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Dual-Tracer PET Using Generalized Factor Analysis of Dynamic Sequences

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Abstract

Purpose—With single-photon emission computed tomography, simultaneous imaging of two physiological processes relies on discrimination of the energy of the emitted gamma rays, whereas the application of dual-tracer imaging to positron emission tomography (PET) imaging has been limited by the characteristic 511-keV emissions.

Procedures—To address this limitation, we developed a novel approach based on generalized factor analysis of dynamic sequences (GFADS) that exploits spatio-temporal differences between radiotracers and applied it to near-simultaneous imaging of 2-deoxy-2- ^{18}F fluoro-D-glucose (FDG) (brain metabolism) and ^{11}C -raclopride (D2) with simulated human data and experimental rhesus monkey data. We show theoretically and verify by simulation and measurement that GFADS can separate FDG and raclopride measurements that are made nearly simultaneously.

Results—The theoretical development shows that GFADS can decompose the studies at several levels: (1) It decomposes the FDG and raclopride study so that they can be analyzed as though they were obtained separately. (2) If additional physiologic/anatomic constraints can be imposed, further decomposition is possible. (3) For the example of raclopride, specific and nonspecific binding can be determined on a pixel-by-pixel basis. We found good agreement between the estimated GFADS factors and the simulated ground truth time activity curves (TACs), and between the GFADS factor images and the corresponding ground truth activity distributions with errors less than $7.3 \pm 1.3\%$. Biases in estimation of specific D2 binding and relative metabolism activity were within $5.9 \pm 3.6\%$ compared to the ground truth values. We also evaluated our approach in simultaneous dual-isotope brain PET studies in a rhesus monkey and obtained accuracy of better than 6 % in a mid-striatal volume, for striatal activity estimation.

Conclusions—Dynamic image sequences acquired following near-simultaneous injection of two PET radiopharmaceuticals can be separated into components based on the differences in the kinetics, provided their kinetic behaviors are distinct.

Keywords

Dynamic PET; Quantitation; Brain imaging

Introduction

It is not unusual to study two biological processes in a single individual with positron emission tomography (PET), either for research or clinical purposes. However, as a practical

matter, such studies require two scan sessions, usually performed on different days, due to constraints on scanner availability, allowance for radioactive decay of isotopes, and patient comfort. The ability to perform these two scans simultaneously would be advantageous—the patient would be in an identical physiological state, it obviates the need for additional scans (reducing cost and increasing patient comfort), and the two studies would be automatically registered. Simultaneous dual-tracer imaging with PET would allow assessment of two physiological processes [1], but it has not yet been successfully achieved clinically because, unlike in single-photon emission computed tomography (SPECT), discrimination on the basis of energy is not possible. Decomposition of simultaneous dual-tracer PET studies must proceed on the basis of contrasting kinetics. There has been substantial work in this area [1–8]. We review the main axes of research previously proposed and describe a technique based on factor analysis that has great potential in analyzing dual-tracer PET studies.

There are many potential clinical applications for simultaneous dual-tracer PET studies. Neurodegenerative disorders collectively describe a range of progressive diseases that afflict millions worldwide. Early, accurate diagnosis can improve patient outcomes by enabling effective neuroprotective treatment. Imaging offers the possibility of noninvasive early diagnosis by detecting functional changes before the presentation of clinical symptoms. Imaging of one aspect of the physiology, however, may not provide a unique diagnosis, leading to potentially ineffective treatment. For example, early differential diagnosis between Parkinson's disease (PD) and progressive supranuclear palsy (PSP) and multiple-system atrophy (MSA) could greatly benefit from characterization of both glucose utilization rate and post-synaptic D2 receptor uptake, which, in combination, are altered uniquely in each disorder [9–12]. For example, glucose utilization rate is much more affected in PSP and MSA than in PD, and 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) would help discriminate between the two diseases, while D2 binding is more diminished in PSP than in PD and MSA. Hence, additional physiological information from a second tracer has the potential to more readily discriminate between disorders.

Unlike dual-tracer SPECT which relies on an energy-spectral property, independent of the state of the subject, simultaneous dual-tracer PET must rely on differences in the kinetics and/or spatial distributions of the tracers, which are physiological or biochemical properties of the system. Koeppe *et al.* [2] reported a technique for determining kinetic parameters from two ^{11}C tracers acquired nearly simultaneously [2]. The basic idea of their method is to fit the total concentration curve measured by PET to the sum of two kinetic models. The decomposition is considered to be successful when the model parameters for both studies are well determined. The kinetic technique did not work well when the two tracers were co-injected; rather, their results showed that the best estimates of the parameters were obtained when a large offset (20 min) was used and the kinetics of the first tracer were fast (and therefore its parameter values well characterized at the time of the second injection). Converse *et al.* studied two monkeys who received bolus injections of ^{18}F -fallypride and, about 100 min later, pulses of ^{18}F fluoromethane. Their results showed that both binding and rCBF could be determined with about 8 % reliability. Kadrmas and Rust [1] have used published data and compartment models to simulate time–activity curves for ^{62}Cu -ATSM, ^{62}Cu -PTSM, and FDG. These calculations were summed in different combinations and with different temporal offsets to mimic dual-tracer studies, allowing study of the feasibility of recovering information, as in separate measurements, either by principal component analysis or compartment modeling. Rust *et al.* [5] have also studied the feasibility of rapid sequential measurement of myocardial blood flow with ^{13}N ammonia during rest and stress. Their pilot study, conducted in six patients with a wide spectrum of blood flow and perfusion reserve, showed that combination modeling of the rest stress study could recover both the rest and stress perfusion with good precision and accuracy.

In summary, prior work relied on fitting combined kinetic models to dual-tracer PET studies. The results show that as the separation between sequential studies increases, combined kinetic modeling becomes more reliable, finally approaching the results obtained in separate studies.

We investigate how our mathematical approach based on factor analysis can offer an alternative way to decompose the total concentration curve into components that could support quantitative analysis of the data. Factor analysis of dynamic sequences (FADS) is a powerful technique that allows the decomposition of a temporal image sequence into a small number of fundamental functions (factors) whose associated spatial distributions are called factor images [13–15]. This, in turn, yields a synthetic representation of the contents of a relatively large dynamic image dataset where the factors can represent uptake of the same tracer by different biological processes, or uptake of different tracers. FADS is well suited to the decomposition of the contributions of two isotopes to the overall signal when these contributions differ spatially, temporally, or spatio-temporally. In PET imaging, we have previously used a factor analysis approach to dynamic ^{82}Rb myocardial perfusion PET, to estimate the left and right ventricular contributions as well as the myocardial uptake while penalizing overlap between the different factor images [16]. This approach was generalized to 5D spectro-temporal images (time + energy + 3D) and shown to yield a significant advantage in terms of the ratio of the number of equations to that of unknowns in the factor analysis problem [12].

In the present work, we developed a new approach, based on generalized factor analysis of dynamic sequences (GFADS), that exploits spatio-temporal differences between radiotracers and applied it to simultaneous imaging of FDG (brain metabolism) and ^{11}C -raclopride (D2) with simulated human and rhesus monkey data. By taking into account the special kinetic behavior of FDG, we show theoretically that GFADS can decompose the experimental data, on a pixel-by-pixel basis, so that one obtains an estimate of the FDG and raclopride kinetics. A further innovation of the present work is that we constrain the solution using spatial and temporal constraints to provide an additional decomposition of the raclopride data into free plus specific and bound tracer. Generalizing, our approach may therefore be more applicable for tracers with slow kinetics, where the compartment model technique requires a larger sample (more imaging time offset) to characterize the first tracer.

Material and Methods

Generalized Factor Analysis of Dynamic Sequences

FADS is a powerful technique for the analysis of dynamic sequences. In the general method, the factors are completely unknown, leading to a degeneracy and an infinite number of solutions [11]. Several techniques have been developed that address this problem and improve the results of factor analysis [17–21]. These techniques are based on the use of *a priori* physiological/anatomic information. Therefore, they are tailored for a particular type of clinical study and cannot be used without modification in different settings. Furthermore, although these techniques increase the range of situations in which unique FADS solutions are achieved, they do not ensure a unique solution in all cases. We have previously developed a technique that is more general than previously reported approaches and can be used in a variety of applications, with a wide range of blood time activity curves (TAC) [16, 22]. In this work, we effect the solution to simultaneous FDG/raclopride imaging by constraining one of the factors to decay with the physical half-life of ^{18}F , thus representing the metabolic trapping of FDG. This constraint was chosen primarily for its simplicity, but another appealing alternative is to require one of the factor curves to have maximal residence time. We also demonstrate that it is possible to address the non-uniqueness of the raclopride factors by penalizing its main effect. In this regard, FADS is performed first by

any factor analysis method such as the apex-seeking [23] or least-squares [21] approaches. Following FADS, a second step is used to minimize the overlap between factor images and, hence, increase the probability of a unique solution. This second step is described and tested in Monte Carlo simulations of realistic dual-isotope dynamic PET studies, and the feasibility of the approach is demonstrated in a primate study.

We represent an arbitrary dynamic sequence of MPET frames by an $N \times M$ matrix A , where N is the number of voxels in a dynamic image. The factor model of the dynamic data assumes that the data matrix can be represented by the following equation:

$$A = CF + n \quad (1)$$

where F contains P factors (time activity curves, $P \times M$ matrix) and n denotes noise in the data. The factor curves define the time course of the factors whose spatial definition is contained in matrix C (the factor image, $N \times P$ matrix). In order to solve Eq. (1), the number of factors P must be known *a priori*. In this work, we describe dual-tracer PET studies with FDG and raclopride with three factors. The imaging period begins 20 min after injection of FDG. To account for the plateau distribution of FDG, we assume the factor curve for FDG is a decaying exponential with the half-life of ^{18}F . We make the simplifying assumption that the kinetic behavior of raclopride can be approximated with two factors, one representing the kinetics of specific binding and the other representing the kinetics of free plus nonspecifically bound tracer. These assumptions serve to ensure that GFADS returns a decomposition in the factors representing the long residence time of FDG, the intermediate residence time of specific raclopride binding, and the shorter residence of nonspecifically bound free + nonspecifically bound tracer.

Estimation of the factor curves (F) and factor images (C) was based on minimization of the least-squares objective function f_{LS} :

$$f_{LS}(C, F) = \sum_{i=1}^N \sum_{m=1}^M \left(A_{im} - \sum_{p=1}^P C_{ip} F_{pm} \right)^2 \quad (2)$$

Non-negativity constraints were applied by adding another penalty term, $f_n(C, F)$, to the objective function (Eq. 3) that is a quadratic function that heavily penalizes negative values of C and F and yields a positive solution:

$$f_n(C, F) = \sum_{i=1}^N \sum_{p=1}^P H(C_{ip}) + \sum_{m=1}^M \sum_{p=1}^P H(F_{pm}), \quad (3)$$

where $H(x)$ is equal to 0 for $x \geq 0$ and equal to x^2 for $x < 0$. This formalism allows the separation of the FDG factor from other ^{11}C -raclopride factors. Equation (3) shows that by separating the terms constraining factor 1 (FDG) from the sum of factors 2 and 3, we obtain the best estimate of FDG and raclopride tissue concentrations possible with GFADS. We show how to extend the method to identify the specific binding and free + nonspecific ^{11}C -raclopride factors under the assumptions made in this work. In addition, we also use an injection offset to calibrate the contribution from the first tracer. Therefore, the total objective function that was used in the first step is:

$$f_{PLS}(C, F) = f_{LS}(C, F) + \delta f_n(C, F), \quad (4)$$

where λ is a penalty coefficient that can be chosen from a range of large values [16, 21]. Entries of matrix A were normalized to be between 0 and 1, and the penalty coefficient was set to 3,500. The total objective function was minimized using the conjugate gradient algorithm.

Consistent with normal metabolic trapping of FDG in the brain [24], the factor image associated with FDG was estimated by forcing the corresponding factor curve to decline in the least squares fitting step with the decay constant of ^{18}F . Furthermore, the gradient was set to zero for the two other factors at the first time point (corresponding to injection time offset) in order to avoid nonuniqueness artifacts in the image of the factor coefficients corresponding to FDG. Because the factor curves and coefficients used in the factor model described by Eq. (1) are not mathematically unique, the result of the optimization described by Eq. (4) cannot be used for quantitative analysis. To address this problem, we generalized the factor analysis approach by implementing a post-processing step following the factor model technique.

In this post-processing step, we minimize the overlap between the factor images. In general, the higher the overlap, the higher the error introduced by the non-uniqueness [17] effects. The overlap minimization is performed by preserving the original least squares fit obtained by minimization of Eq. (4) intact. This is achieved by introducing an oblique rotation matrix R such that $A = (CR)(R^{-1}F)$ [10]. With this definition, the new set of factor images CR and factors $R^{-1}F$ satisfies the least squares fit criteria obtained in the previous optimization step. For a three-factor model considered here, the R is a 3×3 matrix. Since FDG is assumed to be constant, the row and column in R corresponding to FDG factor is a unit vector. It follows that five entries in R are fixed, and the remaining four are optimized. During optimization, we modify the non-fixed entries of this matrix so that overlap between factor images (CR) is minimal, but at the same time, the non-negativity of new factor images and factors is not violated. This is done by minimization of the new objective function $f_{uni}(R)$ given below. The result of this procedure is the set of new factor images CR and factors $R^{-1}F$ which is the final result of the GFADS. The new objective function is:

$$f_{uni}(R) = \sum_{p=1}^P \sum_{q=p+1}^P \sum_{i=1}^N \frac{|CR|_{ip}}{\sqrt{\sum_{i=1}^N (CR)_{ip}^2}} \frac{|CR|_{iq}}{\sqrt{\sum_{i=1}^N (CR)_{iq}^2}} + b f_n(CR, R^{-1}F). \quad (5)$$

where b is the penalty parameter determining the strength of nonnegativity constraints. Note that the first term of the above objective is designed to be at minimum (value of 0) if factor images do not overlap and that there is no voxel i for which any two factor images are nonzero. The terms in the denominators of the above equation are used for normalization. In general, the factor images can be considered as vectors with N dimensions, so the minimal overlap is sought between vectors with unit length. This normalization is necessary because otherwise the overlap would be minimized with all factor images with voxel values equal to zero. The optimization of the above objective function was obtained by the simplex algorithm, and convergence was obtained after 500–800 iterations. We used a simplex algorithm because it is fast and robust for the small number of parameters being optimized (four entries of matrix R). The value of the penalty parameter, b , 0.1 in this work, is not critical for the convergence to a solution when chosen in the range [0.01, 0.1].

In addition to the FDG factor obtained in the first step, the second step yielded two factors representing D2 binding and free + nonspecific D2. Due to the near-instantaneous mixing of free and nonspecifically bound raclopride, it is common to assume [6, 21, 22] that its volume of distribution is spatially constant. We use those criteria to constrain the

decomposition of the raclopride factors. First, striatal and non-striatal volumes of interest (VOIs) were drawn on the factor images, and mean concentrations in both VOIs were obtained, yielding two striatal and two non-striatal values. Then, the striatal factor image was scaled to contain an equivalent mean concentration as the background image factor. The striatal factor (TAC) was scaled by the inverse of this scaling value to retain the correct concentration. Finally, the non-striatal and striatal factor images were summed to produce the free + nonspecific binding factor image (which should be uniform after this process), and the specific-binding factor TAC obtained by subtracting the free + nonspecific (background) factor from the specific + free + nonspecific (striatal) factor. This is illustrated in Fig. 1.

Modeling Dynamic Simultaneous Dual-Tracer PET Studies

The digitized human brain phantom used in our study consisted of 60 brain structures, including the cerebellum, the caudate nucleus, the putamen, the corpus callosum, the hippocampus, and the cortical lobes (frontal, prefrontal, temporal, parietal, occipital). We performed realistic Monte Carlo simulations of random coincidences, pixelated block detectors, light sharing among crystal elements, and dead time in the DST PET/CT in 3D geometry based on the SimSET Monte Carlo simulation software [25, 26]. Activity concentrations in the striata and the rest of the brain were determined based on reported studies with FDG brain metabolism and ^{11}C -raclopride [27–29] and Monte Carlo simulation performed independently. Next, FDG brain metabolism and ^{11}C -raclopride binding studies were generated by combining the individual scans in a population of subjects using five different specific and free + nonspecific D2 TAC that were previously reported in human and nonhuman primate studies [27–29]. Nonuniform attenuation coefficients obtained from the segmented MRI scans were used when propagating photons through the brain and included white matter, gray matter, cerebrospinal fluid, air, etc. The dynamic frames consisted of twenty 2-min and six 10-min acquisitions. Activity distributions of metabolism as well as specific and free + nonspecific D2 concentration were simulated separately, and five dynamic simultaneous dual-tracer studies reconstructed for each of five metabolism and D2 concentration TACs yielding 25 dual-tracer studies. Representative mid-striatal transverse slices of FDG and specific and free + nonspecific ^{11}C -raclopride activity distributions are shown in Fig. 2 (ground truth distributions). Four representative TACs of FDG and ^{11}C -raclopride are shown in Fig. 3 (ground truth TACs). Because simultaneous injection of both tracers is not usually clinically feasible (*i.e.*, FDG requires at least a 20-min uptake period before static imaging is feasible, while ^{11}C -raclopride can be imaged dynamically immediately after injection), the first frame was modeled with FDG alone. At the end of the first frame, ^{11}C -raclopride was injected, and both tracers imaged simultaneously. The timeline of injections and scanning for a brain metabolism/D2 receptor study consists of an injection of FDG followed by a period of uptake of ~20 min and then dynamic imaging starting with FDG alone on board, then injection of ^{11}C and imaging of both tracers for the next 20–100 min. Note that the use of a 20-min FDG lead time is not crucial here—a longer lead time would also be fine because the scanner is not being used during this time. Dynamic dual-tracer studies were generated by the following procedure: low-noise FDG and ^{11}C -raclopride sinograms were generated separately (20 billion decays for each simulation) and scaled at each time frame according to the values in the ground truth TACs. Next, Poisson deviates were generated at each time frame and the resulting noisy sinograms added and reconstructed using ordered subsets expectation maximization (OSEM; four subsets, five iterations) into a single dual-tracer volume. The ground truth specific and free + nonspecific ^{11}C -raclopride and FDG volumes were obtained by reconstructing each tracer separately. Randoms from singles correction was performed in sinogram space. The common attenuation map used to generate both FDG and ^{11}C -raclopride tracers at 511 keV was used in the projector of the OSEM algorithm to compensate for attenuation. In this simulation, we considered only primary photons as we

were interested in estimating the ideal performance that could be achieved in separating the two tracers, assuming perfect scatter compensation. This resulted in a dynamic dual-tracer PET study comprising 27 frames, each $128 \times 128 \times 47$, with a pixel size of $0.27 \times 0.27 \times 0.32$ cm³ that were used as input to the GFADS analysis.

Application of GFADS to simultaneously acquired rhesus monkey brain metabolism/D2 data

The GFADS approach we have developed was applied to simultaneous FDG metabolism/¹¹C-raclopride post-synaptic D2-receptor data acquired from a 6.03-kg adult female rhesus monkey. Trace amounts of FDG and raclopride were injected to ensure that we are imaging under the tracer conditions. Two millicurie of FDG was injected and scanned for 58 min before injection of 4 mCi of ¹¹C-raclopride (specific activity, 1,100 μ Ci/mmol), to ensure the FDG was metabolically trapped in brain tissue. This was used as a validation of our assertion that the FDG is not clearing, but these data were not used in the subsequent GFADS analysis. The data were found to be metabolically trapped (within noise) from 20 min post-injection (Fig. 4), consistent with the offset used in the simulation studies. Dual-isotope dynamic frames were acquired with a Concord microPET P4 scanner (LSO crystal, 2.0 mm transaxial resolution) at Massachusetts General Hospital according to the following protocol: 8×15 , 16×30 , 8×60 , 10×240 s, yielding 58 min of data. Three initial FDG-alone frames of 240-s duration each were included in the final dataset, yielding a total of 70 min of acquisition in a $128 \times 128 \times 63$ -voxel $\times$ 45-frame dataset. A mid-striatal volume was selected for application of GFADS. Projection data were acquired in 3D geometry, corrected for attenuation using a singles-based point source transmission scan and reconstructed with OSEM following exact Fourier rebinning, as is done routinely for the microPET scanner.

Results

Simulated data

Fig. 1 illustrates the concept of generalized factor analysis for simultaneous dual-tracer PET imaging of raclopride. The PET dynamic data are decomposed into factor curves and their corresponding factor images. The factor curves are shown in the graph as: (1) a constant representing metabolic trapping, (2) specific binding kinetics of raclopride, and (3) a curve describing free plus nonspecific binding of raclopride. The factor images are illustrated, showing how they can be combined to represent the local brain concentration of raclopride.

Fig. 2 shows an example drawn from one of the simulation studies. Shown are data on one slice: three images representing “ground truth” and the three-factor images determined by GFADS. The three-factor images correspond to FDG uptake as well as specifically bound and free + nonspecific ¹¹C-raclopride uptake. Fig. 3 shows the correspondence between factor curves (denoted by symbols) and ground truth (denoted by solid lines) for four representative simulations. In most cases, GFADS and ground truth TACs are in close agreement. Analyses show that the errors are less than 7.3 ± 1.3 % for FDG, striatal, and free + nonspecific D2 factors. The ratio of FDG activity concentration in the temporal cortex to that in the ventricle in the reconstructed ground truth image (Fig. 2) was 1.86 compared to 1.85 in the corresponding GFADS factor image. The thalamus-to-ventricle FDG activity ratio was 1.78 in the ground truth FDG activity image compared to 1.77 in the corresponding GFADS factor image. The error in estimation of the ¹¹C-raclopride D2 striatal binding when using GFADS compared to the ground truth image was 5.9 ± 3.6 %. Furthermore, the comparison of the TACs corresponding to the total activity computed from the ground truth or estimated from GFADS shows good agreement between the GFADS

factors and the ground truth TACs for different shapes of TACs corresponding to different realistic uptake patterns of ^{11}C -raclopride in humans and primates.

Rhesus monkey acquisition

A mid-striatal volume was chosen as input to the GFADS method to ensure that specific binding was well represented. GFADS was applied to the entire 128×128 matrix of the mid-striatal volume. We verified that FDG was decreasing exponentially, as predicted by radioactive decay. For this experiment, we contrived the data acquisition protocol to provide three frames containing only FDG. Normalized factor curves (time activity curves) are displayed in Fig. 5, including the first three measured points from the FDG early frames. There was significantly greater variability in the activity estimates of the ground truth FDG obtained directly from the three frames (29 %) as compared to the variability associated with the GFADS FDG factor estimate (14 %). The corresponding mid-striatal factor images are displayed in Fig. 6, and include the combined factors for ^{11}C free + nonspecific binding. The TACs represent the average time activity in a region that samples one side of the striatum. We evaluated our GFADS approach by calculating the error over a striatal VOI between the reconstructed and ground truth FDG frames. Table 1 shows the recovered FDG activity concentrations in a region that samples one side of the striatum and compares them to the original data. The quantitation of FDG activity concentration yielded a bias less than 6 % with respect to the data values estimated when FDG only is on board. The noise in the data can account for this discrepancy as the GFADS algorithm fits the FDG to a perfect decay curve. Furthermore, we compared the total activity estimated with GFADS to that measured from the data in a volume of interest, and our results show very good agreement between the two curves, although the data measured from the volume of interest were much less robust to noise than GFADS.

Discussion

We have presented an algorithm that successfully separates the two near-simultaneously acquired PET radiotracers. Although the determination of the FDG factor could be done with the initial FDG-alone frames and our assumption of metabolic trapping, factor analysis yields a low noise estimate of the FDG TAC as compared to an ROI-based estimation by using the entire dataset to constrain the solution [16]. This is also true for other TAC using ROI as compared to GFADS factor as seen in Fig. 5. We have demonstrated successful results with both simulated human and acquired primate data. In simulated data, GFADS yielded accurate estimates of FDG and ^{11}C -striata and free + nonspecific time activity curves. In primate data, the FDG and total (FDG + ^{11}C -raclopride) activities estimated with GFADS were in good agreement with the activities measured from regions of interest although were much more robust to noise due to the fact that factors are estimated over the entire factor image as opposed to a small region of interest. This result is consistent with our previous finding comparing TAC estimated with GFADS as compared to VOI [16].

Our GFADS algorithm uses a combination of temporal and spatial differences between the tracers to separate the signals. The crucial elements for success of the method are (1) a small offset of scanning times and (2) major difference in kinetic signatures of the two tracers. The algorithm cannot produce a unique solution in its current form if either of these two conditions is violated. If the first tracer is not trapped, then equivalent constraints on the shape of one of the TACs are required. Factor analysis is well suited to this problem because it uses all of the information available in the dynamic series and produces physiologically relevant results when physiological constraints are used. Dual-tracer brain imaging, where one tracer maps a dopamine transporter or receptor function and the other tracer maps perfusion or metabolism, is an ideal application for this algorithm. Separation of signals from simultaneous dual-tracer PET is, in general, a degenerate problem: without the addition

of a priori information about the tracers, it is impossible to distinguish the contribution from each tracer to the overall signal. There must be adequate prior information to provide a unique solution, or the technique is of no practical use. It is important to note that a unique decomposition of the second tracer studies into constituent factors is not necessary. The only requirement is that the sum of the factors, as indicated in Eq. (1), yields a good estimate of the second tracer. In the case of the FDG and raclopride examples presented herein, the second and third factors must sum to yield an estimate of the raclopride curve that would have been measured if a separate experiment had been conducted.

Previous attempts at dual-tracer PET have used substantial injection time offsets for the two tracers (*e.g.*, Koeppe *et al.* [2] found a 20-min offset was optimal for their study; Black *et al.* [8] used 10 min for their dog study). Their approach has the advantages of reduced overall imaging time on the scanner and good characterization of one tracer uncontaminated, but still requires additional imaging time that would preferably be minimized and has the potential to introduce physiological changes and subject motion between the two scans. Our technique requires injection time offset to allow for the distribution of the metabolism tracer, but this is time taken before scanning, when the PET scanner can be used for other patients. Only a few initial frames (~1–2 min in our cases) are required before injection of the second radio tracer. This substantially reduces the scanning time required. The modulated injection method of Converse *et al.* [3] is well suited to a factor analysis approach. They used a region of interest and allowed the fallypride to reach a point where it had little time variability before injection of fluoromethane. Factor analysis could separate the signals well by using the multiple fluoromethane injections to characterize its distribution on top of the slowly varying fallypride signal.

Factor analysis attempts to fit a fixed and predefined number of factors to a dataset. Assuming the number of factors is chosen adequately, this reduces the degrees of freedom in the system to a manageable level, which can then be optimized by a least squares approach. If the factors and factor images are distinct (different temporal and spatial shapes), the algorithm is able to successfully solve for them. If the factor images are identical, there is more degeneracy in the problem and the solution will be non-unique. Constraining the perfusion or metabolism factor with the initial frames defines this factor and allows a unique solution to be found. Noise in the study will also affect the accuracy of our results: if the initial frames are noisy, there is uncertainty in the metabolism factor and factor image, and this introduces an error in the estimation of the other factors and images. However, our generalized factor analysis approach is significantly more robust to noise than a region of interest VOI-based approach as the latter uses a limited number of voxels to determine the time activity curves whereas GFADS uses the entire dynamic activity distribution for that end. For each application, the number of initial frames (and the length of time for each) can be optimized to ensure an adequate signal without significantly extending the scanning time. Further research is needed to provide a full description of the error propagation and temporal correlations imposed by constraining the GFADS solution to be unique.

This algorithm could be applied to any dual perfusion-metabolism/dopamine-neuroreceptor or transporter study, the results of which are useful for discrimination of brain disorders. It may also be useful in oncology applications where the specific, local tumor uptake has different characteristics to the free + nonspecific, background uptake. In this application, tumor metabolism can again be imaged so long as FDG kinetics are prolonged, while the second tracer (such as a hypoxia or proliferation agent) will yield spatially distinct specific and free + nonspecific binding factors.

Conclusion

We have provided a general theoretical framework for effecting dual-tracer PET, using factor analysis. We have modified and extended FADS for semi-simultaneous dual-tracer PET to use spatial differences between different physiologically relevant regions and tested it in the case of metabolism (FDG) and D2 (^{11}C -raclopride) imaging in the brain. Our results show that GFADS yielded estimates of the ground truth time activity curves of both tracers within 8 %. Specific binding and relative activity ratios were estimated within 6 % as compared to the ground truth ratios. When applied to rhesus monkey brain data with simultaneous FDG and ^{11}C -raclopride, activity in the initial FDG time frames was reproduced with an accuracy of better than 10 %. The main limitation on precision is due to the requirement that FDG be spatially and metabolically trapped for the duration of the scan session.

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Fig. 1.

Estimation of specific and free + nonspecific ^{11}C -raclopride. (*Left*) Time activity curves are calculated by subtraction of the (free + nonspecific) factor from the total brain factor after they have been scaled such that the factor images have the same mean values. (*Right*) (free + nonspecific) factor image is calculated by adding the spatially opposed factor images after they have been scaled such that their addition produces a uniform image.

Fig. 2.
Estimated and ground truth activity distributions.

Fig. 3.
Ground truth time activity curves and corresponding factors estimated with GFADS in four different simulated dual-tracer ^{11}C raclopride/FDG PET studies.

Fig. 4. Rhesus monkey striatal VOI time activity curve for an FDG-alone study, demonstrating metabolic trapping kinetics from ~20 min post-injection.

Fig. 5. Resultant time activity factors for FDG and specifically and free + nonspecifically bound ^{11}C -raclopride in a rhesus monkey study. Results were obtained by applying GFADS to a mid-striatal brain volume. Ground truth FDG activity is also shown for the initial three time frames.

Fig. 6. Factor images from application of GFADS to a mid-striatal, whole-brain slice of a dual-tracer rhesus monkey study. (*Left to right*) Ground truth FDG image (data), computed as the average of the initial three time frames; GFADS FDG image, demonstrating the same features as the ground truth image; GFADS specifically bound ^{11}C -raclopride factor; derived free + nonspecifically bound GFADS factor image.

Table 1

Results of quantitation of FDG activity concentration in the striata compared with data from the initial three time frames

Time frame	Activity concentration (data)	Activity concentration (results)	Difference (%)
1	0.205	0.213	3.8
2	0.214	0.208	-3.1
3	0.215	0.202	-5.9