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FDG–PET parametric imaging by total variation minimization

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ABSTRACT

Parametric imaging of the cerebral metabolic rate for glucose (CMRGlc) using [^{18}F]-fluoro deoxyglucose positron emission tomography is considered. Traditional imaging is hindered due to low signal-to-noise ratios at individual voxels. We propose to minimize the total variation of the tracer uptake rates while requiring good fit of traditional Patlak equations. This minimization guarantees spatial homogeneity within brain regions and good distinction between brain regions. Brain phantom simulations demonstrate significant improvement in quality of images by the proposed method as compared to Patlak images with post-filtering using Gaussian or median filters.

1. Introduction

We focus on positron emission tomography (PET) parametric imaging for estimating the cerebral metabolic rate of glucose (CMRGlc) using the [^{18}F]-fluoro deoxyglucose (FDG) tracer. The ability to derive accurate parameters depends upon the quality of data, the quantification method and the numerical algorithm. In this study, we refer to the time activity curve (TAC) from a given tissue location as the *output*, tissue TAC or TTAC, and the TAC from the blood pool (image-derived or arterial blood-sampled) as the *input*, plasma TAC or PTAC. Most existing quantification methods perform well for regions of interest (ROIs), but are not good for voxel level quantification due to the high level of noise. These include graphical methods [20,18], linear least squares, the weighted integration method [3], generalized linear least squares [6,5], nonlinear least squares (NLS) and weighted NLS.

All the algorithms listed above perform the quantification at each voxel location separately; they do not consider the kinetic similarities among neighboring voxels within functionally defined regions. Thus, voxel-by-voxel variation in a functionally homogeneous region may be large because of noise in the data. But, by incorporating the spatial constraint that parameters in a functionally homogeneous region should be similar, in any of the above methods, the quality of the resulting parametric image for the CMRGlc may be improved. Zhou et al. [25], for example, improved the parametric image quality by ridge regression with constraints on the rate constants. There, the estimation of parameters uses a linear components decomposition of the kinetics in which each component represents a functional kinetic curve generated by clustering the TTACs, and the problem is solved voxel-by-voxel. Here we propose the use of a total variation (TV) penalty term which imposes spatial consistency between neighboring voxels.

The total variation penalty was first introduced in the context of image deblurring by Rudin et al. [22]. TV can significantly suppress noise while recovering sharp edges because it does not penalize discontinuities. It has received much theoretical research attention and been utilized in many signal and image processing applications. While it was introduced for PET image reconstruction by Jonsson et al. [13], and Kisilev et al. [15], it has apparently not been applied for parametric PET imaging. Instead of calculating the uptake rate for each voxel by Patlak's method, we propose to minimize the TV of the uptake rate over the entire image while also maintaining a good least squares fit for the Patlak equations at all voxels. Thus the parameters of the whole image are spatially related by the TV and solved simultaneously. The resultant parametric image is expected to have spatial homogeneity over brain regions with similar kinetics and distinct edges between brain regions that have different kinetics. This is validated by phantom simulations.

In addition to proposing the new model with the TV penalty, we also pay careful attention to the computational complexity of the algorithm by taking advantage of implementations for large-scale sparse matrix computations. In contrast to approximating

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the Hessian matrix, as is typical for quasi-Newton methods, our algorithm explicitly and accurately calculates both gradient and Hessian terms. The Hessian is efficiently recalculated at each iteration because of its sparsity. The quasi-minimal residual (QMR) method [7], is used to solve the resulting large-scale linear systems. With this efficient implementation, the procedure described here is computationally feasible.

The rest of the paper is organized as follows: the new algorithm with TV penalty is introduced in Section 2, with relevant computational issues detailed in Appendix A. The experimental data sets are described in Section 3 and results reported in Section 4. Issues relevant to the proposed TV-Patlak method and computational aspects are discussed in Section 5. Conclusions are presented in Section 6.

2. Methods

The Patlak plot has been developed for systems with irreversible trapping [20]. Most often it is applied for the analysis of FDG. The measured TTAC undergoes a transformation and is plotted against a *normalized time*. It is given by the expression

$$\frac{C_T(t)}{C_P(t)} \approx K\frac{\int_0^t C_P(s)\mathrm{d}s}{C_P(t)} + V, \tag{1}$$

where $C_T(t)$ is the measured TTAC (in counts/min/g) and C_P is the PTAC (in counts/min/ml), i.e. the FDG concentration in plasma. For systems with irreversible compartments this plot yields a straight line after sufficient equilibration time. For the FDG tracer, the slope K represents the uptake rate which, together with lumped constant (LC) and glucose concentration in plasma (C_{pg}) allows easy calculation of the CMRGlc $= KC_{pg}$/LC (in mg/min/100 g). The intercept V is given by $V_0 + \nu B$, where V_0 is the distribution volume of the reversible compartment and νB is the fractional blood volume.

The linear relationship (1) can be rewritten as

$$\left(\int_0^t C_P(s)\mathrm{d}s\right) K + C_P(t)V \approx C_T(t), \tag{2}$$

and, assuming m dynamic frames over the period of equilibration, its discretized version is

$$\left(\int_0^{t_j} C_P(s)\mathrm{d}s\right) K + C_P(t_j)V \approx C_T(t_j), \quad j = 1, \ldots, m. \tag{3}$$

In matrix format,

$$A\begin{pmatrix} K \\ V \end{pmatrix} \approx \mathbf{b}, \tag{4}$$

where A is a m-by-2 matrix,

$$A = \begin{pmatrix} \int_0^{t_1} C_P(s)\mathrm{d}s, & C_P(t_1) \\ \int_0^{t_2} C_P(s)\mathrm{d}s, & C_P(t_2) \\ \vdots & \vdots \\ \int_0^{t_m} C_P(s)\mathrm{d}s, & C_P(t_m) \end{pmatrix},$$

and vector $\mathbf{b} = (C_T(t_1), C_T(t_2), \ldots, C_T(t_m))^T$. If we were to solve (4) for each voxel independently we would obtain a parametric image lacking spatial homogeneity and with low signal-to-noise ratio (SNR). Image denoising techniques could then be applied as a separate task to improve the image quality. Instead, obtaining all voxel parameters as a result of a global optimization algorithm with a TV penalty for the entire image, the necessity for postprocessing should be eliminated.

Limiting the discussion here to 2D images (although our application of TV is 3D), we select the active voxels to be quantified by the application of a brain mask, yielding a total of **N** voxels. Eq. (4) holds with common matrix A dependent on $C_P(t)$ for each voxel **i**, but with K, **V** and **b** replaced by $K^{(i)}$, $V^{(i)}$, and $\mathbf{b}_i$, respectively, where $\mathbf{b}_i$ is obtained from the TTAC for voxel **i**. Collecting the unknowns of these **N** voxels in vectors of uptake rates and intercepts

$$\mathbf{x} = (K^{(1)}, K^{(2)}, \ldots, K^{(N)})^T \quad \text{and} \quad \mathbf{y} = (V^{(1)}, V^{(2)}, \ldots, V^{(N)})^T,$$

and requiring (4) in the least squares sense over all voxels, while maintaining minimal TV of the uptake rate for the selected image voxels, yields the global minimization problem

$$\text{(TV-Patlak)}: \quad \min \Phi(\mathbf{x}; \mathbf{y}), \tag{5}$$

$$\Phi(\mathbf{x}; \mathbf{y}) = \|\mathbf{x}\|_{\mathrm{TV},\beta} + \alpha\sum_{i=1}^{N} \|W_i(A(x_i, y_i)^T - \mathbf{b}_i)\|_2^2. \tag{6}$$

Here the total variation norm is given by $\|\mathbf{x}\|_{\mathrm{TV},\beta} = \sum_{i=1}^{N}\phi_i(\mathbf{x})$ with $\phi_i(\mathbf{x}) = \sqrt{(x_i - x_{i_r})^2 + (x_i - x_{i_b})^2 + \beta^2}$, and x_{i_r} and x_{i_b} are the values associated with voxels to the right and below voxel **i**. Theoretically the TV norm is $\|\mathbf{x}\|_{\mathrm{TV},0}$, which is a seminorm on a space of bounded variation [24]. The small constant β is used to avoid the numerical difficulty due to the lack of differentiability at the origin of ϕ_i for $\beta = 0$. The diagonal weight matrix for voxel **i** is given by

$$W_i = \mathrm{diag}\left(\sqrt{\frac{\Delta t_j}{b_{ij}e^{\lambda t_j}}}\right), \quad j = 1, \ldots, m, \tag{7}$$

where Δt_j is the scan duration of the frame at time t_j, λ is the tracer's decay constant and b_{ij} is the value of the i^{th} TTAC at frame j. This weighting is consistent with using a simulation with variance

$$\mathrm{Var}(C_T(t_j)) = Sc\frac{C_T(t_j)e^{\lambda t_j}}{\Delta t_j}, \tag{8}$$

[17]. Sc is a common scale factor that need not be made explicit here because it is absorbed into the parameter α in (6).

The objective function in (5) is convex, and can be solved using a standard Newton-type algorithm [24], Chapter 8. To simplify the expressions we introduce the vector $\mathbf{z} = [\mathbf{x}; \mathbf{y}]$.

Algorithm 1. Given initial guess $\mathbf{z} = [\mathbf{x}; \mathbf{y}]$ and tolerance $\epsilon > 0$

Repeat

1. **Solve for** $\Delta\mathbf{z}$ in

$$\nabla^2\Phi(\mathbf{z})\Delta\mathbf{z} = -\nabla\Phi(\mathbf{z}). \tag{9}$$

2. **Stop if** $|\nabla\Phi^T\Delta\mathbf{z}| \le \epsilon$.
3. **Line search**: Choose step size s.
4. **Update**: $\mathbf{z} = \mathbf{z} + s\Delta\mathbf{z}$.

Further details on the calculation of gradient vector $\nabla\Phi(\mathbf{z})$ and Hessian matrix $\nabla^2\Phi(\mathbf{z})$ are provided in Appendix A. Some other aspects of the algorithm, including discussion about constants α and β, here chosen to be 0.2 and 10^{-8}, respectively, as well as other approaches for the solution of the TV problem are discussed in Section 5.

3. Experimental data

To validate the proposed parametric imaging method we performed experiments with simulated data. The MRI-based high-resolution Zubal head phantom is used to define the brain structures [26]. Each voxel in the slice of 256×256 voxels is of