Improving PET Image Quality and Quantification by Using Motion Correction, Parametric Imaging and MAP Reconstruction

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Title: Improving PET Image Quality and Quantification by Using Motion Correction, Parametric Imaging and MAP Reconstruction

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1. Background

Positron emission tomography (PET) plays an important role in brain imaging as PET images provide quantitative measurements of uptake of a radiopharmaceutical. Important *in vivo* physiological measurements pertinent to cognitive impairment, such as metabolic rate of glucose and deposition of amyloid plaques and neurofibrillary tangles, can be measured using ^{18}F-FDG, ^{11}C-PiB and ^{18}F-AV1451 PET imaging, respectively.

The accuracy of these quantitative measurements depends on factors such as spatial resolution and attenuation correction, and it also depends on patient compliance. Patient motion during a PET brain study will degrade image quality and reduce the accuracy of quantitative measurements of radiopharmaceutical uptake in regions of the brain. It is hypothesized that motion correction will improve the quantitative accuracy of PET brain studies.

The accuracy of quantitative measurements also depends on the type of data acquisition and the method used to analyze the data. Static PET images can be used to quantify uptake at a single point in time whereas dynamic images and compartmental modeling can be used to create parametric images that represent kinetic parameters such as blood flow, blood volume, receptor density or metabolic rates. Parametric imaging has remained a research tool as the scans are lengthy in duration and the analysis is involved. Static imaging is more practical in terms of patient throughput and image interpretation but it can overestimate uptake of a radiopharmaceutical. Therefore, there is renewed interest in applying dynamic imaging and compartmental modeling in clinical studies. It is hypothesized that dynamic imaging in clinical studies will assist in the diagnosis of tumors with low uptake or tumors in high background regions.

PET image quality and quantitative measurements are also influenced by the reconstruction algorithm used to create the images. Statistical iterative reconstruction (IR) algorithms that incorporate corrections for attenuation, scatter and spatial resolution have been shown to improve image quality and quantitative measurements over analytic algorithms such as filtered backprojection. Incorporating time-of-flight information into an IR algorithm further improves the signal to noise ratio of the reconstructed images. Statistical IR reconstruction algorithms need to run through a large number of iterations in order to achieve convergence and provide accurate quantitative information. Unfortunately, the noise in increases as the number of iterations increases which creates images of poor diagnostic quality. Maximum *a posterior* (MAP) or regularized reconstruction algorithms have been developed to suppress noise. These algorithms use penalty functions to model *a prior* information about the reconstructed image and a weighting parameter that controls the influence of the prior constraint and thus the amount of image smoothing, edge preservation and low contrast detail. It has been shown that regularized reconstruction algorithms increase lesion conspicuity and improve the accuracy of quantitative PET measurements.

Motion Correction

Patient motion during a PET brain study will degrade image quality and reduce the accuracy of quantitative measurements of radiopharmaceutical uptake in regions of the brain. In addition, patient motion has a more pronounced effect on uptake measurements as the spatial resolution of PET systems improves and regions of interest become smaller; both issues are important in PET brain imaging. PET brain imaging of subjects with dementia is vulnerable to motion as the scans are long in duration and the subjects are prone involuntary motion. Head restraints are used reduce the amount of motion but do not eliminate it. For example, slow changes in head position and orientation can occur as patients gradually relax as the scan progresses.

Typically, a PET brain study is acquired as a dynamic scan that is comprised of individual frames. A technologist will subjectively assess for patient motion by visual comparison of the position and orientation of the head in each frame. If it is deemed that the patient remained still then all frames will be summed together to create a static image. However, if it is deemed that a patient moved then the frames that contain motion will be discarded and not used to create the summed static image.

Ideally the motion correction process should be fully-automated and objective and any frames that contain motion would be realigned and summed with the non-motion frames instead of being discarded. Moreover, proper motion correction should also realign the PET images to the CT images in addition to realigning the individual frames of the dynamic PET images. This will ensure accurate quantification of uptake measurements as the CT images are used to correct the PET data for attenuation.

Motion can be estimated by constantly monitoring the head position and orientation during the PET scan through the use of external-tracking devices or data-driven methods. The latter approach uses the raw PET data itself to measure the motion. Data-driven methods are attractive as no external equipment is necessary (less setup time, not cumbersome to use) and motion compensation can be applied retrospectively. The effectiveness of data driven motion correction will depend on the temporal sampling of the raw data, the statistical quality of the raw data and whether the radiopharmaceutical distribution changes during a study. In this research study the Siemens data-driven motion correction algorithm will be evaluated in patients undergoing PET brain scans using radiopharmaceuticals ^{18}F-FDG, ^{11}C-PiB or ^{18}F-AV1451.

Parametric Imaging

In PET imaging various quantitative physiological *in vivo* measurements can be made depending on the purpose of the study, the radiopharmaceutical and acquisition technique employed. A quantitative measurement can be made from a single time frame or static image in which the patient is scanned at a specific time after radiopharmaceutical administration; one such measure is the standard uptake value, SUV, which represents the amount of uptake of radiopharmaceutical normalized to the amount of radiopharmaceutical administered and the weight of the patient. Alternatively, quantitative measurements can be made from a dynamic scan in which the uptake of a radiopharmaceutical is measured over time and kinetic parameters such as blood flow, blood volume, receptor density and metabolic rates are subsequently derived from compartmental modeling. (Note that the dynamic scan used in the context of motion correction is a coarse temporal sample scan used to assess patient position and not model radiopharmaceutical kinetics). Compartmental modeling requires dynamic PET scans of long duration: the scan starts at administration of the radiopharmaceutical and continues through the wash-in and wash-out phases of the radiopharmaceutical. Compartmental modeling generally requires an input function that represents the concentration of radiopharmaceutical in the arterial blood supplying the organ of interest. Input functions can be obtained invasively from arterial blood samples or alternatively an image-derived input function is obtained either from the left ventricle, aorta or carotid artery. When the compartmental model is applied, voxel-by-voxel, to every voxel in a 3-D PET volume, parametric images of the resulting kinetic parameters are obtained. For example, the metabolic rate of glucose can be measured with ^{18}F-FDG and the parametric image shows the ^{18}F-FDG metabolic rate in each voxel, rather than uptake.

Computation of kinetic parameters for models that use two tissue compartments (metabolized and unmetabolized radiopharmaceutical) is time consuming as non-linear data fitting procedures are required to solve coupled differential equations. The analysis can be accelerated by linearization, whereby linear least squares fitting procedures are used for the parameter estimation. Patlak and Logan analyses are two 'linearized' methods for estimating kinetic parameters for radiopharmaceuticals that are irreversibly and reversibly bound in the metabolized compartment, respectively. Patlak analysis is used for measurement of metabolic glucose rate using dynamic ^{18}F-FDG scans whereas Logan analysis is used to quantify the distribution volume and binding potential of ^{18}F -AV1451. Static imaging is preferred over dynamic imaging for clinical imaging because the acquisition is quick and SUV analysis is simple. However, static imaging and SUV analysis is a surrogate for glucose metabolism as it measures the total radiopharmaceutical uptake and does not differentiate between metabolized and non-metabolized ^{18}F-FDG in the

blood and intracellular spaces (ie specific or non-specific uptake) or the plasma dynamics. Patlak analysis of ^{18}F-FDG measures the metabolized ^{18}F-FDG and, unlike SUV analysis, is independent of the scan time after administration of ^{18}F-FDG.

There is renewed interest in parametric imaging in clinical oncologic studies involving tumors with low uptake or tumors in high background regions. Siemens have implemented an automated workflow for parametric imaging on the Biograph Vision 600 PET/CT system called FlowMotion Multiparametric PET Suite. Patlak analysis is the only analysis method currently available in the parametric imaging package. The fully-automated acquisition protocol proceeds as follows. First the system will obtain an input function by acquiring dynamic images of the left ventricle as the radiopharmaceutical is administered. Next eighteen dynamic images are acquired by automatically shuttling the imaging table and scanning the patient multiple times. For clinical oncologic studies this second phase is a series of whole body acquisitions while for a brain studies the second phase is a series of brain acquisitions, and for all studies the second phase includes imaging the left ventricle for the input function. The entire process requires minimal operator intervention once the scan ranges are prescribed. The output of the workflow are parametric images generated from Patlak analysis. Alternatively, for radiopharmaceuticals that require Logan analysis, the raw dynamic images can be exported to off-line compartmental modeling software. In this research project the data acquisition and image processing workflow for quantitative parametric analysis of brain and whole body scans will be assessed. Further, the development of in-line Logan parametric analysis will be conducted using patient data.

2. Methods

2.1. Subject Enrollment

Inclusion Criteria

1. 18 years of age or older
2. Subjects who are able and willing to sign the informed consent
3. Subjects who are able to follow verbal commands
4. A negative urine pregnancy test within 48 hours prior to PET imaging procedures in females of childbearing potential
5. Subjects who are scheduled for a PET/CT study under Mayo Clinic Rochester IRB research protocol 08-005553 (Aim 1 cohort only)
6. A positive ^{18}F-FDG oncology PET/CT exam in the last two months (Aim 2 cohort only)

Exclusion Criteria

1. Patients who are unable to lay still for an additional 15 minutes (for Aim 1 cohort)
2. Patients who are unable to lay still for up to 90 min for ^{18}F-FDG scans or up to 100 min for ^{18}F-AV1451 scans (for Aim 2 cohort)
3. Patients who cannot follow the prep instructions

2.2. Aim 1: Motion Correction Cohort

2.2.1. Subject Enrollment

Aim 1 involves the prospective data collection of subjects who are already enrolled in Mayo Clinic Rochester research study [redacted] (PI: Dr [redacted]) and are scheduled to be scanned on the Siemens Biograph Vision 600 PET/CT system (hereafter referred to as the V600-R1) in the PET/CT Molecular Imaging Research Center on Charlton 6 of Mayo Clinic Rochester. To be clear, this is a separate research study in which the [redacted] subjects will be enrolled. In the interest of time subjects will be recruited for this research study and will provide written consent prior to their [redacted] study.

2.2.2. Number of Subjects

We plan to successfully scan 30 subjects for Aim 1. Subjects enrolled in research study [redacted] are administered one of the radiopharmaceuticals ^{18}F-FDG, ^{11}C-PiB or ^{18}F-AV1451 per exam. For this research study we will successfully scan 10 subjects with one of the radiopharmaceuticals for a total of 30 scans in 30 subjects. The purpose of this pilot research protocol is to evaluate the effectiveness of motion correction and therefore the sample size is not designed to measure a statistically significant difference between subjects scanned with and without motion.

It is important to note that the subjects will not receive a second ^{18}F-FDG, ^{11}C-PiB or ^{18}F-AV1451 radiopharmaceutical injection for this research study – the residual radioactivity from their [redacted] study is adequate.

2.2.3. Subject Scanning

Upon completion of their [redacted] study the subjects will be asked if they would like to continue with this research study. If the subjects agree they will remain in Charlton 6. They will be given the option of remaining on the scanning table or having a short break. The data collection for this research study will commence immediately thereafter.

A new exam will be created on the V600-R1 under which the enrolled subjects will be scanned; as mentioned this new exam is a stand-alone, separate exam from the [redacted] study. The subject will be positioned on the imaging table with their head in a head-holder and with their arms by their sides. The helical CT-portion of the PET/CT scan, used for PET attenuation correction (ie a 'CTAC' scan), will then be acquired. Next a 10 min PET scan will be acquired. During the first 3 to 5 min of the PET scan the subjects will remain motionless; this will serve as a baseline reference scan. For the remainder of the scan the subjects will be instructed to move. The motions will include slow oscillating rotations, rapid rotations and translations of various magnitudes. The PET system acquires data in list mode; this allows the data to be retrospectively binned into scans with variable start times and durations.

All PET and CT data acquired under this research study will be transferred to a private PET research partition within PACS. In addition, all PET and CT data will be de-identified and renamed on the PET/CT scanner console. This process creates a copy of the study with all identifiers removed and replaces the subject name and ID with a numerical code. PET and CT data from the de-identified study will be sent to a separate workstation for off-line image reconstruction using Siemens E7 Reconstruction Tool and analysis.

2.2.4. Image analysis

The motion-corrected reconstructed images acquired when the subject was moving will be quantitatively compared to the baseline reference reconstructed images acquired when the subject was instructed to remain still. Metrics such as radiopharmaceutical uptake, contrast to noise ratio and effective spatial resolution will measured. Qualitative assessment of image quality and presence of artifacts will be performed by Dr [redacted].

2.3. Aim 2: Parametric Imaging Cohort

2.3.1. Subject Enrollment

Aim 2 involves the prospective data collection of subjects undergoing brain or whole body oncologic PET/CT scans on the V600-R1.

2.3.2. Number of Subjects

We plan to successfully scan up to 30 subjects for a total of up to 35 PET/CT scans. Specifically, we plan to collect up to ten ^{18}F-FDG brain scans, up to ten ^{18}F-FDG whole body oncologic scans and up to ten ^{18}F-AV1451 brain scans. The research studies will be performed less than two months from a positive clinical finding. Up to five of the subjects in the ^{18}F-FDG whole body oncologic cohort will undergo a repeat study within a week of their initial research study.

The purpose of this pilot research protocol is to evaluate the data acquisition and image processing workflow and therefore the sample size is not designed to measure a statistically significant difference between subjects.

2.3.3. Subject Preparation

Patients will be given prep guidelines to follow prior to reporting to Desk 6B in the PET/CT Molecular Imaging Research Center on Charlton 6 of Mayo Clinic Rochester. The subject will be positioned on the imaging table with their head in a head-holder and with their arms by their sides. A CTAC scan, used for PET attenuation correction, will be acquired. Immediately following the start of the PET scan, a radiopharmaceutical dose will be administered intravenously using an infusion pump followed by a saline flush. The administered radiopharmaceutical radioactivity will be 8 ± 10% mCi ^{18}F-FDG or 9 to 11 mCi ^{18}F-AV1451 for brain scans or 10 ± 10% mCi ^{18}F-FDG for oncology scans. The first 6 min of the PET scan consists of a dynamic acquisition over the heart for measurement of the input function. This is followed by up to 20 brain plus heart passes for patients receiving a parametric brain scan or up to 20 passes from orbits to thighs (which includes the heart) for patients receiving a parametric whole body scan. The total PET scan duration will be up to 90 min for ^{18}F-FDG scans and up to 100 min for ^{18}F-AV1451 scans.

As described in Aim 1, all PET and CT data acquired under this research study will be transferred to a private PET research partition within PACS. In addition, all PET and CT data will be de-identified and renamed on the PET/CT scanner console. This process creates a copy of the study with all identifiers removed and replaces the subject name and ID with a numerical code. PET and CT data from the de-identified study will be sent to a separate workstation for off-line analysis.

2.3.4. Feedback Questionnaire

After completion of a patient study the PET technologist will complete a questionnaire that assesses the data acquisition workflow. Topics such as ease of prescribing the PET/CT exam, starting and monitoring the scanning, reviewing images and overall process of acquiring the scans will be rated on a scale of 1 to 5, with 1 being challenging and 5 being easy.

2.3.5. Image analysis

The metabolic rate of ^{18}F-FDG shown in the parametric images will be compared to SUV from static images (ie a single scan from one of the up to 20 passes). Also, the parametric images created with the measured input function will be compared to parametric images created with a generic, population-based input function. The dynamic series will be analyzed using dedicated compartmental modeling software (PMOD ver 3.5; PMOD Technologies, Zurich); the metabolic rate of ^{18}F-FDG from the parametric images will be compared to the metabolic rate computed using Patlak and two compartment models in PMOD. Logan analysis in PMOD will be used to compute the distribution volume and binding potential of the ^{18}F-AV1451 dynamic scans. In addition, the motion correction software developed in Aim 1 will be used for the parametric brain images.

2.4. Aim 3: MAP Reconstruction Cohort

This aim does not require the prospective collection of patient studies. A total of up to 30 whole body and brain PET studies will be evaluated retrospectively. PET raw data acquired as part of any research study on the V600-R1 system can be used; this includes studies acquired for Aim 2 and for other whole body research studies acquired on the V600-R1. In order to increase the number of studies, de-identified clinical patient studies acquired on the Siemens Biograph Vision 600 PET/CT system installed in Nuclear Medicine on Charlton 1 (to be installed January 2020) can also be used.

As described in Aim 1, PET and CT data will be de-identified and renamed on the PET/CT scanner console. This process creates a copy of the study with all identifiers removed and replaces the subject name and ID with a numerical code. PET and CT data from the de-identified study will be sent to a separate workstation for off-line MAP reconstruction using Siemens E7 Reconstruction Tool and analysis.

2.4.1. Image Review

An appropriate image review such as a single-reader, visual, blinded image quality assessment (or other methods to be identified upon consultation with Siemens) will be performed. Results of MAP reconstruction analysis will not be reported or entered into the patient's clinical record.

3. Data Archival

All subject data will be archived on an external password protected and encrypted hard drive. All reconstructed image data will be transferred to a DICOM archive system for long-term storage. De-identified data will also be transferred to Siemens Healthineers via encrypted data transmission. As required by HIPAA and described above, the study will be de-identified prior to secure transmission to Siemens.

4. Risks and Benefits

4.1. Reasonable Foreseeable Risks or Discomforts to the Patients

4.1.1. *IV:* The risks of IV placement in Aim 2 may include: discomfort at the site of puncture, possible bruising and swelling around the puncture site, infection (rarely), and (uncommonly) faintness from the procedure.

4.1.2. *Fear of Confined Spaces:* Some participants may experience anxiety in the PET/CT scanner; participants will be monitored throughout the scan by the imaging technologist, and scans will be stopped immediately for any participant who is unable or unwilling to continue the procedure.

4.1.3. *Radiation Risks:* The PET/CT procedure of Aim one involves 1 CTAC scan (low-dose CT scans for PET attenuation correction) of the head. A single PET/CT procedure in Aim 2 involves one CTAC scan of the head plus one CT scan of the chest or one whole body CT scan, and it also involves one administration of either ^{18}F-FDG or ^{18}F-AV1451.

4.1.4. *Risk of Disclosure of Protected Health Information:* Safeguards against the risk of disclosing protected health information (PHI) include ensuring all data that contain PHI remain within Mayo Clinic. The imaging data will be stripped of all identifying information and assigned a numerical code before the images are transferred from the enterprise. Only de-identified information will be shared with the Siemens Healthineers. Patient consent forms will be stored in locked files in the office of the study

coordinator and/or principal investigator, and no identifying information will be available to personnel outside of the coordinator(s) and institutional investigators.

4.1.5. *Potential Benefits to Society and Participants (not including compensation):* Participants in the study will not receive any direct medical benefit.

4.1.6. *Costs to Participants from Participating in Research:* Subjects will not incur any costs by participating in this research study.

4.2. *Compensation to the Participants:* Subjects enrolled in Aims 1 will be remunerated $[redacted] for their participation in the study. Subjects enrolled in Aim 2 will be remunerated $[redacted]; those subjects who undergo a repeat study will receive an additional $[redacted].

5. Data Safety Monitoring Board (DSMB)

A DSBM is not required for this protocol. The risk to the subjects in Aim 1 is from the dose of the non-diagnostic CTAC scan, which can be considered low. The risk to the subjects in Aim 2 is from the dose of the radiopharmaceutical and non-diagnostic CTAC scan. Further, this protocol does not involve a large number of subjects, multiple study sites, or highly toxic therapies or dangerous procedures.