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Accelerated PET kinetic maps estimation by analytic fitting method

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ABSTRACT

In this work, we propose and test a new approach for non-linear kinetic parameters' estimation from dynamic PET data. A technique is discussed, to derive an analytical closed-form expression of the compartmental model used for kinetic parameters' evaluation, using an auxiliary parameter set, with the aim of reducing the computational burden and speeding up the fitting of these complex mathematical expressions to noisy TACs.

Two alternative algorithms based on numeric calculations are considered and compared to the new proposal. We perform a simulation study aimed at (i) assessing agreement between the proposed method and other conventional ways of implementing compartmental model fitting, and (ii) quantifying the reduction in computational time required for convergence. It results in a speed-up factor of ~120 when compared to a fully numeric version, or ~38, with respect to a more conventional implementation, while converging to very similar values for the estimated model parameters.

The proposed method is also tested on dynamic 3D PET clinical data of four control subjects. The results obtained supported those of the simulation study, and provided input and promising perspectives for the application of the proposed technique in clinical practice.

1. Introduction

Kinetic parameters' estimation from positron emission tomography (PET) images can provide a greater insight into the diagnosis of several diseases, especially those that involve metabolism, helping clinicians in characterizing among different kinds of pathologies and severity; also, it can assist during the follow-up of treatment response in a more specific way than the simple evaluation of the standard uptake value at a single time point [1].

Kinetic parameters can be estimated from a dynamic PET scan, that consists in acquiring a sequence of 3D PET images over time, to follow the uptake and washout of the radiotracer injected in the imaged object. Then, pharmacokinetic analysis aims to estimate biologically relevant kinetic parameters from the measured concentration in tissue over time, i.e., the tissue's time activity curve (TAC).

The aforementioned pharmacokinetic analysis can be performed using two main approaches: region-of-interest (ROI) kinetic modeling and parametric imaging [2,3]. The ROI-based approach fits the kinetic model to a TAC obtained averaging the values of the voxels inside a selected ROI. Instead, parametric imaging involves the estimation of the kinetic parameters for every voxel, thus providing a representation of their spatial distribution: it is useful to enhance characterization of the regional heterogeneity. However, parametric imaging is high computationally demanding, and more sensitive to noise than the ROI-based kinetic modeling [4].

The standard approach to analyze dynamic PET scans (4D PET) starts with the independent reconstructions of 3D PET images, acquired in consecutive time frames, needed to perform the pharmacokinetic analysis. Iterative reconstruction algorithms, such as the maximum likelihood expectation maximization (MLEM) or the faster ordered-subset expectation maximization (OSEM) methods, are commonly used, even if the filtered back-projection (FBP) method is sometimes preferred [5,6].

The pharmacokinetic analysis of PET data provides an insight into how the injected tracer is involved in various biological processes that may take place inside the patient's body: blood flow, receptor occupancy, and other physiological and metabolic processes. The kinetic model theoretically describes the biology in the underlying tracer distribution, and then, the fitting operation of such a model with measured data allows to estimate a set of parameters which are inherently related to the processes under investigation. Modeling is typically applied to reconstructed PET images as a post-processing step, and it can be

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considered as the actual bottleneck in the performance of parametric imaging estimation.

In the last few years, we have to acknowledge a growing interest in fully 4D image reconstruction techniques [7,8]. This class of reconstruction methods tries to address the problems of noise characterization and limited counts in dynamic emission tomography, by incorporating a theoretical model of the temporal behavior of the radiotracer directly into the image reconstruction algorithm [7–10], allowing for physiologically-meaningful constraints into the reconstruction process itself. Fully 4D direct reconstruction allows reliable estimation of voxel-wise kinetic parameters directly from raw data by exploiting the same mathematical models normally used on a post-reconstruction basis [2,3]. However, such direct approach is highly time-consuming, especially due to the kinetic parameters' estimation step, which needs to be performed multiple times, after each reconstruction iteration.

In this work, we present and validate a technique to derive an analytical closed-form expression of the compartmental model used for kinetic parameters' evaluation, using an auxiliary parameter set, with the aim of reducing the computational burden, and thus to speed up the step of fitting these complex mathematical expressions to raw TACs. To evaluate if, and how much, the proposed solution succeeds in doing so, we performed a comparison of the proposed method with other two alternative algorithms based on numeric calculation. Also, the estimated kinetic parameter values are considered, to verify that the parameters obtained with the proposed method are consistent with the ones estimated by the two alternative implementations.

In the literature, two previous attempts in this direction are presented, but they were either based on a simplified or incomplete theoretical model than the one usually adopted in conventional PET kinetic modeling and discussed in this work [11], or no characterization of the accuracy and precision of the results obtained was provided [12]. Moreover, in this work a detailed description of the reasoning behind the derivation of the proposed solution is presented, allowing for further extension of the approach to a wider number of kinetic models, and ready-to-implement equations for the three most common compartmental models (i.e. one-tissue, two-tissue irreversible, and complete two-tissue models) are provided.

The proposed method is validated using an extensive Monte Carlo simulation, and then applied and tested on real clinical dynamic 3D brain PET data, acquired on a GE Discovery RX PET/CT scanner from control subjects.

2. Materials and methods

2.1. Kinetic modeling with a two-tissues compartmental model

While linear models are often the preferred choice because of their computational efficiency, nonlinear kinetic models allow a more detailed description of the biochemical properties of different tissues [2,3]. Most of these non-linear models are built around the concept of compartments, as a way to describe the temporal behavior of the tracer within the tissue. The unknown parameters of the model are constant transfer rates, related to the movement of the tracer among different compartments.

Following the compartmental model theory [3], the total tracer concentration of a tissue region in time can be modeled as:

$$\hat{C}_T(t) = (1 - f_v)\left[C_p(t) \otimes \sum_{c=1}^{C} \boldsymbol{c}_c(t)\right] e^{-d_k t} + f_v C_{wb}(t) \tag{1}$$

where f_v is the fractional volume of blood in tissue, d_k is the radioactive decay constant of the chosen tracer (e.g. $d_k = \ln(2)/109.8\ min^{-1}$ is the decay time constant for [18F]FDG), $C_p(t)$ is the measured tracer concentration in plasma, $C_{wb}(t)$ is the measured whole blood concentration, and $\boldsymbol{c}_c(t)$ represents the impulse response function (IRF) for the c-th tissue compartment in such a way that the convolution with the arterial input function, $C_p(t)$, yields its instantaneous concentration. The relationship between compartment concentrations models flow and flow rates between them, and it can be described by a set of ordinary differential equations (ODEs):

$$\frac{d}{dt}\boldsymbol{c}(t) = \boldsymbol{K}\boldsymbol{c}(t) + \boldsymbol{L}\boldsymbol{u}(t) \tag{2}$$

where $\boldsymbol{c}(t) = [\boldsymbol{c}_1(t), ..., \boldsymbol{c}_C(t)]^T$, $\boldsymbol{K}$ and $\boldsymbol{L}$ are the kinetic parameter matrices and $\boldsymbol{u}(t)$ denotes the system input. In the common case of a two-tissue compartment model, we have:

$$\boldsymbol{c}(t) = \begin{bmatrix} C_f(t) \\ C_b(t) \end{bmatrix}, \quad \boldsymbol{u}(t) = C_p(t)$$

$$\boldsymbol{K} = \begin{bmatrix} -(k_2 + k_3) & k_4 \\ k_3 & -k_4 \end{bmatrix}, \quad \boldsymbol{L} = \begin{bmatrix} K_1 \\ 0 \end{bmatrix} \tag{3}$$

We can define a vector $\boldsymbol{\Phi} = [f_v, K_1, k_2, k_3, k_4]^T$, that is the vector of the tracer's rate constants, while with $C_f(t)$ and $C_b(t)$ we distinguish between the concentration of the free and bound compartments of a two-compartment tissue model [13].

The ODE system in eq. (3) can be solved analytically to obtain the system impulse response function (IRF):

$$\boldsymbol{c}(t) = \frac{K_1}{(\beta_2 - \beta_1)} \begin{bmatrix} k_4 - \beta_1 & \beta_2 - k_4 \\ k_3 & -k_3 \end{bmatrix} \begin{bmatrix} e^{-\beta_1 t} \\ e^{-\beta_2 t} \end{bmatrix} \tag{4}$$

where $\beta_{1,2} = \frac{1}{2}[(k_2 + k_3 + k_4) \pm \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}]$.

As shown by Gunn et al. [3], this solution can be further simplified by introducing a set of auxiliary parameters $\boldsymbol{\Phi_{aux}} = [f_v, \alpha_1, \alpha_2, \beta_1, \beta_2]^T$:

$$\alpha_1 = K_1 \frac{k_3 + k_4 - \beta_1}{\beta_2 - \beta_1}$$
$$\alpha_2 = K_1 \frac{\beta_2 - k_3 - k_4}{\beta_2 - \beta_1} \tag{5}$$

so that we can express the tissue IRF as a sum of two exponential functions:

$$\boldsymbol{c}(t) = \alpha_1 e^{-\beta_1 t} + \alpha_2 e^{-\beta_2 t} = \sum_{c=1}^{2} \alpha_c e^{-\beta_c t} \tag{6}$$

2.2. Modeling of the input function

Given the tissue impulse response function (IRF), it is known from the system theory that we can model the output of a system as a function of time, i.e. the measured TAC, by a convolution of its IRF and the relevant arterial input function, $C_p(t)$. Combining eq. (6) and eq. (1) we obtain:

$$\hat{C}_T(t) = (1 - f_v)\left[C_p(t) \otimes \sum_{c=1}^{2} \alpha_c e^{-\beta_c t}\right] e^{-d_k t} + f_v C_{wb}(t) \tag{7}$$

This equation is a mathematical model for the observed TAC in a dynamic PET scan, and it can be fitted voxelwise to the measured data, to estimate the relevant unknown parameters. Hence, the PET tracer kinetic modeling requires the measurements of the tracer time-activity curves in both plasma and tissue to estimate the physiological parameters.

The $C_p(t)$ value in eq. (7) can be estimated by using a noisy measurement of the arterial input function (AIF), which could be acquired either by arterial sampling or derived by properly placing a region of interest (ROI) over an artery, from a preliminary reconstruction of the dynamic volume. In both cases, an alternative possibility is to also fit the AIF with a theoretical model, in order to avoid adding another source of noise and uncertainty to the fitting, which may propagate to the estimated kinetic parameters. In the present work, we chose to model the AIF by a combination of exponential terms, which, for fluoro-