	0.265	0.938	0.932
7	2.287	0.350	0.364	0.928	0.929
8	3.190	0.797	0.257	0.935	0.934
9	2.927	0.919	0.231	0.953	0.968
10	2.813	1.554	0.153	0.918	0.927
11	2.651	0.521	0.342	0.933	0.932
12	2.246	0.628	0.247	0.930	0.925
13	3.543	0.781	0.277	0.941	0.941
14	1.908	0.937	0.212	0.941	0.940
15	3.781	0.792	0.257	0.942	0.940
16	2.822	1.152	0.167	0.935	0.935
17	3.070	0.924	0.214	0.951	0.944
18	2.996	0.842	0.222	0.947	0.924
Average	2.662	0.824	0.248	0.936	0.935

different subjects. Moreover, the upper bound 4.0 for θ is never attained, so that partial volume coefficients are always greater than 25%. Additional tests, not reported here, in which we used 1 or 3 clusters in the SIME, provide very consistent results.

C. Quantitative validation with Patlak analysis using the recovered input function

To provide a comparison with the method presented in [10], data from the entire brain volume are clustered to 50 clusters for each subject, and the recovered input then used in Patlak analysis for each cluster tissue TAC.

Fig. 5. Regression analysis on K generated by the Patlak method, for blood samples and recovered input function. Slope 1.021, intercept $1.2e - 5$ and correlation coefficient 1.0000.

Results are compared with those obtained using the blood sampled data, see Table III for all subjects and Figure 5 for subject 5. The results are in excellent agreement, and better than presented in the original reference, [10].

D. Quantitative validation via postestimation of kinetic parameters using the recovered input

To further validate the method, the kinetic parameters were calculated on a cluster by cluster basis not only through the SIME estimated input but also for the measured input from the arterial blood samples. The same Matlab function, "*fmincon*", was utilized for the solution of the nonlinear minimization with known input function, with the same imposed constraints and applied for the same 50 clusters in each case as used in Section III-C. In each case the output peak is automatically aligned with that of the input and blood to tissue spillover is considered. The estimates of the obtained parameters, K_1 , k_2 , k_3 as well as for the parameter $K = K_1 k_3 / (k_2 + k_3)$ were then compared by linear regression, see Figure 6 in which the regression is shown for subject

TABLE III

REGRESSION ANALYSIS FOR K , WHICH IS CALCULATED BY THE PATLAK METHOD FOR EACH CLUSTER, USING THE BLOOD SAMPLES AND THE RECOVERED INPUT. MEAN OF K FOR BOTH INPUTS, REGRESSION PAREMETERS, SLOPE, INTERCEPT AND CORRELATION COEFFICIENTS r , ARE PRESENTED FOR EACH SUBJECT.

Subject	mean K blood input	mean K estimated input	r	slope	intercept
1	$2.5345e-2$	$2.5572e-2$	$1.0000e-0$	1.009	$3.0e-6$
2	$1.8060e-2$	$1.8936e-2$	$9.9999e-1$	1.046	$4.0e-5$
3	$1.6389e-2$	$1.6030e-2$	$9.9999e-1$	0.984	$-1.0e-4$
4	$1.9380e-2$	$1.9669e-2$	$9.9998e-1$	1.014	$1.7e-5$
5	$2.1755e-2$	$2.2256e-2$	$1.0000e-0$	1.023	$5.2e-6$
6	$2.2913e-2$	$2.2604e-2$	$1.0000e-0$	0.986	$2.2e-6$
7	$1.9948e-2$	$1.9675e-2$	$1.0000e-0$	0.986	$-4.5e-7$
8	$1.5685e-2$	$1.5922e-2$	$9.9999e-1$	1.014	$1.2e-5$
9	$1.3549e-2$	$1.4048e-2$	$1.0000e-0$	1.037	$-3.3e-8$
10	$1.8952e-2$	$1.9121e-2$	$1.0000e-0$	1.009	$-5.5e-6$
11	$2.0437e-2$	$2.0989e-2$	$1.0000e-0$	1.027	$2.8e-6$
12	$1.5948e-2$	$1.6736e-2$	$9.9994e-1$	1.052	$-4.1e-5$
13	$2.5184e-2$	$2.5779e-2$	$1.0000e-0$	1.023	$6.7e-6$
14	$2.1261e-2$	$2.1666e-2$	$1.0000e-0$	1.020	$-2.0e-5$
15	$2.7067e-2$	$2.7237e-2$	$1.0000e-0$	1.006	$6.7e-6$
16	$1.5009e-2$	$1.5683e-2$	$9.9993e-1$	1.051	$-9.1e-5$
17	$1.8305e-2$	$1.8458e-2$	$9.9999e-1$	1.011	$-4.3e-5$
18	$1.8494e-2$	$1.8243e-2$	$9.9997e-1$	0.987	$-1.9e-5$

5, Figure 7 in which the regression is shown for a worse set of results for subject 1 and Table IV which lists the slopes, intercepts and correlation coefficients for each subject and each parameter.

Although not all results are presented here, a careful examination of all parameters shows that in no case do any of the parameters reach their bounds, suggesting that the chosen bounds are again appropriate in the context of this analysis.

IV. DISCUSSION

A. The necessity of SIME for fitting parameters defining the input function

In Section II-C.3 we claimed that the fitting of the proposed model with just the three blood samples for $t > \tau$ used to determine the parameters without using SIME would yield an inaccurate estimate. Here we present a comparison between estimates obtained with and without information from the TACs. Specifically we compare the results in which we directly fit the model

TABLE IV

REGRESSION FOR THE PARAMETERS OF THE CLUSTERS COMPARING THE BLOOD SAMPLED AND THE RECOVERED INPUT FUNCTIONS. FOR PARAMETERS k_1, k_2, k_3 AND K , THE CORRESPONDING PARAMETERS ARE, SLOPES s_1, s_2, s_3 AND s_K , INTERCEPTS b_1, b_2, b_3 AND b_K AND CORRELATION COEFFICIENTS r_1, r_2, r_3 AND r_K .

Subject	s_1	s_2	s_3	s_K	b_1	b_2	b_3	b_K	r_1	r_2	r_3	r_K
1	0.91	0.94	0.99	0.99	$1.2e-02$	$1.8e-02$	$2.0e-03$	$8.7e-04$	0.87	0.89	1.00	1.00
2	0.99	1.06	1.12	1.00	$-6.7e-04$	$-4.2e-03$	$5.0e-04$	$1.4e-03$	1.00	1.00	1.00	1.00
3	1.36	0.91	0.64	1.02	$7.0e-03$	$4.0e-02$	$7.6e-03$	$2.5e-04$	0.99	0.99	0.99	0.99
4	0.91	0.95	1.05	0.99	$4.1e-03$	$2.3e-03$	$2.8e-04$	$5.0e-04$	0.99	1.00	0.99	1.00
5	0.83	0.90	1.14	0.93	$4.8e-03$	$1.8e-03$	$-9.5e-04$	$2.1e-03$	0.99	0.99	1.00	0.99
6	1.02	0.89	1.08	0.95	$-6.3e-03$	$2.2e-02$	$3.6e-03$	$1.5e-03$	0.91	0.88	1.00	1.00
7	1.06	1.18	1.01	0.99	$-1.2e-03$	$-2.2e-03$	$2.3e-03$	$2.5e-04$	0.99	0.98	0.97	0.99
8	1.23	1.48	1.21	1.11	$-1.4e-02$	$-4.2e-02$	$-5.5e-03$	$-1.1e-03$	0.94	0.94	1.00	0.99
9	1.06	0.99	0.97	1.02	$5.7e-04$	$7.0e-03$	$3.4e-04$	$2.0e-04$	1.00	0.98	1.00	1.00
10	1.25	1.49	1.06	1.01	$-6.4e-03$	$-1.2e-02$	$1.5e-03$	$6.3e-04$	0.98	0.99	0.99	0.99
11	0.89	0.90	1.06	1.03	$4.1e-03$	$-8.9e-04$	$-2.1e-03$	$-3.1e-04$	0.99	0.98	1.00	1.00
12	1.60	1.28	0.77	1.12	$-1.2e-02$	$1.3e-02$	$7.8e-03$	$-3.6e-04$	0.98	0.99	0.99	1.00
13	0.84	0.91	1.09	1.01	$9.5e-03$	$-1.5e-03$	$-3.4e-03$	$-8.3e-05$	0.99	0.99	1.00	1.00
14	0.90	1.05	0.99	0.97	$5.0e-03$	$3.6e-03$	$6.3e-03$	$1.1e-03$	0.96	0.81	1.00	1.00
15	0.98	1.04	1.02	1.02	$2.2e-03$	$-7.9e-04$	$1.9e-03$	$-3.9e-04$	0.98	0.99	0.98	1.00
16	1.37	1.05	0.80	1.11	$-9.1e-03$	$-1.1e-03$	$-5.0e-04$	$-2.0e-03$	0.99	0.99	1.00	0.99
17	1.00	0.88	0.90	1.01	$3.6e-03$	$1.2e-02$	$2.1e-03$	$-1.1e-04$	0.98	0.97	1.00	1.00
18	1.33	1.18	0.71	0.96	$7.4e-03$	$3.9e-02$	$1.2e-02$	$9.0e-04$	0.90	0.92	0.98	0.99

using extrapolation based on data from the three blood samples and in which we simultaneously fit the blood sample data and the tissue TACs. The calculated results for subject 7 are shown in Figure 8. Without information from the tissue TACs the data on the early time window is shifted too high, $\theta = 3.909$, because of the inability to correctly estimate the partial volume effects.

B. Time Shift between blood samples and the image-derived blood time activity curve

As we can see from the figures, there is always a time shift between the CA-ROI TAC and the measured blood samples for early time. This then raises a question of whether we need to also include a shift of the data on W_1 measured from the CA-ROI to match with that on W_2 which is obtained directly from the three blood samples. We used the arterial blood samples to determine that the actual shift for subject 4 is 10 seconds. The blood samples at approximate times 10, 30 and 60 minutes

Fig. 6. Comparing the two sets of parameters calculated by the estimated and the arterial blood sampled inputs for subject 5.

Fig. 7. Comparing the two sets of parameters calculated by the estimated and the arterial blood sampled inputs for subject 1.

are 0.7150, 0.4487, 0.3130, resp. Supposing all blood samples for $t > \tau$ are shifted by 10 seconds to the right, the differences after fitting all data by (8), the differences at these same three time points are just -0.004 , -0.001 , -0.0005 , resp. with relative errors less than 0.0056. Thus the shift of W_1 relative to W_2 is negligible. In particular, it has already been demonstrated elsewhere that errors of this magnitude in the input function are insignificant in terms of parametric estimation, [20].

Fig. 8. Comparing the input functions estimated with and without using the tissue TACs in the fitting for subject 7. Direct fitting of the blood samples without simultaneously incorporating the tissue TACs yields $\theta = 3.909$, while with SIME $\theta = 2.287$, which yields a much better fit with the baseline blood samples.

C. Advantage of utilizing two windows in defining the input function

The method requires the estimation of τ . This point of continuity between the two windows separates the short window W_1 on which there is rapid accumulation and fast washout of tracer in the input function, from the window W_2 on which the tracer concentration in the input decays smoothly. While τ can be easily defined automatically or manually, its significance is to assure that the most reliable data are used for W_1 and that W_2 can be well-modeled by (4). The use of the linear interpolation on W_1 is a crude simplification, but it is a very good approximation to the real process when τ is very small. Clearly, it is also possible to use higher order fitting [3] rather than linear interpolation on W_1 but with $\tau < 1\text{min}$. the impact will be insignificant. On the other hand, for later time, for which spillover from tissue to blood may contaminate the blood ROI TAC, three samples are utilized to obviate this difficulty. As compared to other image-based input function estimation

methods, [8], [9], [10], [11], [13] and [12], which use the entire CA-ROI TAC for recovery of the input function, the proposed method is more robust to noise in identification of the input function at later times. It avoids the need to superimpose the CA ROI on later time frames which can compound the difficulty with a poor signal to noise ratio due to potential subject movement over the time course of the study.

D. The SIME Procedure

In order to provide reasonable solutions in a cost effective manner, it is important that bounds on the parameters of the nonlinear minimization are provided. Increasing the number of unknowns defining the input function quickly raises the complexity of the nonlinear optimization through the dependence of the fit also on the parameters of the input function. While different weights in the NLS might lead to differences, experiments with the square root of the time duration, or the unweighted case, gave inferior results. The cost function could also be set up so that the two parameters λ and δ can be estimated simultaneously, through the penalized cost functional

$$\begin{aligned} \Phi(\mathbf{x}, \alpha, \delta, \lambda) = & \sum_{i=1}^m \sum_{j=1}^n w_j (y_i^{\text{TAC}}(t_j) \\ & - \alpha_i \cdot y_i(t_j) - (1 - \alpha_i) \cdot u_e(t_j, \theta, \lambda, \delta))^2 \\ & + \gamma \sum_{i=1}^p (\theta v(\tau) e^{-\lambda(\tilde{t}_i - \tau)^\delta} - u_{\text{bs}}(\tilde{t}_i))^2, \end{aligned} \quad (10)$$

in which $u_e(t_j, \theta, \delta, \lambda)$ has four independent variables and would be evaluated only using (5), and without the fit (8). Here, however, we do not propose this approach because we suppose that the increased complexity of the minimization requires more computations and will not necessarily significantly improve accuracy. Moreover, the internal step (8) of obtaining λ and δ from the three blood samples at each iteration, is very fast because of

the simplicity of that data fit.

V. CONCLUSIONS

A reliable semi-automated alternative for input function estimation which uses 3 blood samples has been presented and validated by FDG PET analysis for 18 healthy subjects. Macro parameter K , and micro parameters, K_1 , k_2 and k_3 are well estimated as compared to the use of traditional arterial blood sampling. Because of the generality of the approach, and its relative simplicity for implementation, the proposed method should also work for other tracers. The Matlab-based implementation of the tool is available at web site <http://math.asu.edu/~hongbin>. For future work it is planned to use pharmacokinetic analysis of the tracer input for estimation of the input peak value, such as to possibly separate the estimation of the input from that of the kinetics of the data. It is also of interest to validate the method for use with small animal studies (microPET), [21].

REFERENCES

- [1] D. Feng, S.-C. Huang, and X. Wang, "Models for computer simulation studies of input functions for tracer kinetic modeling with positron emission tomography," *Int. J. Biomed. Comput.*, vol. 32, pp. 95–110, 1993.
- [2] M. E. Phelps, S.-C. Huang, E. J. Hoffman, C. E. Selin, and D. Kuhl, "Tomographic measurement of local cerebral glucose metabolic rate in man with (^{18}F) fluorodeoxyglucose: Validation of method," *Ann. Neurol.*, vol. 6, pp. 371–388, 1979.
- [3] S. Eberl, A. R. Anayat, R. R. Fulton, P. K. Hooper, and M. J. Fulham, "Evaluation of two population based input functions for quantitative neurological FDG PET studies," *Eur. J. Nucl. Med.*, vol. 24, pp. 299–304, 1997.
- [4] S.-C. Huang, M. E. Phelps, E. J. Hoffman, K. Sideris, C. J. Selin, and D. E. Kuhl, "Noninvasive determination of local cerebral metabolic rate of glucose in man," *Am. J. Physiol.*, vol. 238, no. E, pp. 69–82, 1980.
- [5] L. Sokoloff, M. Reivich, C. Kennedy, M. H. D. Rosiers, C. S. Patlack, K. D. Pettigrew, M. Sakurada, and M. Shinohara, "The [^{14}C] deoxyglucose method for the measurement of local cerebral glucose metabolism: theory procedures and normal values in

- the conscious and anesthetized albino rat," *J. Neurochem.*, vol. 28, pp. 897–916, 1977.
- [6] PET-Working Group. (2005) PET Working Group: NIH/NIA Neuroimaging Initiative. [Online]. Available: <http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/NeuroscienceOfAging/Summary+%E2%80%93PET+Working+Group.htm>
- [7] S. Takikawa, V. Dhawan, P. Spetsieris, W. Robeson, T. Chaly, R. Dahl, D. Margouleff, and D. Eidelberg, "Noninvasive quantitative fluorodeoxyglucose PET studies with an estimated input function derived from a population-based arterial blood curve," *Radiology*, vol. 188, pp. 131–136, 1993.
- [8] J.-E. Litton, "Input function in PET brain-studies using MRI defined arteries," *J. Comp. Ass. Tom.*, vol. 21, no. 6, pp. 907–909, 1997.
- [9] M. Liptrot, K. H. Adams, L. Martiny, L. H. Pinborg, M. N. Lonsdale, N. V. Olsen, S. Holm, C. Svarer, and G. M. Knudsen, "Cluster analysis in kinetic modelling of the brain: A noninvasive alternative to arterial sampling," *Neuroimage*, vol. 21, no. 2, pp. 483–493, 2004.
- [10] K. Chen, D. Bandy, E. Reiman, S.-C. Huang, M. Lawson, D. Feng, L.-S. Yun, and A. Palant, "Noninvasive quantification of the cerebral metabolic rate for glucose using positron emission tomography, ^{18}F -fluorodeoxyglucose, the Patlak method, and an image-derived input function," *J. Cereb. Blood Flow Metab.*, vol. 18, pp. 716–723, 1998.
- [11] L. M. Wahl, M. C. Asselin, and C. Nahmias, "Regions of interest in the venous sinuses as input functions for quantitative PET," *J. Nucl. Med.*, vol. 40, no. 10, pp. 1666–1675, 1999.
- [12] M. C. Asselin, V. J. Cunningham, S. Amano, R. Gunn, and C. Nahmias, "Parametrically defined cerebral blood vessels as non-invasive blood input functions for brain PET studies," *Phys. Med. Biol.*, vol. 49, no. 6, pp. 1033–54, 2004.
- [13] S. M. Sanabria-Bohorquez, A. Maes, P. Dupont, G. Bormans, T. de Groot, A. Coimbra, W. Eng, T. Laethem, I. D. Lepeleire, J. Gambale, J. M. Vega, and H. D. Burns, "Image-derived input function for $^{[11]\text{C}}$ flumazenil kinetic analysis in human brain," *Mol. Imag. Biol.*, vol. 5, no. 2, pp. 72–78, 2003.
- [14] D. G. Feng, K.-P. Wong, C.-M. Wu, and W.-C. Siu, "A technique for extracting physiological parameters and the required input function simultaneously from PET image measurements: Theory and simulation study," *IEEE Trans. Inform. Technol. Biomed.*, vol. 1, no. 4, pp. 243–254, 1997.
- [15] A. Nelson, F. Miraldi, R. F. Muzic Jr., G. P. Leisure, and W. E. Semple, "Noninvasive arterial monitor for quantitative oxygen-15-water blood flow studies," *J. Nuclear Medicine*, vol. 34, no. 6, pp. 1000–1006, 1993.
- [16] H. Guo, R. Renaut, K. Chen, and E. Reiman, "Clustering huge data sets for parametric PET imaging," *Biosystems*, vol. 71, no. 1-2, pp. 81–92, 2003.
- [17] K.-P. Wong, D. Feng, S. R. Meikle, and M. J. Fulham, "Simultaneous estimation of physiological parameters and the input function - In vivo PET data," *IEEE Trans. Inform. Technol. Biomed.*, vol. 5, no. 1, pp. 67–76, 2001.
- [18] M. E. Raichle, W. R. Martin, P. Herscovitch, M. A. Mintun, and J. Markham, "Brain blood flow measured with intravenous ^{15}O - H_2O II. Implementation and validation," *J. Nucl. Med.*, vol. 24, pp. 790–798, 1983.
- [19] The Mathworks, *Optimization Toolbox User's Guide*, March 2005.
- [20] K. Chen, S.-C. Huang, and D.-C. Yu, "The effects of measurement errors in the plasma radioactivity curve on parameter estimation in positron emission tomography," *Phy. Med. Biol.*, vol. 36, no. 9, pp. 1183–1200, 1991.
- [21] S.-C. Huang, H.-M. Wu, K. Shoghi-Jadid, D. B. Stout, A. Chatzi-ioannou, H. R. Schelbert, and J. R. Barrio, "Investigation of a new input function validation approach for dynamic mouse microPET studies," *Molecular Imaging and Biology*, vol. 6, no. 1, pp. 34–46, 2004.

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