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Spatio-temporal pharmacokinetic model based registration of 4D PET neuroimaging data

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ABSTRACT

In dynamic positron emission tomography (PET) neuroimaging studies, where scan durations often exceed 1 h, registration of motion-corrupted dynamic PET images is necessary in order to maintain the integrity of the physiological, pharmacological, or biochemical information derived from the tracer kinetic analysis of the scan. In this work, we incorporate a pharmacokinetic model, which is traditionally used to analyse PET data following any registration, into the registration process itself in order to allow for a groupwise registration of the temporal time frames. The new method is shown to achieve smaller registration errors and improved kinetic parameter estimates on validation data sets when compared with image similarity based registration approaches. When applied to measured clinical data from 10 healthy subjects scanned with [^{11}C]-(+)-PHNO (a dopamine D3/D2 receptor tracer), it reduces the intra-class variability on the receptor binding outcome measure, further supporting the improvements in registration accuracy. Our method incorporates a generic tracer kinetic model which makes it applicable to different PET radiotracers to remove motion artefacts and increase the integrity of dynamic PET studies.

Introduction

Over the last three decades, the development of positron emission tomography (PET) has provided neuroscientists with a unique tool to investigate the neurochemistry of the human brain in vivo. By labelling the molecule of interest with a radioactive nuclide, a PET scanner is able to record the changing spatial distribution of the radiotracer over a period of time following its intravenous injection into the subject. Each radiotracer has its own distinct behaviour in vivo, and the ever increasing library of these tracers allows for imaging of a range of biochemical, physiological and pharmacological processes. Quantitative analysis of the underlying biological process of interest from such rich 4D spatio-temporal data sets requires the application of an appropriate tracer pharmacokinetic model to either the regional or voxel based time-activity curves (TACs) toderive model parameters of interest. The integrity and validity of analyses derived from a dynamic PET scan is therefore dependent on the accuracy of the TAC data, which can be corrupted by subject motion that alters the voxel-to-tissue mapping. The scan duration is usually 1 or 2 h long, during which some subject motion is inevitable. Therefore, correction for inter-frame subject motion is of fundamental importance in dynamic PET pharmacokinetic analysis. Fig. 1 illustrates an example for dynamic brain PET data obtained with [^{11}C]-(+)-PHNO, a dopamine D3/D2 receptor imaging ligand, from two different subjects with differing levels of motion artefacts and the impact on the TACs derived from anatomical regions of interest.

There are various ways to conduct motion correction of dynamic PET scans. During the scan, the subject's movement can be recorded with external monitoring systems, either with fiducial markers or camera based tracking (Bloomfield et al., 2003; Buehler et al., 2004; Koshino et al., 2010; Montgomery et al., 2006; Raghunath et al., 2009; Rahmim et al., 2007; Zhou et al., 2009). These methods require extra equipment with calibration, and are limited in application due to either discomfort or the unreliable estimation of motion. Alternatively, there exist image-based methods for correcting for motion that employ image registration techniques to establish the spatial correspondence across the time frames. Image-based registration of temporal frames is usually based solely on spatial voxel-intensity based similarity, either to a static magnetic resonance (MR) image of the subject (Searle et al., 2010) (widely applied but not always available), a specific dynamic PET reference frame (e.g. the maximum or time-averaged intensity frame) (Costes et al., 2009; Keller et al., 2012; Wardak et al., 2010) or the neighbouring frames which are subject to low signal-to-noise ratio (SNR). However, these methods do not optimally account for the changing spatial

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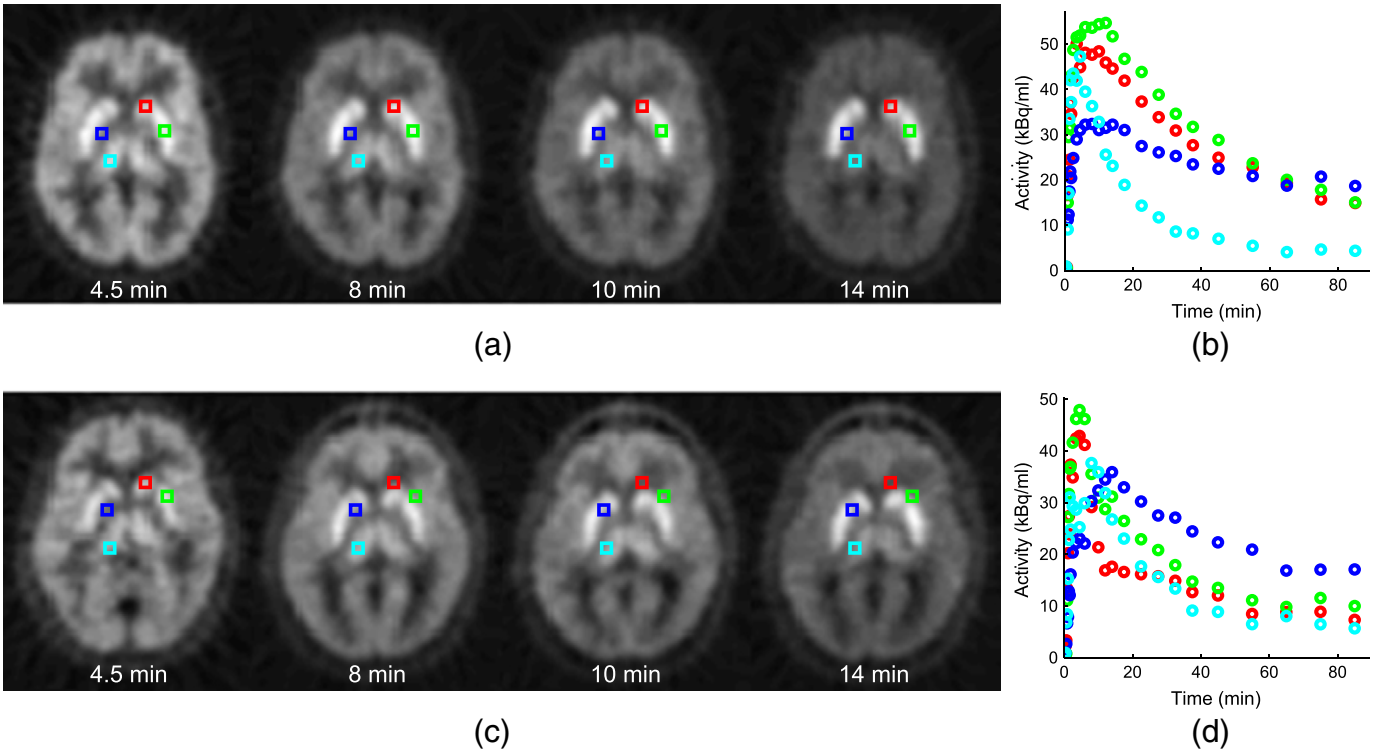

Fig. 1. Subset of [^{11}C]-(+)-PHNO PET temporal frames (times are mid-frame times) from an axial slice, for a subject with little motion (a) and a subject with significant motion (c), with voxels from various functional structures depicted in colours which are spatially fixed to demonstrate the displacement caused by motion. TACs from these voxels are shown in corresponding colours for both subjects in (b) and (d) respectively. The subject motion gives rise to altered functional TACs particularly in (d).

distribution over time which can lead to mis-alignments particularly for images with low uptake. To address such registration problems in dynamic imaging, tracer pharmacokinetics have been incorporated into the registration process for dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) and dynamic contrast enhanced-computed tomography (DCE-CT) to account for the signal change due to the contrast agent (Bhushan et al., 2011; Buonaccorsi et al., 2007). In DCE-MRI, the pharmacokinetic models describe the diffusion of the contrast agent from the blood pool into the extracellular space. The most widely used pharmacokinetic models, namely the Tofts (extended Tofts), Kety and Brix models, are based on a configuration of two-tissue compartments (2TC) (Tofts et al., 1999). In dynamic PET, however, the tracer kinetics may be more complex (depending on the tracer) and may vary across different regions within the image, and thus just selecting a single fixed model may not be appropriate (Bentourkia and Zaidi, 2007; Schmidt and Turkheimer, 2002; Watabe et al., 2006).

In this work, we present a registration method to correct for the subject motion in dynamic PET imaging which incorporates a data-driven tracer pharmacokinetic model. We first introduce the general tracer kinetic model that is used as the temporal model in the overall spatio-temporal registration scheme. We formulate the spatio-temporal registration as a maximum likelihood problem, and present a complete description of an efficient solution for the non-negative least squares problem and a robust registration approach, based on our preliminary work in Jiao et al. (2012a,b). The method is first validated using a software phantom to determine the impact on recovery of the true tissue time activity curves and the estimated tracer kinetic model parameters of interest on segmented brain structures. The performance testing was conducted at a range of motion levels and noise levels. The performance is compared with a conventional registration method based solely on an image similarity metric. Finally, we also assess the impact of the spatio-temporal based registration method on measured human brain [^{11}C]-(+)-PHNO data sets from 10 healthy subjects. Its performance on reducing intra-class variation by removing variability caused by subject motion is shown to be better than the conventional method.

Methods

General tracer kinetic model

To incorporate tracer kinetic information into the registration process, it is necessary to specify a tracer kinetic model that is able to describe the behaviour of the tracer data. This kinetic model should be able to describe differing tracer behaviour across all voxels in the image and ideally generalise to different radiotracers. In addition, the model should be robust to noise and computationally efficient as the kinetic information will be calculated at each step in which the cost function is evaluated.

We chose to use spectral analysis (Cunningham and Jones, 1993), which is a data-driven kinetic modelling technique that characterises the target tissue as a nonnegative sum of exponentials convolved with the plasma input. Contrary to a model-driven technique that would require the a priori specification of one particular compartmental structure, spectral analysis is capable of describing nearly all linear compartmental systems (Schmidt, 1999) and therefore is ideal for our spatio-temporal model based registration approach. We introduce an iterative solution to the non-negative least squares problem to increase the calculation efficiency over the traditional algorithm proposed by Lawson and Hanson based on double loops (one loop nested) (Lawson and Hanson, 1995).

System impulse response function (IRF)

The IRF of a plasma input compartmental model (Gunn et al., 2001) is defined as a sum of exponentials as follows:

$$\mathrm{IRF} = \sum_{i=1}^{N} \phi_i e^{-\theta_i t} \tag{1}$$