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Multi-resolution Bayesian regression in PET dynamic studies using wavelets

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In the kinetic analysis of dynamic PET data, one usually posits that the variation of the data through one dimension, time, can be described by a mathematical model encapsulating the relevant physiological features of the radioactive tracer. In this work, we posit that the remaining dimension, space, can also be modeled as a physiological feature, and we introduce this concept into a new computational procedure for the production of parametric maps. An organ and, in the instance considered here, the brain presents similarities in the physiological properties of its elements across scales: computationally, this similarity can be implemented in two stages. Firstly, a multi-scale decomposition of the dynamic frames is created through the wavelet transform. Secondly, kinetic analysis is performed in wavelet space and the kinetic parameters estimated at low resolution are used as *priors* to inform estimates at higher resolutions.

Kinetic analysis in the above scheme is achieved by extension of the Patlak analysis through Bayesian linear regression that retains the simplicity and speed of the original procedure. Application to artificial and real data (FDG and FDOPA) demonstrates the ability of the procedure to reduce remarkably the variance of parametric maps (up to 4-fold reduction) without introducing sizeable bias. Significance of the methodology and extension of the procedure to other data (fMRI) and models are discussed.

Keywords: PET; Kinetic modeling; Wavelets; Bayesian regression; Patlak plot; FDG; FDOPA

Introduction

In positron emission tomography (PET), kinetic models are used to extract quantitative parameters through the mathematical description of the time activity course (TAC) of the radiotracer uptake in the organ of interest. Compartmental models, or derived computational simplifications, are applied to the TACs of anatomical regions of interest (ROIs) or to each pixel of the image sequence, and the model parameters are estimated (Blomqvist, 1984; Mazoyer et al., 1986).

In this context, mathematical models are intended as suitable approximations of the relevant physiological processes. Until now, the considerable literature in the field has developed models for one data dimension only, time, in that there does not seem to be any physiological quality in the remaining dimension, space. Further consideration of the property of a dynamic PET acquisition, however, may tell that this quality indeed exists.

PET is meant for the imaging of living organs (as opposite to inert objects). It is a feature of an organ that the physiological properties of its components at different resolutions share a similarity of some degree. Likewise, we can say that the kinetic parameters of a small area of tissue have a quantitative resemblance to the same parameters when averaged over a larger area inclusive of that region.

We have translated this observation into a novel approach for the generation of parametric maps from PET studies. The idea is to create, firstly, a multi-resolution decomposition of the PET dynamic acquisition. Next, the kinetic parameters are calculated starting at the lowest resolution and then proceeding to the finer scales using the estimates of the lowest resolution as *priors*.

The statistical advantage of this procedure compared to traditional pixel-by-pixel estimation is that the superior quality of the parameter estimates at lower resolutions, where noise is low, can be used to regularize estimates at the noisier levels down to the single pixel resolution. Note that, compared to traditional Bayesian approaches, *prior* information must not be specified in advance but is generated from the data.

The principle of multi-scale self-similarity in physiological processes has been explored before (Bassingthwaighte et al., 1989), particularly in the context of fractal analysis, and recently used in the analysis of PET images (Dimitrakopoulou-Strauss et al., 2001; Kalliokoski et al., 2001; Strauss et al., 2004; Venegas and

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Galletti, 2000) as well as in the analysis of fMRI time-series (Bullmore et al., 2001; Shimizu et al., 2004), but, to our knowledge, it has not been implemented in a computational method for PET.

Previous general Bayesian approaches to kinetic modeling (Sparacino et al., 2000) and more specific attempts in PET (O'Sullivan and Saha, 1999; Turkheimer et al., 2003b; Wilson et al., 1988) have relied on the implementation of physiological constraints on the model parameters and have achieved interesting reduction of variability in parameter estimates.

In this manuscript, we provide a simple but efficient method for the implementation of scale self-similarity through Bayesian linear regression. We describe the details of the methodology and undertake its validation through simulated and real PET data. The focus of the application is the production of parametric maps but, as it will be clear further on, the method has a straightforward extension to TAC obtained from regions of interest.

Theory

Multi-resolution kinetic modeling is achieved through two sequential steps. Firstly, the multi-scale decomposition of PET images is performed by application of the wavelet transform (WT) (Mallat, 1989). Subsequently, parameter estimates obtained at the lowest resolutions are used as *priors* for the following levels through Bayesian statistical modeling (Gelman et al., 1995). Finally, the parametric map in wavelet space is transformed back to produce a parametric map in native image space.

Multi-resolution decomposition in wavelet space

The multi-scale decomposition of PET dynamic images in wavelet space and subsequent application of standard kinetic modeling has been described before (Turkheimer et al., 2000, 2003a), and it will only be summarized here.

Let $\beta(s)$ be the spatial distribution of the parameter of interest, where s indexes space as $s{:}s=(x,y,z)$. $\beta(s)$ is estimated from $V(s,t)$, the time-changing distribution of a suitable radioactive tracer measured with PET. $V(s,t)$ consists of M serial scans $V(s,t_1)$, $V(s,t_2)$, …, $V(s,t_M)$ indexed by the M mid-frame times t_i.

The mathematical relationship between the kinetic of the radiotracer and the parameter is implemented by the operator $\eta(\ )$ so that:

$$\beta(s)=\eta(V(s,t)) \tag{1}$$

where $\eta(\ )$ can be of linear or nonlinear form and is usually derived from a compartmental model.

Let $Y(s,t)=V(s,t)+\varepsilon(s,t)$ be the measured realization of the dynamic sequence V that is corrupted by the noise process ε. Frames $Y(s,t_1)$, $Y(s,t_2)$, …, $Y(s,t_M)$ are images reconstructed from sinograms ideally at their highest resolution. Direct application of model in Eq. (1) to $Y(s,\ t)$ generates the pattern

$$\beta(s)=\eta(Y(s,t))=\eta(V(s,t)+\varepsilon(s,t)). \tag{2a}$$

If $\eta(\ )$ is linear, then Eq. (2a) can be written as:

$$B(s)=\eta(V(s,t))+\eta(\varepsilon(s,t))=\beta(s)+\zeta(s), \tag{2b}$$

and $\zeta(s)$ is the noise of the spatial pattern $B(s)$.

Alternatively, the kinetic operator $\eta(\ )$ can be applied in wavelet space. The discrete wavelet transform (DWT) in 3 dimensions is applied to each frame of the dynamic acquisition $Y(s,t)$ generating an equivalent dynamic sequence in wavelet space $Y^W(w,t)$ where t is again time and w spans the three-dimensional (3D) wavelet space. We define the DWT operator as W and W^{-1} is its inverse. Formally, each frame in wavelet space $Y^W(w,t_i)$ is obtained as:

$$Y^W(W,t_i)=W(Y(s,t_i)). \tag{3}$$

Kinetic analysis is performed in wavelet space as:

$$B^W(W)=\eta\left(Y^W(W,t)\right). \tag{4}$$

The parametric map in wavelet space $B^W(w)$ can then be projected back into native space by application of the inverse DWT. Since the DWT is a linear and orthogonal operator, if $\eta()$ is also linear, then the estimation problem in wavelet space is equivalent to that of image space (Turkheimer et al., 2003a) and:

$$B(s)=W^{-1}\left(B^W(W)\right). \tag{5}$$

There are a number of advantages in performing kinetic modeling in wavelet space, amplification of the signal-to-noise ratio and noise decorrelation being the two most commonly described (Cselenyi et al., 2002; Turkheimer et al., 2000). Here, we take advantage of the multi-resolution property of the decomposition whose elements, the wavelets, can be put in relation through an appropriate model.

Linear regression in wavelet space

In standard practice, the generation of parametric maps in PET relies on some form of linear regression, the two most popular approaches being the Patlak plot for irreversible radiotracers (Gjedde, 1981; Patlak and Blasberg, 1985; Patlak et al., 1983) and the Logan plot for those with reversible kinetic (Logan et al., 1990, 1996), and relation in Eq. (5) is therefore granted. Note, however, that the linearization procedure leading to the regression for the Logan plot introduces distortions in parameter space (Slifstein and Laruelle, 2000). For the purposes of this work, we therefore focused on the Patlak plot for irreversible radiotracers (see Discussion).

After a suitable time post-injection of the radiotracer, the kinetic of an irreversible radiotracer can be approximated by the linear model:

$$C_T(t)\sim bC_p(t)+m\int_t^0 C_p(\tau)d\tau. \tag{6a}$$

In Eq. (6a), $C_T(t)$ is the total tissue radioactivity, $C_p(t)$ is a suitable input function (see the Materials and methods section for details on the implementations for specific radiotracers) and b and m the regression parameters. The following simplification

$$\frac{C_T(t)}{C_p(t)}\sim b+m\frac{\int_t^0 C_p(\tau)d\tau}{C_p(t)} \tag{6b}$$

transforms the estimation problem in the linear regression problem:

$$y_0=X_0\beta_0 \tag{6c}$$

Parameters of the model are the regression coefficients $\beta_0=[b\ m]'$, where $'$ indicates the transpose.

In wavelet space, the regression in Eq. (6c) consists of the $M\times 1$ response variable $Y_0=\frac{y^W(w,t)}{C_p(t)}$, and the $M\times 2$ predictor matrix $X_0=\left[I_{M,1}\ \frac{\int_0^t C_p(\tau)d\tau}{C_p(t)}\right]$, where $I_{M,1}$ is an $M\times 1$ identity vector.