Dual Estimation of Activity Maps and Kinetic Parameters for Dynamic PET Imaging

Jingjia Xu, Huafeng Liu, Pengcheng Shi and Fei Gao

Abstract Due to rapid adoption of dynamic PET, the dual estimations of the activity maps and kinetic parameters have been attracting a lot of attention. In this paper, we propose a novel approach to solve this problem by using Dual-Kalman Filter (DKF) based on state space framework. One Kalman Filter is adopted to reconstruct the activity maps and the other is to estimate the kinetic parameters, where each filter uses the estimation results from the other one as initialization, then the two filters are solved iteratively until convergence. In addition, this approach combines the compartmental model guided activity map reconstruction and the state space based kinetic parameter estimation. The simulation experiments are presented by both utilizing DKF and other methods based on fitting the compartmental model. The final results show the more robust and accurate performance using proposed method.

Keywords Positron emission tomography · Parameter estimation · Dynamic reconstruction · Compartmental model · Dual filter

1 Introduction

In nuclear medicine, PET (Positron Emission Tomography) is emerging as one of the leading modalities in the biomedical research and clinical diagnostic procedure. Dynamic PET imaging plays a more and more important role in research, which reveals the dynamic metabolism of specific organs and tissues through imaging the spatiotemporal distributions of injected radiotracers *in vivo*. The dynamic changes

J. Xu (✉) · P. Shi · F. Gao
Rochester Institute of Technology, Rochester, NY 14623, USA
e-mail: Xujingjia.zju@gmail.com

F. Gao
e-mail: Gaofei.rit@gmail.com

H. Liu
Zhejiang University, Hangzhou, China
e-mail: liuhf@zju.edu.cn

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of these spatiotemporal distributions reflect several complex events and can be represented by compartment models and kinetic parameters [3]. The compartmental model describes the tracer metabolism and is widely used in the dynamic PET research. The kinetic parameters are used to quantify the distribution of the radiotracer throughout the tissues or the organs.

The estimation methods for activity maps include conventional Expectation Maximization (EM) methods, accelerated Ordered Subset Expectation Maximization (OSEM), Maximum A Priori (MAP) and state space framework [1]. The estimation of kinetic parameters is more difficult [2, 5, 8]. Generally, the methods include indirect and direct methods. The indirect methods first reconstruct the activity maps and then fit the results to specific compartment models. These methods are simple and easy to implement, because activity reconstruction and kinetic modeling are performed in two separate steps. However, the noise distribution which should be spatially variant and object dependent is not modeled in the kinetic analysis, this will lead to suboptimal results. The direct methods estimate parametric images from dynamic PET sinograms directly, and theoretically they should be more efficient, however, the algorithms are often difficult to implement and are limited to the specific models.

In this paper, we proposed a novel method for dual estimation of activity maps and kinetic parameters for dynamic PET imaging. Formulating the two estimations by using DKF based on our state space frameworks which have inherent ability to deal with noise distribution, we set one Kalman Filter to reconstruct the activity maps from dynamic PET data and the other to estimate the kinetic parameters, where each filter uses the estimation results from the other one as initialization, then the two filters are solved iteratively until convergence. The DKF method combines the compartment model guided activity map reconstruction [7] and state space based kinetic parameter estimation, and the merits of this iterative estimation yield more robust and accurate estimation of both activity maps and kinetic parameters. Data sets from computer simulations are conducted for quantitative analysis and validation.

2 Methodology

2.1 Compartmental Model

In the PET tracer kinetic research, there are many models,such as none-compartmental model and compartmental model, proposed to describe the process of tracer distribution in the organs and tissues. Compartmental model is generally utilized to describe movement of tracer between different physically or chemically distinct state and compartments. In this paper, a two-tissue compartmental model, widely validated in many radioligand tracers, is the main algorithm in dynamic PET research. The two-tissue compartmental model use the the first-order ordinary differential equations to depicted the exchange of tracer between the compartments illustrate in Fig. 1 and

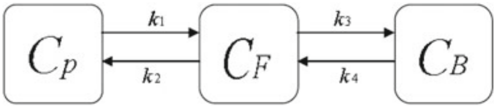


Fig. 1 The two-tissue compartmental model

Eqs. (1–3):

$$\begin{aligned} \frac{dC_{Fi}}{dt} &= k_{1i}C_P(t) + k_{4i}C_{Bi}(t) - (k_{2i} + k_{3i})C_{Fi}(t) \\ \frac{dC_{Bi}}{dt} &= k_{3i}C_{Fi}(t) - k_{4i}C_{Bi}(t) \\ C_{Mi}(t) &= C_{Fi}(t) + C_{Bi}(t) \end{aligned} \quad (1)$$

where the $C_P(t)$, $C_{Fi}(t)$ and $C_{Bi}(t)$ represent the tracer concentration in the plasma, the tracer concentration in the tissues and the metabolites of tracer concentration in the tissues, respectively. The model depends on the kinetic parameters k_1, k_2, k_3 and k_4, which specify tracer exchange rates between the compartments in the units of inverse minutes (min^{-1}), and C_{Mi} is the total tissue activity.

The other parameter $K_r = k_1k_3/(k_2 + k_3)$ is proportional to the regional cerebral metabolic rate for metabolized tracers and to the uptake of tracer, which is one of the main parameters used to evaluate the accuracy of our proposed method.

2.2 Compartment Model Guided Activity Map Estimation

The activity map estimation has been specifically interpreted in the [7], which puts forward the state space representation for the dynamic reconstruction where the compartmental model is guided as a continuous-time system equation and the image data is expressed in a measurement equation. The general form of the framework for the activity map reconstruction for voxel i as follows:

$$\begin{aligned} \dot{x_i}(t) &= a_i x_i(t) + b_i\widetilde{C_P}(t) + \nu(t) \\ Y &= DX(t) + e(t) \end{aligned} \quad (2)$$

where $X(t) = \{x_1(t), x_2(t), \ldots, x_n(t)\}$ describes all the pixels in one frame image, and each pixel is defined as $\dot{x}_i(t) = \begin{bmatrix} \dot{C_{Fi}}(t) \\ \dot{C_{Bi}}(t) \end{bmatrix}$, $a = \begin{bmatrix} -(k_{2i} + k_{3i}) & k_{4i} \\ k_{3i} & -k_{4i} \end{bmatrix}$ and $b = \begin{bmatrix} k_{4i} & 0 \end{bmatrix}$; and measurement matrix is $D = CT_r$, where C is the image matrix and T_r is the transformation matrix with the block diagonal; $\nu(t)$ and $e(t)$ are the process and measurement noise, respectively, which are Gaussian distribution with zero mean and the covariance matrix of the process and measurement Q and R, respectively.

2.3 State Space Formulation of Kinetic Parameter Estimation

State Space Formulation *The state equation*. As discussed in the previous Sect. 2.1, the parameters k_1, k_2, k_3 and k_4 represent tracer exchange rates between the compartments and the values of the parameters are assumed to be barely changed for one tracer in the same organ or tissue. The form of state equation of parameter estimation adopted in current study assumes a static, discrete-time linear function as follows:

$$\left[k_1 \ k_2 \ k_3 \ k_4 \right]_{(t)} = \left[k_1 \ k_2 \ k_3 \ k_4 \right]_{(t-1)} \quad (3)$$

Defining $T_i = \left[k_1 \ k_2 \ k_3 \ k_4 \right]_i^T$ and also introducing a system noise term $\widetilde{\nu}(t)$, the state equation for all voxels expresses as:

$$T(t) = T(t-1) + \widetilde{\nu}(t) \quad (4)$$

The measurement equation. By applying the compartmental model to all the voxels, the measurement equation for any voxel i is governed from the Eqs. (1) and (2) as:

$$\begin{bmatrix} \dot{C_{Fi}}(t) \\ \dot{C_{Bi}}(t) \end{bmatrix} = \begin{bmatrix} C_P(t) & -C_{Fi}(t) & -C_{Fi}(t) & C_{Bi}(t) \\ 0 & 0 & C_{Fi}(t) & -C_{Bi}(t) \end{bmatrix} \times T_i \quad (5)$$

With the subscript i denoting different voxel locations, the above measurement equation can be expressed in a compact notation as:

$$y(t) = D_i \cdot T_i(t) + \widetilde{\mu}(t) \quad (6)$$

where
$y(t) = \left[\dot{C_{Fi}}(t) \ \dot{C_{Bi}}(t) \right]^T$
$D_i = \begin{bmatrix} C_P(t) & -C_{Fi}(t) & -C_{Fi}(t) & C_{Bi}(t) \\ 0 & 0 & C_{Fi}(t) & -C_{Bi}(t) \end{bmatrix}$ and $\widetilde{\mu}(t)$ is the measurement noise.

Equations (7) and (9) have formed a standard state-space representation for estimating kinetic parameters, in which the parameters serve as static variable state equation and the reconstruction data convey the discrete sampling in the measurement equation.

Kalman Filter Solution The Kalman Filter (KF) strategy, which has been applied to solve the state space equations, estimates a process by using a form of feedback control: the filter estimates the state at some time and then obtains feedback in the form of measurement. Thus the equations for KF are divided into two groups: the time update equations and the measurement update equations [6]. The KF has been proved that can resolve the estimate problem in the state space principles for PET image reconstruction. KF uses the feedback control method to reach convergence and obtain the optimal solution, and the detail of this algorithm explains in the [4]. The specific equations for the time and measurement updates are presented as follows:

Time-update equations:

$$\mathbf{x}(t) = A\mathbf{x}(t^-) + B\mu \tag{7}$$

$$\mathbf{P}(t) = A\mathbf{P}(t^-)A^T + Q \tag{8}$$

Measurement-update equations:

$$\mathbf{x}(t) = \mathbf{x}(t^-) + K(y - D\mathbf{x}(t^-)) \tag{9}$$

$$\mathbf{P}(t) = (I - KD)\mathbf{P}(t^-) \tag{10}$$

$$K = PD(DPD + R)^{-1} \tag{11}$$

where the term $P(t)$ denotes the covariance of the estimation error and $P(t^-)$ denotes the covariance of the estimation error of $x(t^-)$. K is called the KF gain.

The above solutions are to estimate the state of a discrete-time controlled process that is governed by a discrete-time linear stochastic difference equation. However, the process to be estimated is continuous-time sometimes. In this case, the time and measurement update equations are required to do some transformations [6]:

$$\dot{\mathbf{x}} = A\mathbf{x}^- + Bu \tag{12}$$

$$\dot{P} = AP^- + P^-A^T + Q \tag{13}$$

$$K = PD^T R^{-1} \tag{14}$$

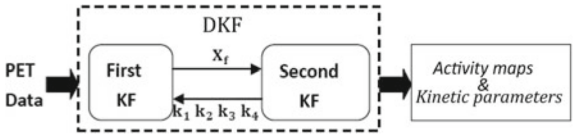
2.4 Dual Estimation Framework

The first Kalman Filter: the PET data as the observation $y(t)$ and kinetic parameters as the known variable, a KF estimate the activity map quantity X_f, where the f means the frame of the reconstruction images. In this process, this framework of the state-space, as Eq. (1), is a continuous-time system, and the compartmental model is the priori, so that the processing noise covariance matrix Q is very little.

The second Kalman Filter: estimate the kinetic parameters from the sequence of X_f. The set of Eqs. (7) and (8) defines the discrete-time state-space representation employed to estimate the kinetic parameters k_1, k_2, k_3 and k_4.

Hence, the process of DKF algorithm is expressed in Fig. 2. the first KF is to reconstruct the activity maps using the kinetic parameters as known parameters, while the other is to estimate the kinetic parameters using the estimation of activity maps as known parameter. Every iteration using the update activity maps and the update kinetic parameters as the known condition respectively to optimize the results until both of the estimations are convergence.

Fig. 2 The principle of the Dual Kalman Filter



3 Experiment and Result

3.1 Experiments with Zubal Phantom

The computer simulation experiments are used to evaluate the accuracy and robustness of the proposed method. Our simulation experiments are based on a Zubal Phamtom. Figure 3a shows a schematic representation of the Zubal Phamtom with three ROIs selected and a background, indicated ROI 1, 2, 3 respectively. The simulated tracer is 11C-acetate and the phantom is digitized at 96 × 96 pixels and forward parallel projection data is calculated at 96 × 96. Time frames of emission images are generated using two-tissue compartmental model and the plasma function, $C_P(t)$, is generated using the Feng Input function [1]:

$$C_P^{acetate}(t) = \left[1 - 0.88\left(1 - e^{-\left(\frac{2ln2}{15}t\right)}\right)\right] C_P^{FDG}(t) \tag{15}$$

$$C_P^{FDG}(t) = (A_1 t - A_2 - A_3)e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + e^{-\lambda_3 t} \tag{16}$$

With $A_1 = 851.1225\,\mu\text{Ci/mL/min}$, $A_2 = 20.8113\,\mu\text{Ci/mL}$, $A_3 = 21.8798\,\mu\text{Ci/mL}$, $\lambda_1 = 4.133859\,\text{min}^{-1}$, $\lambda_2 = 0.01043449\,\text{min}^{-1}$, $\lambda_3 = 0.1190996\,\text{min}^{-1}$.

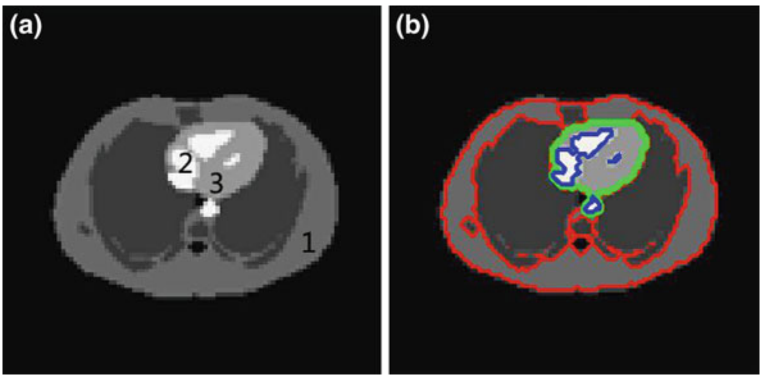


Fig. 3 The schematic representation of the experiments, **a** is Zubal Phantom. **b** is the segmentation of activity map

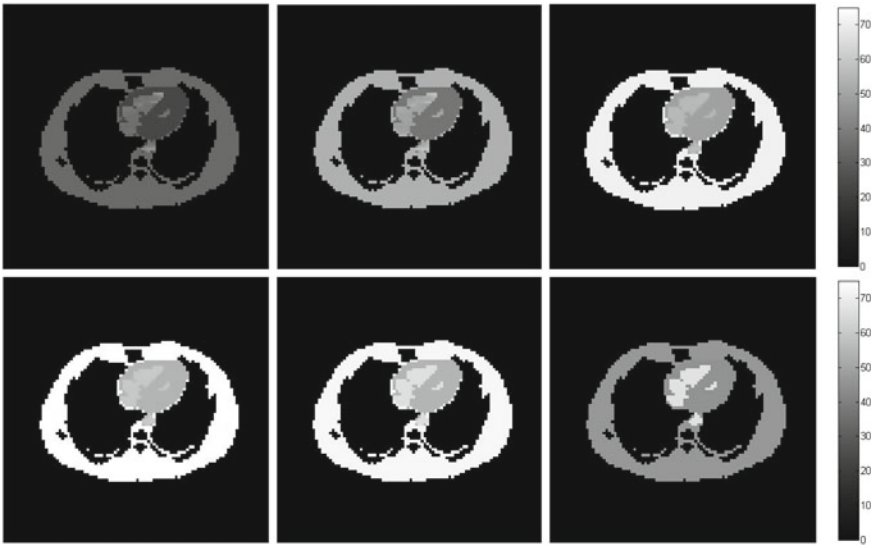


Fig. 4 The estimated activity maps including the 3rd, 7th, 11th, 15th, 20th, 25th time frame

28 frames of dynamic acquisition are performed as 7×0.2 min, 8×0.5 min, 5×1 min, 4×2 min and 4×5 min, total scan time is 40 min.

To evaluate the estimation performances, we take quantitative analysis on the results, by defining the error between the reconstruct result and ground truth as follow:

$$bias = \frac{1}{N_p} \sum_{i=1}^{N_p} \frac{|XR_i - XT_i|}{XT_i} \tag{17}$$

where N_p is the total number of pixels, XR_i is the final estimation result of pixel i, and XT_i is the true value of corresponding pixel i. Figure 4 shows the estimated activity maps from the dynamic PET data, at frame 3, 7, 11, 15, 20 and 25, and the Table 1 summarizes the calculated bias value of the reconstructed images from different time frames. The reconstructed images preserve the image quality at the same level as the results in [7].

Meanwhile, the parameters estimated are summarized in the Table 2. To reduce the calculation time during the experiment, we segment the activity maps as the Fig. 3b, and get the average value of the kinetic parameters via calculating the mean of each ROI.

Comparative study of parameter estimation was taken between existing techniques and our proposed method. The technique, we apply in the comparative study, is the LMWLS estimation algorithm from the COMKAT, which is a software package for compartmental modeling oriented for biomedical image quantification. It should be noted that, for fair comparison, in the fitting procedures, the activity maps from

Table 1 Statistical studies of activity maps

	*frame*3	*frame*7	*frame*11
bias	0.0282	0.0235	0.0124
	*frame*15	*frame*20	*frame*25
bias	0.0160	0.0155	0.0968

Table 2 The parameters estimation using DKF and the LMWLS, compared with the true value (TV)

ROI1	k_1	k_2	k_3	k_4	K_r
TV	0.6518	0.2276	0.0531	0.0388	0.1252
DKF	0.6484	0.2199	0.0526	0.2111	0.1233
LMWLS	0.8302	0.2705	0.0232	0.0009	0.0656
ROI2	k_1	k_2	k_3	k_4	K_r
TV	0.4504	0.2287	0.0725	0.0141	0.1085
DKF	0.4469	0.2172	0.0716	0.0200	0.1108
LMWLS	0.7491	0.3381	0.0044	0.9768	0.0096
ROI3	k_1	k_2	k_3	k_4	K_r
TV	0.7307	0.5369	0.1776	0.0143	0.1816
DKF	0.7252	0.5176	0.1672	0.0109	0.1771
LMWLS	0.9616	0.7192	0.1851	0.0789	0.1968

the our estimation framework are used as the input activity curves for the LMWLS algorithm to estimate the kinetic parameters.

The calculated bias values of the estimated parameters from two methods are demonstrated in the Table 3. Comparing with the variance calculation, it is demonstrate that the variance calculation has no priority to the bias calculation and at the same time it is limited by the four pages requirement, so in this paper, we don't display the variance calculation. The bias of k_1 from our method is about 0.01, but that from the LMWLS is more than 0.25. At the same time, k_2 estimation is 0.05 in our method while around 0.35 in the LMWLS. As we all known, in parameter estimations of 2 compartment model based problem, k_4 is the most difficult one to estimate. By our method, the bias of k_4 is less than 4.4, however, the biggest bias of the LMWLS reaches 66.515. Consequently, the parameter K_r is also adopted to evaluate the algorithm. To some extent it shows that our method can maintain higher accuracy in dual estimation of activity maps and kinetic parameters.

Table 3 Statistical studies of estimated parameters

ROI1	k_1	k_2	k_3	k_4	K_r
$bias_{DKF}$	0.0053	0.0341	0.0096	4.4379	0.0154
$bias_{LMW}$	0.2735	0.1882	0.5632	0.9768	0.4680
ROI2	k_1	k_2	k_3	k_4	K_r
$bias_{DKF}$	0.0079	0.0503	0.0128	0.4114	0.0212
$bias_{LMW}$	0.6630	0.4783	0.9393	66.515	0.9115
ROI3	k_1	k_2	k_3	k_4	K_r
$bias_{DKF}$	0.0076	0.0359	0.0583	0.9235	0.0248
$bias_{LMW}$	0.3159	0.3394	0.0422	4.5375	0.0837

4 Conclusions

Dual estimation of the activity maps and kinetic parameters for dynamic PET imaging is presented in this paper. The procedure is realized by DKF, where one KF is to reconstruct the dynamic images and the other is to estimate the kinetic parameters, and each one uses the results from the other one as initialization, finally, the two filters are solved iteratively until convergence. The simulated experiments indicate that DKF can estimate the activity maps and kinetic parameters robustly and accurately.

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