Quantifying Brain $[^{18}F]$FDG Uptake Noninvasively by Combining Medical Health Records and Dynamic PET Imaging Data

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Abstract—Full quantification of regional cerebral metabolic rate of glucose ($rCMRglu$) with $[^{18}F]$fluorodeoxyglucose ($[^{18}F]$FDG) positron emission tomography (PET) imaging requires measurement of an arterial input function (AIF) curve, which is obtained with an invasive arterial blood sampling procedure during the scan. We previously proposed a non-invasive simultaneous estimation (nSIME) method that quantifies binding of a PET radioligand by combining individual electronic health records (EHR) information and a pharmokinetic AIF (PK-AIF) model. Initially applied only to $[^{13}C]$DASB data, in this study we validate nSIME for a different radioligand, $[^{18}F]$FDG, adapting the algorithm to the specific distribution and metabolism of this radioligand. We evaluate the impact of the PK-AIF model, the number of $[^{18}F]$FDG-specific soft constraints, and the type of predictive strategy. The accuracy of nSIME is then compared to a population-based approach. All analyses are conducted on 67 $[^{18}F]$FDG PET scans with arterial blood data available for comparison. nSIME performance is optimal for $[^{18}F]$FDG when using the PK-AIF model, two soft constraints, and an aggregate model to predict the soft constraint values. Higher correlation and lower Bland-Altman spread against gold standard $rCMRglu$ values based on arterial blood measurements are observed for nSIME ($r = 0.83$, spread = 1.55) compared to the population-based approach ($r = 0.77$, spread = 2.12). nSIME provides a data-driven estimation of both amplitude and shape of the AIF curve at the individual level and potentially enables non-invasive quantification of PET data across radioligands, avoiding the need for arterial blood sampling.

Index Terms—Arterial input function (AIF), electronic health record (EHR), positron emission tomography (PET) imaging

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I. INTRODUCTION

Positron emission tomography (PET) allows for in vivo measurement of tissue metabolism and neurochemistry [1], [2]. $[^{18}F]$fluorodeoxyglucose ($[^{18}F]$FDG) is a PET radioligand widely used to quantify glucose metabolism for the investigation, for example, of tumors and neurological disorders such as Alzheimer’s disease [3]–[6].

Current gold standard full quantification of regional cerebral metabolic rate of glucose ($rCMRglu$) from $[^{18}F]$FDG PET data requires measuring an arterial input function (AIF), which is the radioligand concentration level in plasma over the duration of the scan, by assaying blood samples acquired from an arterial line during scanning. Insertion of an arterial line is a relatively invasive procedure with potential complications, and the subsequent blood assays are not always reliable, adding measurement errors. The procedure is costly, discomforting for the patient and exposes clinical staff to additional radiation. Consequently, approaches alternative to arterial blood sampling have been proposed [7]–[12].

Image-derived input function (IDIF) approaches have been proposed for $[^{18}F]$FDG [7], which recover the AIF directly from the PET images by identifying cranial blood pools in the field of view. These structures are limited in size, and their signal is sensitive to motion artifacts and partial volume effect. IDIF also requires a fast acquisition protocol of the PET images, to accurately recover the initial part of the AIF curve, and a few blood samples for calibration of the recovered IDIF. Alternatively, population-based input function (PBIF) approaches have been validated for $[^{18}F]$FDG [9]–[12], which derive a template AIF curve by normalizing individual AIF (obtained via arterial blood sampling) from a large population of subjects scanned with the same radioligand. The template is then individually calibrated to the subject using a scaling factor. PBIF methods rely on the assumption that the AIF has a constant shape across subjects, but in fact, kinetic and metabolic profiles can vary across individuals [13], [14].

Simultaneous estimation (SIME) is another promising approach that has been validated [15] as an alternative, less invasive method for recovering the AIF. SIME is based on a mathematical model for the AIF, and estimates the free parameters of such model together with the parameters of the model that describes the radioligand kinetics in the tissue, by...
simultaneously fitting multiple brain regions at once. However, SIME still requires at least one blood sample to be included as a constraint within the algorithm cost function to ensure AIF identifiability. Instead of obtaining this blood sample, we have shown previously that it may be possible to predict the constraint variable from non-invasive patient information [16]. More recently, a fully non-invasive SIME (nSIME) framework was introduced that combines electronic health records (EHR) with dynamic PET data to estimate the AIF for $[^{11}C]$DASB, a radioligand used to image the serotonin transporter [17]. Differently from the original SIME [15], nSIME adds multiple soft constraints within the algorithm cost function, and predicts such constraint variables from EHR and PET data using pre-trained models, instead of deriving them from the subject blood sample.

The key innovation of this work is the application of nSIME for use with $[^{18}F]$FDG by adapting, optimizing, and validating the algorithm for this radioligand. The utility of EHR-based predictions needs in fact to be assessed for each radioligand, as the EHR variables predictive of its pharmacokinetics and metabolism are not known a priori, and can vary across radioligands. Preliminary results of this application were published in [18], which is expanded upon here with several new technical contributions: 1) comparison of nSIME to gold standard quantification; 2) rigorous characterization of both SIME and nSIME with one and two constraints using a more advanced predictive algorithm; 3) comparison of the proposed pharmacokinetic AIF model to the previously used 3-decreasing exponential model; 4) addition of an AIF curve shape selection procedure; and 5) benchmarking nSIME against a non-invasive population based approach.

II. MATERIALS AND METHODS

A. Subjects and Associated Data

PET, EHR, and magnetic resonance imaging (MRI) data were acquired as part of a study of patients with mild cognitive impairment (MCI), mild Alzheimer’s disease (AD) and age-matched healthy controls. The study was approved by the Institute Review Board of the New York State Psychiatric Institute and Columbia University [19]. EHR were collected prior to the PET scan and included demographics, clinical details, clinical laboratory test results, urinalysis, and vital parameters. PET data included regional brain time activity curves (TACs), injected dose of $[^{18}F]$FDG (ID), injected mass of $[^{18}F]$FDG, and radioligand specific activity. The AIF was determined using full arterial blood sampling. Eighty-nine PET scans were previously acquired from 58 subjects. Only scans with a fully sampled AIF, TACs and EHR were included in the final dataset, which includes 67 PET scans from 49 subjects. The 67 scans include 46 baseline and 21 follow-up assessments at ~1.5 years (Table I).

B. PET-related Data Acquisitions and Pre-Processing

For details of the acquisition protocols, we refer to [19]. Briefly, PET images were acquired on an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN). After a 10-minute transmission scan, a bolus injection of $[^{18}F]$FDG (178.4 MBq ± 9.9 MBq across scans) was administered intravenously. Emission data were acquired in 3D mode for 60 minutes with 26 frames of increasing duration. Images were reconstructed on a 128 x 128 matrix (pixel size 2.5 x 2.5 mm²), after attenuation and scatter correction. Fourteen arterial blood samples were drawn during scan. Samples were centrifuged and plasma radioactivity measured using a well counter. Cold glucose concentration in blood was measured by a glucometer before and after the PET scan, and values averaged. The prefrontal cortex (PFC), cingulate (CIN), hippocampus (HIP), parahippocampal gyrus (PIP) and grey matter cerebellum (CER) were labeled on MRI scans by a trained technician [20], [21]. Regions of interest (ROI) masks were transferred to motion-corrected and MRI co-registered PET images, and TACs extracted as average activity in each ROI over time. The sum of mean activity in the whole brain from 2.5 to 10 minutes post-injection ($TACsum$) was also derived. A preliminary analysis found that $TACsum$ in this time window is strongly correlated to $[^{18}F]$FDG plasma concentration.

C. EHR Data

EHR include laboratory data on individual subjects that are used to compose a list of 83 initial predictors (Table II). EHR measures include demographics, clinical information, clinical laboratory test results (chemistry and hematology), urinalysis and vital parameters (HR, BP) pre- and post-PET scan.
Average of pre- and post-PET scan values were added for HR, and systolic and diastolic blood pressure. Secondary measures derived from sex, age, height, weight, and hematocrit include body mass index (BMI), body surface area (BSA), estimated total blood volume (eTBV), total plasma volume (eTPV), estimated resting metabolic rate (eRMR), pulse pressure (PP), mean arterial pressure (MAP), and estimated cardiac output (eCO), which approximates the stroke volume (SV). Glomerular filtration rate (eGFR) was calculated using blood urea nitrogen (BUN) and albumin (Albumin), and adjusted for individual BSA [22]. Standard clinical formulae were used for the calculation of albumin-corrected calcium (rCalcium), blood viscosity, anion gap, BUN:Creatinine (BUN:Crt) ratio and plasma osmolarity [17].

For each scan, a PBIF was also derived from height and weight according to the approach proposed in [23], and the area under the curve of such PBIF included as an additional potential predictor variable (AUCpopul). Of specific interest was whether this variable would be selected in the final predictive algorithm as part of the general comparison of nSIME against the PBIF based approach.

D. Gold standard rCMRglu

A two-tissue irreversible compartmental model is fit to each ROI TAC separately, using the arterial-blood-based AIF [24]. Estimates of the model free parameters are obtained by minimizing the error between measured data and TAC fit using a nonlinear least squares estimator. rCMRglu is then calculated as a function of the model parameters.

E. Pharmacokinetic AIF Model

nSIME uses a mathematical model to describe the AIF (Cp), which is common across all brain ROIs. The free parameters of the AIF model are estimated together with those describing the radioligand kinetics in tissue by fitting TACs from multiple ROIs simultaneously. The original implementation of SIME [15] used a 3E-AIF model, which fits a straight line to the peak (infusion phase), followed by a combination of three-exponentials after the peak (elimination phase). For nSIME, we previously introduced a pharmacokinetic (PK) model for the AIF, where infusion and elimination phases are both nonlinear and share parameters, for a more physiologically accurate description of drug delivery [17]. Specifically, we used the three-compartment PK model reported in Equation 1, where $\theta^{PK} = [B_i, \lambda_i, t_i, T]$ denotes the vector of free parameters of the model, $B_i$ is a scaling constant, $\lambda_i$ is the rate constant of the $i$th compartment, $t_i$ is the radioligand infusion delay and $T$ is the infusion duration.

$$C_p^{PK}(t|\theta^{PK}) = \begin{cases} \sum_{i=1}^{3} B_i e^{-\lambda_i(t-t_i)} - 1, & t < T \\ \sum_{i=1}^{3} B_i e^{-\lambda_i T} - 1 e^{-\lambda_i(t-t_i)}, & t \geq T \end{cases} \quad (1)$$

The PK-AIF model was fitted to the arterial blood-derived measurements for all scans, to derive physiological ranges for the parameters in $\theta^{PK}$, which are used as parameter bounds (minimum and maximum physiological values) and as initial parameter estimates (mean physiological values) within the nSIME algorithm.

F. Non-invasive Simultaneous Estimation (nSIME)

Differently from the gold standard approach, SIME fits multiple TACs at once and requires only one blood sample acquired at some time point post-injection. The optimal sampling time is radioligand-specific, and for $[18F]FDG$ is 40 minutes post-injection [15]. The AIF value at this time point is referred to here as AIF40. nSIME removes the need for acquiring any blood sample by incorporating a predicted value of AIF40 (pAIF40) as a constraint variable within its cost function. The predicted area under the curve of the AIF (pAUC), derived from the integration of the estimated AIF model, is introduced as a second constraint variable for nSIME to improve robustness and accuracy of the estimation process originally proposed [15]. While AIF40 describes one aspect of the AIF curve shape (tail height), the AUC captures characteristics of the global shape and scaling, and provides a more stable measure as it is calculated from multiple time points [17]. The soft constraint variables pAIF40 and pAUC are incorporated into the nSIME cost function described in (2).

$$\Phi(t, \theta^{PK}, \psi^{tac}, ..., \psi^{tac}) = \sum_{r=1}^{R} \sum_{j=1}^{J} w_j |y_{ij} - C(t_j|\theta, \psi)|^2 + \nu[pAIF40 - C_p(t_{opt}|\theta)]^2 + z[pAUC - AUC(\theta)]^2 \quad (2)$$

The first term in Equation (2) minimizes over $R$ ROIs and $J$ time points the squared distance between the measured TAC, $y_{ij}$, and the TAC predicted by the model, $C(t_j|\theta, \psi)$, where $\theta$ and $\Psi$ are the parameters of AIF and $[18F]FDG$ kinetic models for the $r$th ROI, respectively. The second term represents the soft constraint on AIF40, as the difference between pAIF40 and the corresponding value in the AIF model at time $t_{opt} = 40$ min, $C_p(t_{opt}|\theta)$. The third term is the soft constraint on AUC, given as the difference between pAUC and the AUC of the AIF curve model $C_p(t|\theta)$. The weights $\nu$ and $z$ balance fitting of the observed TACs and adherence of the modeled AIF to the two constraints ($\nu = 100$ and $z = 5$, as suggested in [17]). As done previously for $[18F]FDG$ [15], 5 ROIs (CER, CIN, HIP, PFC and PIP) were used within nSIME.

rCMRglu can then be estimated for each ROI from the $\Psi$, estimated via nSIME as rCMRglu = $C_p(t_{opt}|\theta)$, where LC is the lumped constant (assumed equal to 0.65 here [25]) that converts rates of $[18F]FDG$ uptake and phosphorylation into rates of glucose use, and $K_1, k_2, k_3$ are the micro-parameters of the $[18F]FDG$ kinetic model in tissue.

G. Selection of EHR-based Predictors

The soft constraint variables pAIF40 and pAUC were predicted from EHR data only, using multiple linear regression models identified through a predictive algorithm. Initially, a screening procedure was applied to the whole set of EHR predictors (Table II) to select variables that are more strongly correlated to ground-truth measures $C_p(t_{opt}|\theta)$ and
AUC(θ). The procedure uses squared Pearson’s correlation coefficient, $r^2$, in linear regressions, with individual EHR variables as the predictors, and the ground-truth measure as the response variable.

This screening process is divided into 3 main steps [17] and runs separately for response variables $C_p(t|θ)$ and $AUC(θ)$, thus obtaining a set of potential predictors for each constraint: 1) each predictor variable is retained if its correlation $r^2$ with the response variable is greater than 0.1; 2) each predictor variable is normalized for injected dose and retained if the correlation between the normalized and response variable is greater than the correlation between the injected dose itself and response variable; 3) all possible multiple regression models that include two predictors at a time are fitted with and without interaction terms, and the interaction term is selected if the correlation of the model with the interaction term is greater than the correlation of the model with only the two predictors. Furthermore, the $r^2$ of the model must be greater than 0.3 for $C_p(t|θ)$, and 0.4 for $AUC(θ)$, and the p-value of the interaction term smaller than 0.05.

H. Predictive Model Design

We used a predictive algorithm previously described in [17], to separately predict pAIF40 and pAUC from EHR data only using leave-one-out cross-validation. The aggregated model approach selects the regression model with the highest bootstrapped correlation to blood-based mAIF40 and mAUC in the training data, each time excluding a different scan from the training set, and yields multiple models that are then aggregated to predict pAIF40 or pAUC. The number of predictors in each regression model was limited to two; three- and four- variable models were excluded in preliminary analyses, as they did not improve prediction accuracy, likely due to the small sample size.

I. Simulated Annealing

For each scan, nSIME ran using the subject-specific predicted pAIF40 and pAUC values, without vascular correction of the TACs. Stochastic simulated annealing was used to solve the proposed optimization problem [15]. The nSIME-derived AIF with the smallest full width half maximum (FWHM) across 5 repeated runs was selected automatically for calculating CMRglu. Five runs were used because, in some instances, it can take from 1 to 5 runs for SIME to converge to parameters that reconstruct an AIF curve with a typical physiological shape. AIF FWHM was calculated as the horizontal distance at mid height around the peak of the AIF curve. This helps to eliminate AIF curves with wide peaks.

J. Experimental Design and Evaluation Setup

First, we tested the performance of the aggregate model selection in estimating pAIF40 and pAUC. Constraint variables predictions were compared against the arterial blood-derived measured values (mAIF40 and mAUC) using Pearson’s correlation coefficients and Bland-Altman (BA) plots. Second, we tested whether the PK-AIF model provides a better fit of the AIF curve and adds stability within nSIME

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Only variables with a frequency of greater than 3.0% are shown.
A. Quality of the PK model for AIF applied to $[^{18}F]FDG$

Fits of the PK model in (1) to blood-derived AIF samples are illustrated in Fig. 1 for three representative cases. Correlations of the derived constraint variables with blood-based values are: $r = 0.99$ for AIF-40 and $r = 0.99$ for AUC. The range of values for the PK model parameters $\theta^k$ obtained in the considered cohort were: $t_2 [0.49, 1]$ (min), $T [0.19, 1]$ (min); $B_1 [0, 0.5]$, $B_2 [0.15, 0.9]$, $B_3 [0.54, 2.91]$ ($\mu$Ci/mL); $l_2 [0, 0.02]$, $l_2 [0.21, 1.70]$, $l_2 [0.54, 10]$ (min$^{-1}$).

B. Performance of Predictor Selection

The screening procedure selected a total of 40 predictors for pAIF-40 and 38 for pAUC (frequently selected predictors are reported in Table III). TACsum, RWD, and ID were frequently selected for both constraint variables. Other frequent predictors included triglycerides for pAIF-40, and BSA and ColdGluc2 for pAUC. The aggregate model approach yielded the following correlation values between predicted and blood-based values: $r = 0.78$ (pAIF-40) and $r = 0.82$ (pAUC). Results of the predictions are reported in Fig. 2 as scatter plots and as BA plots.

C. PK-AIF versus 3E-AIF

Using the PK-AIF model improves correlation between nSIME with measured mAIF-40 and gold standard rCMRglu values ($r = 0.89$) compared to the 3E-AIF model ($r = 0.85$), and yields a smaller bias, closer to 0 (Fig. 3). Notably, there are also fewer outlier errors when the PK-AIF model is used.

D. Using One Versus Two Constraints

Using nSIME with blood-based soft constraint values leads to correlations between nSIME-derived and AIF-based rCMRglu values of $r = 0.90$ when using only mAIF-40 (Fig. 4a-b) and $r = 0.94$ when using both mAIF-40 and mAUC (Fig. 4c-d). Moreover, the spread between the 95% limits of agreement in the BA plots is reduced from 1.29 to 1.01 when using two soft constraints, while biases are similar and close to...
0. Using nSIME with non-invasively predicted soft constraint variables leads to correlations between nSIME-derived and AIF-based rCMRglu values of \( r = 0.79 \) when using only \( pAIF40 \) (Fig. 5a-b), and \( r = 0.83 \) when using both \( pAIF40 \) and \( pAUC \) (Fig. 5c-d). The BA plots spread is reduced from 1.72 to 1.55 when using two soft constraints, with a slightly higher bias equal to 0.15.

E. Comparison of nSIME with the PBIF approach

rCMRglu estimates obtained using the population approach proposed in [23] are reported in Fig. 6. Compared to nSIME, with two predicted soft constraint variables, correlation is lower for PBIF (0.77 vs. 0.83), spread is higher (2.12 vs. 1.55), and bias is higher (0.43 vs. 0.15).

F. Individual ROI and group analyses

Correlation between rCMRglu estimated with nSIME and those calculated using the gold standard based approach are \( r = 0.759 \) and \( r = 0.768 \) for PAR and PCN, respectively, comparable to individual correlations for the five ROIs used to estimate the nSIME AIF, \( r = 0.693\text{-}0.798 \).

There is a significant difference in rCMRglu between CTR and AD groups: for the gold standard approach, CIN (\( p = 0.015 \)), PAR (\( p = 0.0004 \)), and PCN (\( p = 0.0005 \)); for nSIME, CIN (\( p = 0.016 \)), PAR (\( p = 0.00006 \)), and PCN (\( p = 0.0002 \)).

IV. DISCUSSION

In this study we extended the use of nSIME to \( ^{18}\text{F} \)FDG, with the goal of eliminating the need for arterial blood sampling during PET scanning. Our results indicate that the nSIME framework can accurately quantify rCMRglu from \( ^{18}\text{F} \)FDG data, outperform the population based approach, and achieve comparable group discrimination to the gold standard.

High correlations with arterial blood-derived values were achieved with the aggregate predictive model from [17]. The predictors that most frequently appeared for both constraints were \( TACsum \), \( RDW \), and \( ID \). Triglycerides were also frequently included for prediction of \( pAIF40 \), whereas weight/height-derived variables (e.g., \( BSA \), \( eRMR \), \( eTPV \) and \( ColdGlu2 \)) were more important for predicting \( pAUC \). The ID is directly related to the distribution of the radioligand in the blood. \( BSA \) may impact the volume of blood into which the radioligand is diluted, and has been used in the past as a normalization factor for the AIF [10], [26] and to predict other blood-related anchor values [16]. Notably, the relationship between weight/height-derived variables and \( AUC \) has already been identified in [17] for \([^{11}\text{C}]\)DASB. An interesting finding is the selection of \( RDW \) and triglycerides, which were not identified as predictors for \([^{11}\text{C}]\)DASB. One possible explanation is that \( RDW \) is related to metabolic balance and red blood cell homeostasis [27] and thus partially reflects each subject metabolic profile. Triglycerides have been associated with inflammation-related \( ^{18}\text{F} \)FDG uptake in arterial plaques [28], which could influence blood availability of the radioligand, especially in the older MCI and AD subjects in this study. Triglycerides may also affect lipid membrane composition and thus a variety of cellular functions that in turn could impact glucose uptake and utilization. Finally, unlike \([^{11}\text{C}]\)DASB, \( HR \) and \( BP \) do not appear to be relevant for \( ^{18}\text{F} \)FDG-based prediction, possibly because \( ^{18}\text{F} \)FDG is metabolized throughout the body whereas \([^{11}\text{C}]\)DASB is primarily metabolized by the liver.

It should be noted that both data collection and subject inclusion criteria were not specifically designed for this retrospective analysis. Furthermore, EHR data used in this study were gathered within hours to months before the PET scan, therefore limiting the accuracy of our analysis. A prospective data collection could contribute to even more accurate prediction and to fewer outliers, thus improving overall performance of the proposed non-invasive method.

In a separate analysis (data not shown), we compared the performance of the aggregate model with that of a simplified approach, which selects just a single regression model with the highest bootstrapped correlation. We found that the aggregate model yields slightly better performance, consistent with our
previous results with $^{11}$C]DASB.

Our findings support the use of the PK-AIF model rather than a 3E-AIF model, as it yields an improvement in nSIME performance itself. The inclusion of the AUC as a second soft constraint into the nSIME cost function significantly improved the algorithm performance for estimating rCMRglu. Indeed, constraining not only the AIF at a specific time point (AIF40), but also its overall AUC, aids in accurately reconstructing the shape of each individual AIF curve, making nSIME a more personalized approach compared to other methods for non-invasive estimation of AIF. nSIME also outperformed the PBF approach, showing higher correlation and lower spread and bias in the rCMRglu estimates vs. gold standard values.

Individual ROI results show that nSIME is applicable to ROIs beyond those that are used to estimate the AIF. Group analyses suggest that discrimination between CTR and AD is comparable between nSIME and the gold standard.

The technical contributions presented here enabled nSIME to be adapted for accurate quantification of the $[^{18}]$FDG radioligand, by demonstrating that using two constraints, the PK-AIF model, and the AIF curve shape selection improves overall performance against the gold standard and also outperforms a non-invasive population based approach. nSIME shows potential for future research and clinical application, as it eliminates the need for arterial blood sampling or for the estimation of spillover and recovery coefficients as in the case of IDIF methods.

V. CONCLUSION

We propose a totally non-invasive nSIME approach for the estimation of $[^{18}]$FDG rCMRglu values from brain PET images that takes advantage of pharmacokinetic theory, health record data and predictive algorithms. The advantage of using nSIME over a population-based input function approach is demonstrated. The high correlation values and small bias in quantification errors support the applicability of nSIME to the widely used $[^{18}]$FDG radioligand and should be investigated further in specific prospective studies and additional radioligands. Our results advocate for the development of larger databases of PET images, and of radioligand blood sampling and EHR data, as part of a more general push toward a big-data approach in quantitative PET imaging.

REFERENCES