Non-Invasive Quantification of Physiological Processes with Dynamic PET using Blind Deconvolution

Chi-Hoi Lau, Daniel Pak-Kong Lun, Dagan Feng
Department of Electronic Engineering
The Hong Kong Polytechnic University, Hung Hom, Hong Kong
e-mail: enpklun@polyu.edu.hk Fax: (852) 23628439

Abstract

Dynamic Positron Emission Tomography (PET) has opened the possibility of quantifying physiological processes within the human body. On performing dynamic PET studies, the tracer concentration in blood plasma has to be measured, and acts as the input function for tracer kinetic modelling. In this paper, we propose an approach to estimate physiological parameters for dynamic PET studies without the need of taking blood samples. The proposed approach comprises two major steps. First, a wavelet denoising technique is used to filter the noise appeared in the projections. The denoised projections are then used to reconstruct the dynamic images using filtered backprojection. Second, an eigen-vector based blind deconvolution technique is applied to the reconstructed dynamic images to estimate the physiological parameters. To demonstrate the performance of the proposed approach, we carried out a Monte Carlo simulation using the fluoro-deoxy-2-glucose model, as applied to tomographic studies of human brain. The results demonstrate that the proposed approach can estimate the physiological parameters with an accuracy comparable to that of invasive approach which requires the tracer concentration in plasma to be measured.

1. Introduction

Dynamic Positron Emission Tomography (PET) has been playing an important role in quantification of physiological processes within the human body[1]. On performing dynamic PET studies, radioactive tracer is injected into the patient. Projections are recorded by a PET scanner and a sequence of dynamic images are then reconstructed. Tissue time activity curves (TTACs) are extracted from the regions of interest (ROIs), and finally, physiological parameters are estimated by fitting the TTACs to a pre-assumed tracer kinetic model using optimization techniques. The studies also require the measurements of tracer concentration in blood plasma, i.e. the plasma time activity curve (PTAC), which acts as the input function for the kinetic model.

PTAC are usually obtained by direct arterial blood sampling. This process is invasive, time-consuming and requires extra-staff. It introduces additional radiation exposure to clinical personnel and increases the possibility of spreading infestous diseases. Therefore, it is desirable to have methods which enable quantification of physiological processes with reduced number of blood samples so that the inconvenience caused can be minimized.

Recently, Carson et al[2] and Watabe et al[3] have proposed techniques that completely eliminate the process of blood sampling. Both methods are developed for estimating the regional cerebral blood flow (rCBF) using PET. However, their extensions to more complex models, e.g. fluoro-2-deoxy-glucose (FDG) model, still need further investigation. In fact, the solutions are likely to be computationally demanding.

In this paper, we propose an approach to estimate the physiological parameters for a pre-assumed tracer kinetic model when performing dynamic PET studies, without taking arterial blood samples. The approach consists of two major steps. First, the wavelet transform is used for the denoising of the projections[4]. Second, an eigen-vector based blind deconvolution[5] algorithm is applied to estimate the physiological parameters. This technique is applied to estimate the regional cerebral metabolic rate of glucose (rCMRGlc) based on FDG model[1]. The performance of the proposed approach is demonstrated using the Monte Carlo simulation. The result illustrates that the proposed approach can provide a comparable performance as that of invasive approach which requires the input curve to be measured.

2. Traditional Parameter Estimation Approach

The traditional parameter estimation approach for dynamic PET studies can be illustrated by using the FDG model[1]. The FDG model is a mathematical model employed to determine the transport rate constants of radioactive FDG after it has been injected intravenously into the human body. The FDG model, as shown in figure 1, consists of three compartments, (1) the blood pool region which represents the concentration of FDG in plasma, i.e. PTAC, (2) the concentration of free FDG in tissue, Ce(t), and (3) the concentration of FDG-6-phosphate in tissue, Cm(t). The various concentrations in tissue can be solved (see [1]) in terms of PTAC:

$$Ce(t) = \frac{k_1}{\alpha_2 - \alpha_1}((k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4)e^{-\alpha_2 t}) \otimes PTAC(t) \quad (1)$$

$$Cm(t) = \frac{k_1 k_3}{\alpha_2 - \alpha_1}(e^{-\alpha_1 t} - e^{-\alpha_2 t}) \otimes PTAC(t) \quad (2)$$

$$Ci(t) = \frac{k_1}{\alpha_2 - \alpha_1}((k_3 + k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_3 - k_4)e^{-\alpha_2 t}) \otimes PTAC(t) \quad (3)$$

where Ci(t) is the total ^{18}F activity in tissue, i.e. TTAC, the symbol $\otimes$ denotes the operation of convolution integral, and

$$\alpha_1 = (k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4})/2$$
$$\alpha_2 = (k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4})/2 \quad (4)$$

Since Ci(t), or equivalently TTAC, can be measured with PET scanner, and PTAC can be obtained by taking blood samples, the values of the rate constants, k_1-k_4, of FDG model can be estimated by performing a non-linear least square optimization.

The estimated k_1-k_4 are then used to calculate the metabolic rate of glucose in a local region, Ri, given as

$$Ri = \frac{1}{LC}\frac{k_1 k_3}{k_2 + k_3}Cp \quad (6)$$

where LC denotes the lumped constant, accounting for the differences between FDG and glucose in transportation and phosphorylation, and Cp denotes the cold glucose concentration in plasma. Both LC and Cp are assumed constant and can be determined in advance. We are interested to the parameter Ri because it represents the activity of a particular part of human body. This gives a useful information to medical practitioner in various diagnostic applications.

One of the disadvantages with this approach is that it requires repeated measurements of PTAC at different instants up to a

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sufficient long time interval (usually more than 60 minutes). The blood collection and processing is invasive, time consuming and requires extra clinical staff. It also introduces additional radiation exposure and increases the possibility of spreading infestous diseases to the clinical personnel. We thus investigated an alternative method which can estimate the kinetic rate constants, k_1-k_4, and hence Ri, for the FDG model without measuring PTAC.

3. Dynamic PET studies using Blind Deconvolution

3.1 Denoising

The fundamental of the proposed approach is the use of a blind deconvolution technique which is based on eigen-vector decomposition[5]. Since the computation of eigen-vector is sensitive to noise, we employed a denoising step before the blind deconvolution. Among the numerous denoising methodologies in the literature, linear low pass filtering[6] is the most commonly used approach since it is easy to implement with the standard convolution backprojection method. However, the linear low pass filtering approach unavoidably blurs the edges and causes the loss of structural information of the original image. Another way of denoising is to model the emission process as a random process and to use reconstruction algorithms based on the statistical model[7]. However, this technique are usually computationally expensive and is not suitable for daily operation. Therefore, in this paper, we choose to use a denoising approach which is based on the wavelet transform[4]. Wavelet denoising has the advantage of preserving the structural information of the image when filtering the noise. In addition, when comparing with other wavelet denoising approaches[8], the chosen approach also has the advantages of non-iterative reconstruction and simple computation which make it favorable for daily clinical usage. Details of the wavelet denoising can be found in [4]. After wavelet denoising is applied to filtering the noise, the blind deconvolution is used to estimate the kinetic parameters based on the dynamic images reconstructed from the denoised projections.

3.2 Blind Deconvolution

The study of blind deconvolution attracts much importance recently in the areas of communication, signal processing, as well as geophysics. Its major objective is to estimate the input or the system transfer function only from their convolution output. This seemingly impossible problem has been shown to have closed form solution. The current blind deconvolution approaches can be divided into two classes. The ones that rely on high order statistic[9] often require the input function to fulfill a certain kind of statistical characteristics, e.g. identical and independent distribution (i.i.d.), that may be difficult to achieve in some applications. The ones that rely on second order statistic seems to have less requirement on the input data, transfer function, as well as the noise of the output[5]. In this paper, multi-channel blind deconvolution technique in this class is adopted.

A block diagram for the problem of multi-channel blind deconvolution is shown in figure 2. It is assumed that the number of unknown channels is greater than one. For simplicity, the two-channel case will be considered here. As applied to our problem, the output signals of the unknown system is the tracer concentration in tissue, i.e. TTACs. These curves are the results of the convolution integral of PTAC(t) with the impulse response of the FDG models, $FDG_i(t)$. They are given as follows:

$$TTAC_i(t) = FDG_i(t) \otimes PTAC(t) \quad i=1,2 \qquad (7)$$

Provided an appropriate sampling rate, the convolution integral as shown in (7) can be approximated by a discrete linear convolution. The advantages of using a discrete linear convolution rather than a convolution integral are, first, we can speed up the computation, and more importantly, we can apply various well-established digital signal processing techniques to improve the performance in estimating the physiological parameters. Nevertheless, it is never possible to attain such a sampling rate in real practice. For TTAC, usually only 22 samples taken in an irregular time interval are obtained. Fortunately, due to the smoothness of the input and output functions, the discrete linear convolution can still be used by re-sampling the irregularly sampled data to the required sampling rate using an interpolation. Figure 3 shows the difference between the TTACs obtained by mathematically performing the convolution integral to the PTAC and FDG model and that obtained by using discrete linear convolution. The difference of them in average is less than -54 dB. This result shows that we can safely approximate the convolution integral in (7) by discrete linear convolution.

Both unknown channels in figure 2 are fed by the same unknown input function, i.e., the PTAC. The two unknown channels of the system are the FDG models with different kinetics of, for example, brain grey matter (Region 1) and white matter (Region 2), respectively. The impulse response of the FDG model is given as follows:

$$FDG_i(t) = A_{i,1}e^{-\lambda_{i,1}t} + A_{i,2}e^{-\lambda_{i,2}t} \quad i=1,2 \qquad (8)$$

where $A_{i,1} = \frac{k_{i,1}}{\alpha_{i,2}-\alpha_{i,1}}(k_{i,3}+k_{i,4}-\alpha_{i,1})$, $A_{i,2} = \frac{k_{i,1}}{\alpha_{i,2}-\alpha_{i,1}}(\alpha_{i,2}-k_{i,3}-k_{i,4})$

$$\lambda_{i,1} = \alpha_{i,1}, \ \lambda_{i,2} = \alpha_{i,2} \ \text{ and } i=1,2 \qquad (9)$$

Eqn. 8 can be discretized and expressed in Z domain using the following rational system transfer function,

$$Fi(z^{-1}) = \frac{Ni(z^{-1})}{Di(z^{-1})} \qquad i=1,2 \qquad (10)$$

where $Ni(z^{-1})$ and $Di(z^{-1})$ are the polynomials in z^{-1} of order Ni and Di, respectively. They are related to the kinetic parameters of the FDG model as follow:

$$N_i(z^{-1}) = (A_{i,1}+A_{i,2}) + (A_{i,1}e^{-\lambda_{i,2}} + A_{i,2}e^{-\lambda_{i,1}})z^{-1} \qquad (11)$$

$$D_i(z^{-1}) = (1-e^{-\lambda_{i,1}}Z^{-1})(1-e^{-\lambda_{i,2}}Z^{-1}) \qquad (12)$$

The roots of $Ni(z^{-1})$ and $Di(z^{-1})$ may be inside and/or outside the unit circle. It is also assumed that the channel transfer functions have no common poles and zeros.

The re-sampled TTACs are sent to a two-channel adaptive system shown in figure 4. The channel transfer functions are finite order polynomials $Wi(z^{-1})$ with order Wi. That is, the adaptive channels are FIR, with

$$Wi(z^{-1}) = w_{i,o} + w_{i,1}z^{-1} + \ldots + w_{i,Wi}z^{-Wi} \qquad i=1,2 \qquad (13)$$

The polynomial coefficients $w_{i,k}$ are assumed to be adaptable via some algorithms. We can also express the polynomial coefficients in vector form as follow:

$$Wi(z^{-1}) = \left[w_{i,0}, w_{i,1}, \ldots, w_{i,Wi}\right]^T \text{ and } W = \left[W_1^T, W_2^T\right]^T \qquad (14)$$

Denotes Xi(t) as the re-sampled TTACs, such that,

$$Xi(t) = \left[x_i(t), x_i(t-1), \ldots, x_i(t-Wi)\right]^T \text{ and } X(t) = \left[X_1^T(t), X_2^T(t)\right]^T \qquad (15)$$

We define the error signal, $e(t)$, as:

$$e(t) = W^T X(t) \qquad (16)$$

and the mean-squared-error, $\varepsilon(W)$, as

$$\varepsilon(W) = \sum_{t=0}^{\tau} |e(t)|^2 \qquad (17)$$

where τ is the length of the time interval. Assuming that the observation signals are noise free, there is a simple relationship between the roots of the unknown FDG channels and the root of the adaptive channels. Assuming that the adaptive channel orders are chosen such that,

$$W_1 = N_2 + D_1 \text{ and } W_2 = N_1 + D_2 \quad (18)$$

then, the unique family of solutions for $W_1(z^{-1})$ and $W_2(z^{-1})$ that minimize $\varepsilon(W)$ is given by

$$W_1=\alpha N_2(z^{-1})D_1(z^{-1}) \text{ and } W_2(z^{-1})= -\alpha N_1(z^{-1})D_2(z^{-1}) \quad (19)$$

where α is an arbitrary constant. With the above family of solutions, we have $\varepsilon(W) = 0$. Thus if some W can be found for which $\varepsilon(W) = 0$, then the set of Ni and Di will be the solutions and can be obtained by factorizing $W_1(z^{-1})$ and $W_2(z^{-1})$. Finally, the rate constants, k_1-k_4, of the FDG model can be obtained by equation (9), (11) and (12).

To calculate the family of Wi that satisfies $\varepsilon(W)=0$, we make use of an eigen-vector decomposition approach similar to that in [5]. More specifically, we calculated $W_1(z^{-1})$ and $W_2(z^{-1})$ as follows:

1. Based on the signal observed through the multi-channel, i.e. TTACs, produced a data matrix, A_x, as follow:

$$A_x = \left[X^T(\Gamma), X^T(\Gamma-1),\ldots, X^T(1)\right]^T \quad (20)$$

2. From A_x, we compute the sample correlation matrix defined as $R_x = A_x^T A_x$.
3. Then compute the eigen-vector, q, corresponding to the smallest eigenvalues of R_x.
4. Partition q into sub-vectors q_1 and q_2 and obtain the channel transfer function Q_1 and Q_2.
5. The set of transfer function thus obtained by Q_1 and Q_2 provides a basis for the solutions for $W_{esti,1}$ and $W_{esti,2}$.

Lastly, we estimate the parameters by minimizing the following cost function using nonlinear least square curve fitting:

$$\phi_2(k_1,k_2,k_3,k_4) = \sum_{i=1,2} \left| W_{predicted,i} - W_{esti,i} \right|^2 \quad (21)$$

where $W_{predicted,i}$ is the model predicted transfer function for adaptive channels given as (19) and $W_{esti,i}$ is the transfer function calculated from the observable TTACs.

In summary, the proposed approach can be stated as follow: first, the wavelet denoising is applied to filter the noise in the projections. This denoised projections are then reconstructed using the filter back projection algorithm. From the reconstructed dynamic images, two TTACs are then extracted from ROIs, e.g. one from the grey matter and the other from the white matter. The two TTACs are then re-sampled to the required rate using interpolation. Based on these two curves, the blind deconvolution technique is applied to estimate the parameters of interest, k_1-k_4.

4. Simulation Method and Results

To validate the present method, we carried out a Monte Carlo simulation study. In our simulation, we generated the PTAC[10] numerically as the input function. We assume that the time delay of the input function model is equal to zero. The mathematical expression of this simplified input function model, PTAC(t), is given as follows:

$$PTAC(t) = (B_1 t - B_2 - B_3) \exp(\mu_1 t) + B_2 \exp(\mu_2 t) + B_3 \exp(\mu_3 t)$$

where, as previously published [10]:

$B_1 = 851.1, B_2 = 21.88, B_3 = 20.81$ [μCi/ml]

$\mu_1 = -4.134, \mu_2 = -0.1191, \mu_3 = -0.0104$ [1/min]

The transport rate constants, k_1-k_4, for the FDG models are obtained from [1] and are listed in Table 1. The derived parameter, K, which is proportional to the metabolic rate of glucose and is equals to $k_1*k_3/(k_2+k_3)$, is also shown in Table 1. It is used as a reference for the comparison of the performance of different methods. Based on the simulated PTAC and the FDG model, TTACs (sampling schedule) were generated according to (3). These curves are reformatted into dynamic images using the Hoffman brain phantom. The phantom is partitioned into two regions corresponding to the two different kinetics which are typical of brain white matter and grey matter, respectively. Sinogram data are generated with 64 projections, each with 64 bins, assuming 360° rotation. The simulation did not include attenuation, scatter or distance dependent detector response. The projection data were scaled to count densities which might be expected for dynamic PET imaging (with 2k counts/sec in the last frame-interval). Poisson noise were added to the projection data.

Four methods for analysis were compared:

(1) Traditional parameter estimation method as stated in section 2.
(2) Proposed blind deconvolution method without denoising.
(3) Traditional parameter estimation method with denoising.
(4) Proposed blind deconvolution method with denoising.

For each method, k_1-k_4 are estimated and the parameter, K, is evaluated. The simulations were carried out for one hundred independent realizations to obtain average performance for each method. The percentage errors compared to the true parameters (bias) and the coefficient of variation (CV) of the estimated k_1-k_4 and K's were determined.

Table 2 shows the bias and CV of the estimated k_1-k_4 and K of different regions using the four different methods as indicated above. As can be seen, when blind deconvolution is applied without wavelet denoising, there is significant bias for the result. This is because the calculation of the eigen-vector is sensitive to noise. When noise exists, the eigen-vector calculated based on the sample correlation matrix is biased. As a result, the parameters estimated will deteriorate. However, when wavelet denoising is applied to filter the noise in the projections, followed by the blind deconvolution, the result significantly improved. Furthermore, the bias of estimated k_1 is better than the other methods. This is because of the larger value for k_1 as well as the fact that two regions are analyzed simultaneously in the proposed blind deconvolution method. The bias of the estimated k_2, k_3 and K are comparable to that of invasive method. Although k_4 is still much larger because of its small value, the existence of k_4 does not very much contribute to the calculation of K. Hence the error incurred is not significant to the final result as a whole. For the CV, the proposed method with denoising is always lower than the other methods.

5. Conclusion

In this paper, we proposed an approach for estimating physiological parameters from dynamic PET studies, without the requirement of taking any blood samples. The proposed approach comprises two major steps: wavelet denoising is used to filter the noise in projections, and blind deconvolution is used for parameter estimation. We have performed a Monte Carlo simulation to investigate the performance of the proposed approach. The results demonstrate that the approach can estimate the physiological parameters with an accuracy comparable to that of invasive approach which requires the whole PTAC to be measured. Since the proposed approach obviates the taking of blood samples, it is non-invasive, simple and it minimizes the possibilities of radiation exposure to clinical personnel and the possibility of spread of infestous

diseases. Therefore, the proposed technique has widespread clinical appeal.

Acknowledgement

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	k_1	k_2	k_3	k_4	K
Region 1	0.1200	0.1070	0.0440	0.0059	0.0350
Region 2	0.0740	0.1030	0.0290	0.0038	0.0163

Table 1: The transport rate constants, k_1-k_4, and K for the FDG models.

	Region 1					Region 2				
Bias (%)	k_1	k_2	k_3	k_4	K	k_1	k_2	k_3	k_4	K
Traditional method	0.62	-1.26	3.41	12.33	2.78	6.66	0.67	10.06	36.72	12.57
Blind Deconvolution without denoising	-0.03	-43.77	48.57	361.98	90.99	0.03	45.91	73.67	562.01	12.23
Traditional method with denoising	-0.80	-1.10	3.02	16.73	1.48	0.62	2.82	6.99	15.93	3.46
Blind deconvolution with denoising	0.00	-3.35	4.93	36.74	6.02	0.00	4.23	7.48	57.04	2.32
CV (%)	k_1	k_2	k_3	k_4	K	k_1	k_2	k_3	k_4	K
Traditional method	2.35	9.80	23.47	82.35	11.15	4.35	11.00	27.74	102.65	13.87
Blind Deconvolution without denoising	0.02	62.69	25.75	61.73	41.83	0.02	24.99	33.42	66.89	7.34
Traditional method with denoising	1.27	7.12	16.61	59.87	7.95	2.19	6.11	12.72	77.65	7.17
Blind deconvolution with denoising	0.00	4.43	4.63	26.48	6.22	0.00	4.37	6.86	35.80	2.00

Table 2: The bias (in percentage) and CV (in percentage) of the estimated k_1-k_4 and K for the four different methods.

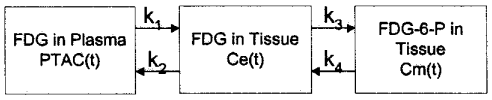

Figure 1: FDG model.

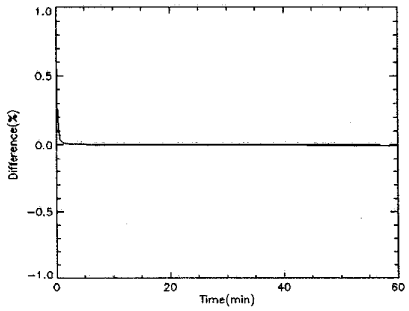

Figure 3: Difference between the TTACs obtained by mathematically performing the convolution integral to the PTAC and FDG model and that obtained by using discrete linear convolution.

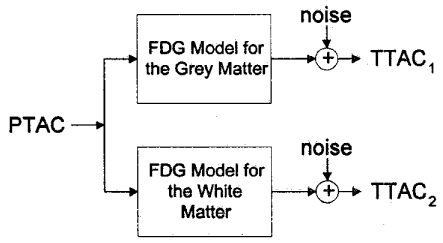

Figure 2: Block diagram for the problem of two-channel Blind Deconvolution

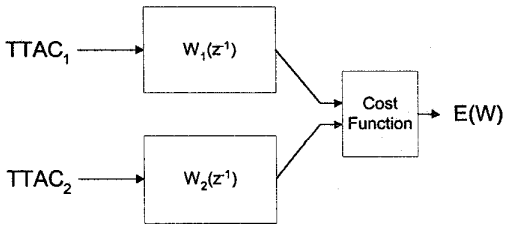

Figure 4: Two-channel adaptive system.