FDOPA KINETICS ANALYSIS IN PET IMAGES FOR PARKINSON'S DISEASE DIAGNOSIS BY USE OF PARTICLE SWARM OPTIMIZATION

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ABSTRACT

Positron emission tomography (PET), with many kinds of radioactive tracers, have been used widely for molecular imaging. In order to retrieve useful information and render a diagnosis from measured PET images, the compartment models that originated from the area of pharmacokinetics have been employed extensively for data analysis. The unknown parameters in the models are usually solved by use of curve-fitting approaches. However, the accuracy of the fitting methods are usually below satisfactory level when there exist a large number of unknown parameters. As a result, some small-valued parameters are often neglected to reduce the number of unknowns. But such a reduction can lead a loss of some important information. In this work, we propose the particle swarm optimization (PSO) method to analyze the modeling problems with a better efficacy and tested our method by solving the ^{18}F Fluoro-3,4-dihydroxyphenyl-l-alanine (FDOPA) kinetic model in Parkinson's disease diagnosis.

Index Terms— Positron emission tomography (PET), Particle swarm optimization (PSO), FDOPA kinetics, compartmental models

1. INTRODUCTION

Positron emission tomography (PET) can display radioactive concentration of tracers over time. In order to interpret the functional meaning of the acquired data, each physiologically separate pool of tracer substances can be assumed as an individual compartment. Different physiologically interested compartments are related with corresponding reaction constants in the assumed compartment model [1]. Compartment models are widely used to investigate the kinetics of radioactive tracers, such as the production, distribution, and transport of tracers in interested regions of animals [2]. The mass transport equations of the interested substance can be described by ordinary differential equations (ODEs) in which reaction constants appear in the production/consumption term.

The major objective of the kinetic analysis in PET images is to estimate the relevant physiological parameters and to find an optimal set of parameters that minimize the difference between the projected substance concentration and the measurements [3]. However, typical estimation methods like nonlinear least-squares, curve fitting or graphic analysis are limited due to the large number of unknown parameters in the model [4, 5]. The results found are often those with local minimum residual as opposed to the global one. As a result, simplified models that combine multiple parameters into macro parameters and/or neglect some small-valued parameters are often adopted to reduce the total number of unknown variables.

However, such strategies may cause errors and complicate the estimation process, particularly in a model with a large number of unknown parameters. In this work, we applied the particle swarm optimization (PSO) method [6] to quickly solve the estimation problem. PSO is widely used in optimization problems with the benefits of global searching the potential solutions, quick convergence, easy operation, and high computing performance. In order to validate our method, we applied this method to a well-studied case of ^{18}F Fluoro-3,4-dihydroxyphenyl-l-alanine (FDOPA) kinetics in analyzing Parkinson's disease [7].

2. MATERIALS AND METHODS

2.1. Compartment model for FDOPA

The commonly used model to describe the kinetic behavior of FDOPA in the striatum and reference tissue is shown in Fig. 1 [8]. In this model, parts $A(t)$, $B(t)$, and $C(t)$ are employed to respectively describe the metabolic mechanisms of the tracer in striatum and reference tissue, and the reaction mechanism of 3-OMFD in the brain tissue. The change of radioactivity concentration in striatum can be considered the combination of C_1, C_2, and C_3 denoting the concentrations of FDOPA, L-3,4-dihydrox-6-[^{18}F]fluoro-3-O-methylphenylalanine (3-OMFD), and 6-[^{18}F] fluorodopamine (FDA), respectively.

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The parameters K_1 and K_2 are the reaction constants relating the compartments of FDOPA in plasma and tissue of the striatum. K_3 is the reaction constant associating FDOPA and FDA in striatum, and K_4 is the clearance rate constant from the FDA to plasma. The reaction constants K_5 and K_6 are respectively the forward and reverse transport rate constants between 3-OMFD in plasma and the compartment of 3-OMFD in striatum tissues. Reference tissue can also be described as a kinetic compartment model that is similar to striatum except for the production of FDA. The concentration changes in each compartment model can be described as follows

$$\begin{bmatrix} dC_1/dt \\ dC_2/dt \\ dC_3/dt \\ dC_{p1}/dt \\ dC_{p3}/dt \\ dC_{\mathrm{fd}}/dt \\ dC_{\mathrm{omfd}}/dt \end{bmatrix} = \tag{1}$$

$$\begin{bmatrix} K_1 & -(K_2+K_3) & 0 & 0 & 0 & 0 & 0 \\ 0 & K_3 & -K4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & K_5 & -K_6 & 0 & 0 \\ K_{p1} & 0 & 0 & 0 & 0 & -K_{p2} & 0 \\ 0 & 0 & 0 & K_{p5} & 0 & 0 & -K_{p6} \\ -K_1 & K_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -K_5 & K_6 & 0 & 0 \end{bmatrix} * \begin{bmatrix} C_{\mathrm{fd}} \\ C_1 \\ C_2 \\ C_{\mathrm{omfd}} \\ C_3 \\ C_{p1} \\ C_{p3} \end{bmatrix}.$$

2.2. PSO algorithm

PSO algorithm, inspired by the behavior of bird flocking, is used to describe the evolutionary computation process of searching for the optimal solution. In analogy to a flock of birds searching for food, $Particles$ are considered the independent units that search for the best solution in the searching area. $Objectivefunction$ calculates the mismatch between the measurement projected by each particle and the true measurement, and evaluates the fitness of the solutions achieved by each particle thus far. *Pbest* and *Gbest* respectively denote the best position achieved by each particle and within the population, and these two parameters are also the critical factors determining the next search velocity. In each iteration step, PSO evaluates the quality of the candidate solution by comparing the objective function with a preset convergence threshold value. As iterations proceed, the $Gbest$ will ultimately approach the best solution. The PSO algorithm can be described as

$$V(n+1) = V(n) + C_1 rand(Pbest - Location(n)) + C_2 rand(Gbest - Location(n)) \tag{2a}$$

and

$$Location(n+1) = Location(n) + V(n+1), \tag{2b}$$

where the number of the iteration step is denoted by n; the location of each particle is denoted by $Location(n)$; the parameters C_1 and C_2 are regarded to as the learning coefficient, and the variable $rand$ is a random number between 0 and 1.

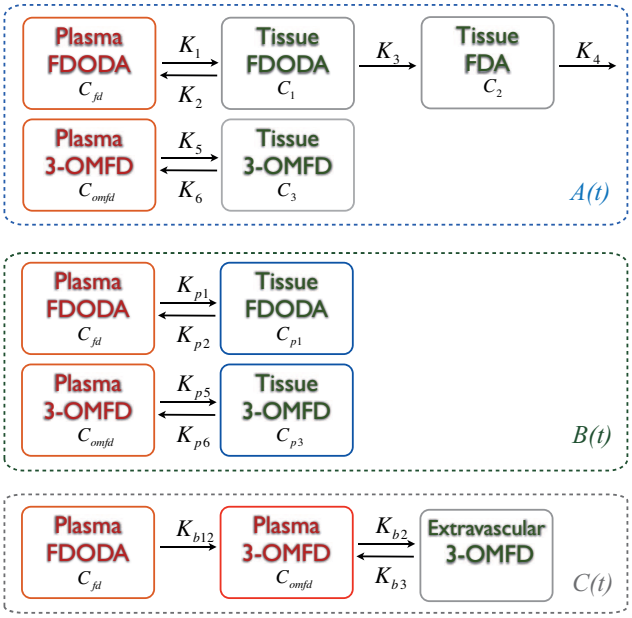


Fig. 1. Compartment model for FDOPA kinetics

2.3. Time Activity Curve From PET image

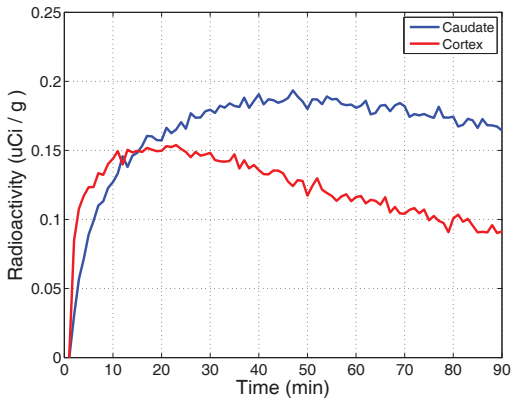
In this article, we chose two regions of interest (ROIs), i.e., caudate and cortex regions, which are referred to as striatum and reference tissues, respectively. The time activity curves (TACs) analyzed in this work are based on the fitted TAC equations of Yoshida et al. [10], who extracted TACs from Cumming and Gjedde [9]. In Ref. [10], the TAC of a normal rat or one with Parkinson's disease takes on the following form

$$a_1 \mathrm{e}^{-m_1 t} + a_2 \mathrm{e}^{-m_2 t} - (a_1 + a_2 + a_3)\mathrm{e}^{-m_3 t} + a_3, \tag{3}$$

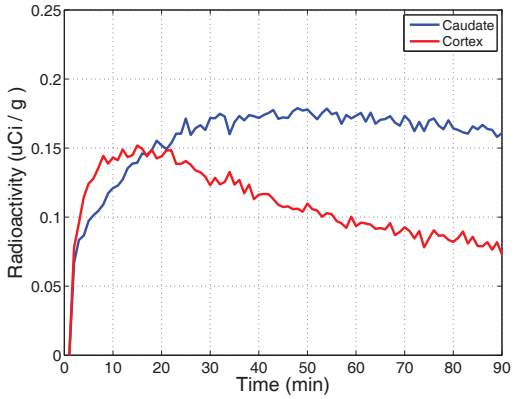
where a_1, a_2, a_3, m_1, m_2, and m_3 are the fitting coefficients whose values differ for normal and diseased rats. We applied Eq. (3) with the values listed in [10] to generate the TACs. A white gaussian noise with SNR 50(dB) was added to Eq. (3), and the resulting TACs are shown in Fig. 2.

2.4. Paramaters Estimation via PSO Method

Ideally, the simulated concentration from the kinetic compartment model over time should be identical to the measurement data, which are extracted from the ROI in the PET images over time. Generally speaking, the objective of PSO algorithm in the modeling applications is to minimize the least squares value of the difference between the measurement data and the predicted data estimated by the kinetic model. Each reaction rate constant in the model is unknown. The radioactivity concentrations of striatum (C_s) and reference tissue (C_r) can be estimated from the combination of models



(a) Patients with Parkinson's disease



(b) Patients with out Parkinson's disease

Fig. 2. Time activity curve with gaussian noise

$A(t)$ and $B(t)$ in Fig. 1 as follows:

$$\begin{aligned} C_S &= C_1 + C_2 + C_3 + V * C_w b(t) \\ C_r &= C_{\mathrm{p1}} + C_{\mathrm{p3}} + V * C_w b(t), \end{aligned} \tag{4}$$

where V and $C_w b(t)$ are the blood volume in tissue and total radioactivity in whole blood, respectively. In this work, we assumed the blood volume in rat tissue can be neglected [11]. The concentration of each compartment can be described by ODEs mentioned above, and the concentration in each single compartment are always influenced by those of periphery compartments. In PET kinetic analysis, only compartments associated with the measurement data are needed. In order to separate the concentration from periphery compartments, we use Laplace methods to transform the ODEs into a set of nonlinear algebraic equations. After the Laplace transform, the concentration of striatum and reference tissue in the Laplace domain will be denoted as $\mathcal{L}C_S$ and $\mathcal{L}C_R$, which can be calculated by algebraic methods. In order to analyze with the data obtained from PET image in time domain, we applied the inverse Laplace transform to the $\mathcal{L}C_S$ and $\mathcal{L}C_R$.

The objective function that the PSO algorithm aims to minimizes takes on the following form.

$$1/2 \sum_{i=1}^{N} (M(i) - C(i))^2, \tag{5}$$

where $M(i)$ and $C(i)$ are the measurement data and simulated concentration from the kinetic model, respectively, and N is the number of sampling points. After the iterative calculations, we can get all the reaction rate constants with the desired converged conditions. Knowledge of these reaction rate constants can aid to diagnose whether a patient is healthy or not.

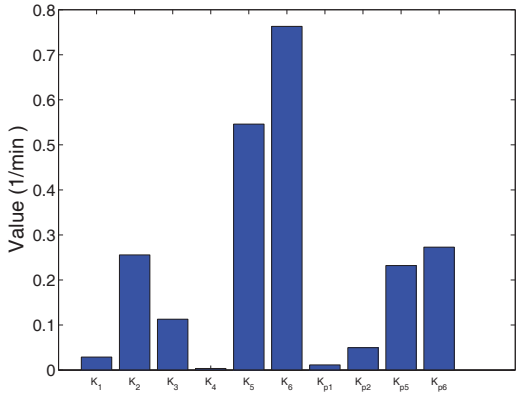
3. RESULTS AND DISCUSSION

The distribution volume of 3-OMFD in brain tissue is assumed to be unity, according to previous experiments or estimations [9]. That is a valuable biological information for us to validate the correctness of our estimation. The average distribution volume of 3-OMFD in striatum and reference tissue can be estimated by K_6/K_5 and $K_{\mathrm{p6}}/K_{\mathrm{p5}}$, respectively. The distribution volume in striatum and reference tissue in patient's brain and in healthy brain obtained by use of our method are 1.39, 1.17, 1.38, 1.02, which are reasonable as they do not deviate much from unity.

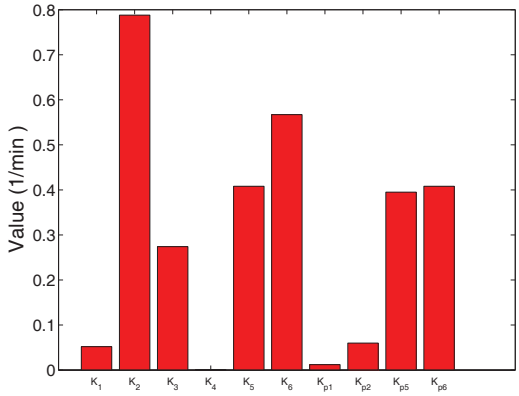
All the reaction constants in the compartment models can be estimated using PSO algorithm without ignoring any parameters. The results of which are shown in Fig. 3. The key reaction constant in the FDOPA study is K_3 [2], which is regarded as the transformation rate from FDOPA to FDA. The primary enzyme causes the transformation of FDOPA to FDA is aromatic amino acid decarboxylase (AAADC) in striatum. The amount of AAADC will be insufficient due to the disorder of the nigrostriatal-pathway in patients with Parkinson's disease. As a result, the values of K_3 estimated from patients with Parkinson's disease are on average lower than those of normal people. Thus K_3 is often used as the key indicator in the diagnosis of Parkinson's disease. In this work, the estimated K_3 of diseased and normal rats are 0.27 and 0.11, respectively, which are consistent and can lead to the same diagnosis with the previous study [2].

4. CONCLUSIONS

We applied PSO to estimate the parameters in compartment models. Specifically, we applied this method to analyze FDOPA kinetics, and are successful on estimating all the parameters relevant to the physiological characteristics of FDOPA. Our method can obtain values that are consistent with the existing biological information; therefore, the PSO algorithm could be useful for determining reaction constants from PET images. All the parameters can be estimated without ignoring or merging some of them, and the values of the key parameter K_3 estimated in this work are consistent with



(a) Parameters estimation for rats with Parkinson's disease



(b) Parameters estimation for healthy rats

Fig. 3. Results of estimation of parameters from rats.

previous researches and thereby can facilitate the retrieval of important physiological information.

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