A general algorithm for optimal sampling schedule design in nuclear medicine imaging

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Abstract

Optimal sampling schedule (OSS) is of great interest in biomedical experiment design, as it can improve the physiological parameter estimation precision and significantly reduce the samples required. A number of well designed algorithms and software packages have been developed, which deal with the instantaneous measurements at discrete times. However, in nuclear medicine tracer kinetic studies, the imaging systems, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), take measurements (images) based on continuous accumulation over time intervals. In this case, the existing algorithms cannot be used to design OSS so as to reduce the image frame numbers. In this paper, a general OSS design algorithm for the accumulative measurement is proposed. The potential usefulness of the algorithm is demonstrated by its designing OSS in [18F] fluoro-2-deoxy-D-glucose (FDG) studies with PET to estimate the local cerebral metabolic rate of glucose. The robustness of parameter estimation using the OSS with respect to intra-subject and inter-subject parameter variations is also presented. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Experiment design; Optimal sampling schedule; Computer simulation; Positron emission tomography; Tracer kinetic modeling; Parameter estimation

1. Introduction

Optimal sampling schedule (OSS) is of great interest in biomedical experiment design, as its use can improve the physiological parameter estimation precision and significantly reduce the number of samples required. DiStefano introduces the advantages of using the experiment design as a tool in dynamic studies of biomedical systems in which very limited data is available [1]. Since then, the OSS design has been investigated extensively to provide guidelines for experiments to optimally arrange the limited number of samples and to conduct cost effective...
studies. Several well designed algorithms which deal with the instantaneous measurements at discrete times, have been developed for finding the OSS design in model-based physiological and pharmacological studies, based on the Fisher information matrix criterion [2–5]. A comprehensive review on experiment design criteria can be found in [26].

In nuclear medicine tracer kinetic studies, however, the imaging systems, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), take images (image frames) by dividing the total scanning time frame into many contiguous intervals and recording the accumulated radioactive counts continuously over each interval into each image frame. Due to this intrinsic difference from instantaneous sampling, the existing algorithms cannot be used to design OSS in order to improve the estimation quality and reduce the number of image frames. Furthermore, it is impossible to obtain replicated measurements from individual scanning intervals [4,5,7]. Therefore, the OSS design has to be reformulated in this new circumstance. For convenience, we shall use PET as our reference imaging system in the following description.

In this paper, a general algorithm for finding the OSS design for the accumulative measurement (which is the measurement of average count rates in a subinterval) is proposed. Several key novel steps incorporating the characteristics of the accumulative measurement and handling the interval merging are presented. The minimum number of image frames is systematically found and properly arranged, based on the D-optimal design criterion, given an initial sampling schedule and a set of optimal design criterion, which is the measurement of average number of image frames is systematically found and properly arranged, based on the D-optimal number of image frames. Furthermore, it is impossible to obtain replicated measurements from different time segments [4,5,7]. Therefore, the OSS design has to be reformulated in this new circumstance. For convenience, we shall use PET as our reference imaging system in the following description.

In this paper, a general algorithm for finding the OSS design for the accumulative measurement (which is the measurement of average count rates in a subinterval) is proposed. Several key novel steps incorporating the characteristics of the accumulative measurement and handling the interval merging are presented. The minimum number of image frames is systematically found and properly arranged, based on the D-optimal design criterion, given an initial sampling schedule and a set of a priori estimated parameters. The potential usefulness of the algorithm is demonstrated by its application to the design of [18F]fluoro-2-deoxy-D-glucose (FDG) PET studies to estimate the local cerebral metabolic rate of glucose (LCMRGlc). In addition, intra-subject and inter-subject parameter variations are investigated to evaluate the robustness of parameter estimation using the OSS approach.

2. The D-optimality

2.1. The system-experiment model

Consider a single-input single-output (SISO) dynamic system [1,5] on the observation interval $[t_0, T]$ with $t_0$ and $T$ representing the start and end times, respectively, and

$$
\dot{x}(t, p) = f[x(t, p), u(t); p] \quad (1)
$$

$$
x(t_0, p) = x_0 \quad (2)
$$

$$
y(t, p) = g[x(t, p); p] \quad (3)
$$

$$
h[x(t, p), u(t); p] \geq 0 \quad (4)
$$

$$
z(t_k) = y(t_k) + e(t_k), \quad k = 1, 2 \cdots, N \quad (5)
$$

$$
y(t_k) = \frac{1}{\Delta t_k} \int_{t_{k-1}}^{t_k} y(t) \, dt \quad (6)
$$

where $x$ is a $n$-dimensional state vector; $t$ represents the time abscissa; $u$ and $y$ are scalar input and output functions; $f$ and $g$ are linear or non-linear functions which describe the structure of the system and output configuration, parameterized by the $P$-dimensional parameter vector $p$. $h$ represents all other available knowledge about the system relating $x$, $u$, and $p$. We assume that the parameters in $p$ are identifiable [8,9] and they can be estimated given measurements $z(t_k)$, which is the noisy corrupted measurement of $y(t_k)$ in Eq. (6), sampled at $N$ discrete times $t_k$; and $e$ is the measurement error, assumed to be additive and zero mean with known variance $\sigma^2(t_k)$. Note the difference of representation in Eq. (6) from the conventional continuous system sampling at discrete times. Instead of sampling at discrete times, the PET imaging system obtains its measurements from different time segments. A PET sampling protocol can be represented as a sequence of $N$ time intervals, viz.,

$$
S = \{I_1, I_2, \ldots, I_N\}
$$

where $I_k = [t_{k-1}, t_k]$ is the $k$th sampling (or scanning) interval with end points $t_{k-1}$ and $t_k$, $k = 1, 2, \ldots, N$. Time $t_0$ is the start point of the study and usually it equals zero. In Eq. (6), $\Delta t_k = t_k - t_{k-1}$ is the length of $I_k$ and $y(t_k)$ is
the tracer concentration to be measured. Note also that \( y(t_k) \) is actually a function of \( I_k \) instead of the value of \( y \) at \((t_{k-1} + t_k)/2\) as regarded in common practice.

2.2. The D-optimality criterion

Assumed that the measurement noise \( e \) is additive with zero mean and with a distribution function which is independent of the parameter estimates, \( p \). The D-optimality criterion is defined as

\[
\Psi(M) = \text{det}(M)^{-1}
\]

(7)

where \( M \) is the Fisher information matrix (to be described later) of the process or system, and \( \Psi \) is the criterion function to be optimized. By the above definition, a D-optimality experiment is obtained by maximizing the determinant of the Fisher information matrix. It has been one of the widely accepted criteria for experiment design as it possesses a convenient geometric interpretation and is invariant to any non-degenerated transformation in model parameters [10,11]. In this study, the D-optimality criterion is adopted in the OSS design of brain FDG–PET studies.

2.3. The noise variance structure

It is important to use an appropriate variance structure in the optimization procedure. Based on the fact that the noise level in PET measurement is related to both the count rate and the scanning length, the variance structure of the measurement error can be described as

\[
\sigma_k^2 = c \frac{y(t_k)}{\Delta t_k}
\]

(8)

where \( c \) is a proportionality constant which determines the noise levels in \( z(t_k) \) [13].

The variance structure given in Eq. (8) accounts for the effect of the length of the scanning time on the measurement and it has been widely used in tracer kinetic modeling with PET [13–16]. This variance model is equivalent to an experimental PET variance model as demonstrated by Jovkar et al. [17]. Eq. (8) plays an important role in incorporating the PET measurement features in the derivation of the OSS design of PET. It is also used to add noise to \( y(t_k) \) in order to simulate the actual output function obtained in practical applications and to investigate the effect to noise on the estimated parameters.

2.4. Parameter estimation

The integral estimation method [12,20] which tries to match the averaged values of the model outputs with PET measurements over the corresponding scanning intervals, was adopted in this study. The following objective function was used in parameter estimation

\[
F(p) = \frac{1}{\sigma_k^2} \left[ \frac{N}{\Delta t_k} \int_{t_{k-1}}^{t_k} y(t) \, dt \right]^2
\]

(9)

where \( p \) is the parameter vector \([k_1, k_2, k_3]^T\) in the FDG model (to be described later); \( \bar{y}_k \) denotes the measurements (PET-measured tracer activity) over interval \( I_k \); and \( \sigma_k^2 \) is the variance of the measurement noise in \( \bar{y}_k \).

2.5. The Fisher information matrix approach

Let \( \hat{p} \) be the unbiased estimates of \( p \). According to the Cramér–Rao theorem, the covariance matrix of \( \hat{p} \), denoted by \( \text{COV}(\hat{p}) \), has the inverse of the Fisher information matrix \( M \) as a lower bound [27]. Furthermore, if the weighting matrix used in the least-squares fitting is the inverse of the data covariance matrix, then a first order approximation for \( \text{COV}(\hat{p}) \) is,

\[
\text{COV}(\hat{p}) \approx M^{-1}
\]

(10)

where \( \approx \) indicates an approximation and \( M^{-1} \) is the inverse of the Fisher information matrix \( M \), which is a measure for parameter information in the data. Under the assumption of Gaussian measurement errors and independent measurements, the element in the \( i \)th row and \( j \)th column of \( M \), denoted by \( m_{ij} \), can be calculated [5,8] from the following,

\[
m_{ij} = \sum_{k=1}^{N} \frac{1}{\sigma_k^2(t_k)} \left[ \frac{\partial y(t_k)}{\partial p_i} \frac{\partial y(t_k)}{\partial p_j} \right]
\]

(11)

where \( \sigma_k^2(t_k) \) is the variance of the measurement error of \( y(t_k) \).
Eqs. (10) and (11) relate (via the partial derivative of \( y(t_k) \) with respect to \( p \)) sampling schedule \( S \) to the covariance matrix \( \text{COV}(\hat{p}) \) which gives a measure of the precision of \( \hat{p} \). Therefore, by adjusting sampling schedule \( S \), some scalar function of the covariance matrix \( \text{COV}(\hat{p}) \) can be optimized. Finding a sampling schedule which minimizes (or maximizes) some scalar functions (for instance, maximization of the determinant of \( M \) in this study) is called the information matrix approach [2,3].

Now, we formally define the following as our cost function,

\[
\Psi(S) = \det(M) \quad (12)
\]

where \( \Psi(\cdot) \) is the cost function to be optimized against sampling schedule \( S \) and \( \det(M) \) represents the determinant of \( M \). Traditionally, a sampling schedule \( S_O \) is said to be optimal if

\[
\Psi(S_O) = \max_S \{ \Psi(S) \} \quad (13)
\]

Note that Eq. (12) is equivalent to Eq. (7) except that the instantaneous sampling schedule is optimized by Eq. (7) while the sampling schedule for interval is optimized by Eq. (12). Detailed mathematical formulation of the information matrix approach can be found elsewhere [28].

2.6. The optimal sampling schedule design

The proposed algorithm (to be described later) always converges, as there are finite number of intervals to start with and \( \Psi(\cdot) \) increases monotonically. After the algorithm converges, the initial sampling intervals will be merged into few numbers of different intervals, each of which may have duplicates. Due to the merging operation in the optimization procedure, the resulting sampling schedule at which \( \Psi(\cdot) \) gains its maximum from the iterative search is in the form,

\[
S_D = \{I_1, n_1), (I_2, n_2), \ldots, (I_d, n_d)\}
\]

where \( d \) is the number of different intervals in the obtained sampling schedule after the algorithm converges; \( (I_k, n_k) \) means that there are \( n_k \) duplicates for interval \( I_k \) and \( \sum_{k=1}^{d} n_k = N \). One explanation to the above \( S_D \) is that in order for the sampling schedule to be D-optimal the \( N \) measurements should be obtained in such a way that \( n_k \) replicated measurements are obtained from interval \( I_k \). This is similar to the instantaneous sampling situation where the instantaneous replicated measurements are required at individual time points in order for the sampling schedule to be optimal [4,5]. However, PET or other nuclear medicine modalities often cannot provide duplicated samples. Therefore, the non-duplicate sampling intervals

\[
S_O = \{I_1, I_2, \ldots, I_d\}
\]

are obtained by ignoring all the replicates, which is similar to the instantaneous optimal sampling design. This reduced number of sampling schedule, \( S_O \), is referred to as the OSS design for nuclear medicine imaging in the sequel. While the use of \( S_O \) could provide the maximum precision in the estimated parameters, the accuracy and precision of the estimated parameters based on \( S_O \) are expected to be comparable with those based on \( S_I \) (see the case study in Section 4). There are quite a number of significant advantages of using \( S_O \), the optimized sampling schedule, which will be discussed in Section 5.

3. The algorithm

3.1. The iterative procedure

According to the information matrix approach as described in the previous section, a D-optimal sampling protocol \( S_O \) is the one at which the cost function \( \Psi(\cdot) \) takes its maximum. The optimization problem is generally non-linear and an optimal design is therefore, obtainable numerically. Fig. 1 presents the flowchart of the iterative procedure for maximizing the cost function and finding the optimal sampling schedule.

The relaxation procedure, which is similar to the one given in [4] in terms of its general frame, is described hereafter. It iteratively, adjusts the scanning intervals, given an initial sampling schedule \( S_I = \{I_1, I_2, \ldots, I_N\} \), a set of \( a \text{ priori} \) parameter estimates, and the two end points of the whole observation interval \([t_0, T]\).
There are two loops as shown in the flowchart. The outer loop corresponds to the iteration. The variable CURRENTCOST is used to record the maximum \( \Psi(S) \) obtained at each iteration and its initial value is calculated from \( S_i \). At the end of each iteration, the convergence condition is checked. The variable CURRENTCOST is compared with LASTCOST to see if the difference between them is greater than a predefined tolerance value. A difference greater than the predefined tolerance will cause the procedure to continue. At the beginning of each iteration, LASTCOST is updated to the maximum \( \Psi(S) \) found in the last iteration.

The inner loop corresponds to the examination and adjustment of each individual interval in the sampling schedule. There are \( N^{(i)} \) different intervals in the \( i \)th iteration \( (i = 1, 2, \ldots) \) with \( N^{(1)} = N \). In this loop, each interval is inspected and adjusted towards the direction in which \( \Psi(S) \) increases. Unlike the algorithms as described in [4,5], which adjust the individual sampling times, our algorithm adjusts the individual sampling intervals instead. Adjusting an interval in the optimization procedure is different from adjusting the discrete time point. Special considerations have to be given and special operation has to be introduced, which are described in the following.

### 3.2. Interval adjustment

Fig. 2 illustrates two neighboring intervals \( I_k \) and \( I_{k+1} \) and their end points. In adjusting interval \( I_k \), only the change of its end point \( t_k \) is considered. The end point \( t_k \) can be moved to the left and right, or it can stay where it is in the adjustment, according to the following rule:

**Rule 1**  

- \( t_k \) not move: if no increase in cost function.
- \( t_k \) move left: if \( \Psi_{\text{move-left}} \geq \Psi_{\text{move-right}} \),
- \( t_k \) move right: if \( \Psi_{\text{move-left}} < \Psi_{\text{move-right}} \).

where \( \Psi_{\text{move-left}} \) and \( \Psi_{\text{move-right}} \) represent the cost after slightly (e.g. 1% of \( \Delta t_k \)) moving \( t_k \) to left and right, respectively. By ‘no increase in cost function’ in Rule 1 we mean that both \( \Psi_{\text{move-left}} \) and \( \Psi_{\text{move-right}} \) are less than the cost before the slightly movement of \( t_k \). If \( t_k \) is adjusted, it will continue to move until \( \Psi(\cdot) \) stops increasing or the lower found, the value of which is set in advance, is reached. This corresponds to the second square box in Fig. 1. Note that the adjustment of \( I_k \) will cause \( I_{k+1} \) (hence \( y(t_{k+1}) \)) to change simultaneously, which must be taken into account in the calculation of the cost function \( \Psi(\cdot) \).

In the circumstance that \( \Psi(\cdot) \) is decrease in the adjustment, a local search is carried out to search for a maximum of \( \Psi(\cdot) \) in the duration, which is after the last increase and before the first decrease. A very simple strategy, which further uniformly refines the duration and finds the maximum, is employed here in the local search. Faster
4. Case study

The developed algorithm was applied to find an OSS design for the FDG model, which is used to quantitatively calculate the LCMRGlc with PET [19]. The three-parameter FDG model is used in this case study. The use of optimal sampling schedules together with the four-parameter [19] and five-parameter [20] FDG models can be found in [21].

4.1. The FDG model

Fig. 4 shows the three-parameter FDG model which represents the FDG concentration in plasma $C^*_p$, the FDG concentration in tissue $C^*_t$, and the phosphorylated FDG (FDG-6-PO$_4$) concentration in tissue $C^*_m$, respectively. The three parameters $k_1$, $k_2$, and $k_3$ in the model are the rate constants representing the tracer transport rates in this dynamic system. Parameters $k_1$ and $k_2$ represent forward and reverse transport rates across the capillary and their units are ml g$^{-1}$ min$^{-1}$ and min$^{-1}$, respectively. Parameter $k_3$ is the rate constant for phosphorylation of FDG and it has the unit min$^{-1}$. Details of this FDG model and its assumptions can be found elsewhere [22].

Mathematically, the FDG kinetics in tissue, i.e. the tissue time–activity curve (TTAC), is given by

$$C^*_t(t) = C^*_p(t) + C^*_m$$

where

$$I_k$$

and

$$I_{k+1}$$

should be considered.

$$\Delta t_k$$

Fig. 3. Merging intervals $I_k$ and $I_{k+1}$ should be considered.

Fig. 4. The three-compartment FDG model with three parameters $k_1$, $k_2$, and $k_3$.

procedures such as the well-known Fibonacci search procedure [4] can be used as well. Nonetheless, the simple search strategy used can serve our purpose very well, and the searching speed is not a problem.

Special consideration on reducing the frame duration in the algorithm is applied to ensure that there is sufficient long duration for acquiring PET measurement. Since PET obtains measurements based on continuously scanning over time intervals, the length of the sampling interval would affect the quality of the acquired measurement [18]. For example, if the sampling interval is too short, the signal-to-noise ratio will be very low and poor quantitative information may be inferred. Therefore, a lower bound is needed for each interval to prevent it from becoming too short in the adjustment. Currently, a uniform lower bound which is equal to 10 s for the scanning intervals is used in the algorithm, and it is a reasonable lower bound on sampling interval for PET measurement. In the event that the lower bound is reached in the adjustment and the cost function $\Psi(\cdot)$ is still increasing, a special operation — merging operation — may take place.

3.3. Merging operation

Fig. 3 demonstrates a situation in which $I_k$ is left adjusted but the lower bound is reached while the cost function $\Psi(\cdot)$ is still increasing. In this case, the merging of two intervals $I_k$ and $I_{k+1}$ are considered according to the following rule:

Rule 2 If \((\Delta t_k \leq BOUND) \text{ AND } (\Psi_{after-merge} > \Psi_{before-merge})\)

Then Merge intervals $I_k$ and $I_{k+1}$

In Rule 2, the value of the lower bound, $BOUND = 10$ s as discussed above, is set in advance. $\Psi_{before-merge}$ and $\Psi_{after-merge}$ represent the values of the cost function before and after the merging operation, respectively. Since two intervals are merged into one, the resulting frame may be more reliable as the larger the time frame, the smaller the variance $\sigma^2(t_k)$ (Eq. (8)) and more reliable measurement can be achieved, although, the total number of intervals is reduced.
and it is the convolution of the system impulse-response function with the tracer concentration in plasma $C_p^*(t)$.

$$C_p^*(t) = \left[ \frac{k_1k_3}{k_2 + k_3} + \frac{k_1k_2}{k_2k_3} e^{-(k_2 + k_3)t} \right] \otimes C_p(t) \quad (15)$$

The LCMRGlc is calculated in the following way [19]

$$\text{LCMRGlc} = \frac{1}{LC} \frac{k_1k_3}{k_2 + k_3} C_p \quad (16)$$

where $LC$ is the lumped constant whose value embodies the difference between FDG and glucose in transport and phosphorylation; $C_p$ denotes the ‘cold’ glucose concentration in plasma and it can be obtained from peripheral blood sampling. In this study, we are only interested in parameter $K = k_1k_3/(k_2 + k_3)$.

4.2. The data set

We have 28 sets of estimated $k_1$, $k_2$, and $k_3$ available from brain dynamic FDG studies on three human subjects. These 28 sets of estimated parameters correspond to 28 regions of interest (ROI’s) from both the grey and white matter areas of the three subjects. The tracer kinetics corresponding to these 28 sets of estimated parameters are illustrated in Fig. 5a–c. These TTAC’s are generated according to Eqs. (6) and (15)...

Fig. 5. The curves used in the simulation. (a) the nine curves corresponding to the nine parameter sets from subject 1, (b) the ten curves corresponding to the ten parameter sets from subject 2, (c) the nine curves corresponding to the nine parameter sets from subject 3; (d) the three real PTAC’s from the three subjects.
Table 1
The $S_I$ used and the $S_D$ and $S_O$ derived. The scanning intervals are expressed in seconds

<table>
<thead>
<tr>
<th>$S_I$</th>
<th>10 × 12, 2 × 30, 2 × 60, 1 × 90, 1 × 210, 2 × 300, 1 × 600, 3 × 1800</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_D$</td>
<td>(332, 13), (1731, 5), (5137, 4)</td>
</tr>
<tr>
<td>$S_O$</td>
<td>332, 1731, 5137</td>
</tr>
</tbody>
</table>

(15) with the use of the corresponding plasma time–activity curve (PTAC) as shown in Fig. 5d. Notice from Fig. 5a–c that there are a broad range of parameter variations both in the same subject and in different subjects. These 28 sets of parameters are used as the nominal parameters in the following simulation.

4.3. The OSS design for TTAC

To estimate the LCMRGlc in dynamic brain FDG-PET studies, the measurements of $C_P^*(t)$ (i.e. the PTAC) is usually obtained from peripheral blood sampling and the measurement of $C_i^*(t)$ (i.e. the TTAC) is obtained from the reconstructed PET images. Therefore, what we are concerned with here is to find the OSS design for TTAC only.

Basically, the algorithm needs two inputs — an initial sampling protocol $S_I$ and a set of a priori estimated parameters. In addition, an input function, i.e. a PTAC, is needed to calculate the system output. In the current case study, a sampling protocol used in practice, which consists of 22 intervals, was chosen as $S_I$ [23]. This schedule is referred to as the conventional sampling schedule (CSS) in the sequel. It is expressed as the number of intervals multiplied by the length of the interval in seconds, as shown in the first row of Table 1. For example, 10 × 12 represents 10–12 s intervals. The averaged parameters $[k_1, k_2, k_3]^T = [0.0811, 0.2288, 0.0399]^T$ from the 28 sets of estimated parameters as described above were used as the set of a priori estimated parameters. The averaged PTAC obtained from the three real PTAC’s (Fig. 5d) was used as the input function as shown in Fig. 6a. The TTAC corresponding to the averaged parameter set and the averaged PTAC is given in Fig. 6b. Finally, the study duration $[t_0, T]$ is chosen to be [0, 7200], i.e. 7200 s or 2 h. Starting from the initial sampling schedule $S_I$, the $S_D$ and $S_O$ were derived from the algorithm as shown in the second and the third rows of Table 1, respectively. The graphical descriptions of the image frames using $S_I$ and $S_O$ are given in Fig. 6c and d. For this three-parameter FDG model, the minimum number of image frames required is exactly three, which is quite consistent with the result in previous studies [3,5–7,24]. That is, the number of samples in OSS is generally equal to the number of unknown parameters in the model for a wide class of models. The $S_D$ given in Table 1 shows how intervals are clustered from $S_I$.

4.4. Computer simulation

As the OSS design $S_O$ is derived by using a set of a priori parameter values and a fixed input function PTAC, we need to investigate if the use of $S_O$ is effective when there are inevitable parameters variations (in different locations of the same subjects or in different subjects) and measurement noise in practical applications. This aspect of using $S_O$ is examined via computer simulation. We choose the previously described 28 parameter sets as nominal parameters to investigate the effect of using $S_O$ on parameter estimation and to examine the impact of parameter variations in the same subject (intra-subject) and in different subjects (inter-subject) on parameter estimation with $S_O$.

The effect of noise on parameter estimation is also studied. Six noise levels, which correspond to averaged deviations ranging from 7 to 35% in the measurements with $S_I$, were added to TTAC’s in the simulation. The averaged deviation is calculated as the average of the deviations in all the measurements with $S_I$. By varying the value of $c$ in Eq. (8), different averaged deviations, hence different noise levels in measurements, are generated. These noise levels are comparable with those used in [13,17].

For each of the 28 sets of parameters, 1000 simulations were performed at each of the six noise levels with the use of both $S_I$ and $S_O$. 

4.5. Comparison of parameter estimation

In this study, the coefficient of variation (CV) and the percentage error of the estimated parameter were used mainly as criteria to characterize and compare the estimation results. For a parameter with true value \( k \), let \( \hat{k} \) be the mean of its estimates, S.D. be the sample standard deviation, and \( \Delta k = |k - \hat{k}| \) the bias. The percentage error of the estimated parameter mean \( \hat{k} \) from its true value \( k \) is defined as \( (\Delta k / |k|) \times 100\% \) and the CV of \( \hat{k} \) is calculated as S.D. / |\( \hat{k} \)|.

4.6. Statistical analysis

Fig. 7a–d plot the typical CV’s of the estimated parameters, for both the conventional and optimal sampling schedules at the highest noise level used in simulation. The CV results of arbitrarily selected four parameter sets from each of the three subjects is presented. Set-ij means that it is the jth arbitrarily selected parameter set from subject i, where \( i = 1, 2, 3 \) and \( j = 1, 2, 3, 4 \). It can be seen from the figure that CV’s of \( \hat{k}_1 - \hat{k}_3 \) and \( \hat{K} \)
from using both OSS and CSS are quite comparable, although, those from OSS are just slightly larger than that of CSS. The estimated parameter $\hat{K}$ has the smallest CV's when compared with $\hat{k}_1 - \hat{k}_3$. This is due to the fact that its calculation is very insensitive to the errors in $\hat{k}_1 - \hat{k}_3$, i.e., the errors in $\hat{k}_1 - \hat{k}_3$ are compensated each other in calculating $\hat{K}$ [19]. These results on CV's of the estimated parameters suggest that the use of OSS design is as effective as the use of CSS in terms of parameter estimation precision.

Fig. 8a–d illustrate the percentage errors in $\hat{k}_1 - \hat{k}_3$ and $\hat{K}$ at the highest noise level for the 12 parameter sets. Again, the results for OSS and CSS are quite comparable, suggesting that parameters can be estimated very accurately using OSS. Finally, we can also notice from Figs. 7 and 8 that the parameter estimation using the OSS design is quite insensitive to both the intra-subject and the inter-subject parameter variations.

4.7. Effects of noise

Errors in the estimated parameters are usually caused by the measurement noise. Six noise levels
Fig. 8. Comparison of percent errors in $\hat{k}_1$, $\hat{k}_2$, $\hat{k}_3$, and $\hat{K}$ from both CSS and OSS. The results were obtained with the highest tissue noise level used in simulation.

Table 2
The averaged CV’s (in %) in $\hat{k}_1$, $\hat{k}_2$, $\hat{k}_3$, and $\hat{K}$ from the 28 parameter sets at all the six noise levels

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$\hat{k}_1$ OSS</th>
<th>$\hat{k}_2$ CSS</th>
<th>$\hat{k}_3$ OSS</th>
<th>$\hat{k}_3$ CSS</th>
<th>$\hat{K}$ OSS</th>
<th>$\hat{K}$ CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.18</td>
<td>2.71</td>
<td>5.02</td>
<td>4.15</td>
<td>2.30</td>
<td>1.93</td>
</tr>
<tr>
<td>2</td>
<td>6.40</td>
<td>5.44</td>
<td>10.07</td>
<td>8.35</td>
<td>4.58</td>
<td>3.86</td>
</tr>
<tr>
<td>3</td>
<td>9.46</td>
<td>8.14</td>
<td>14.88</td>
<td>12.46</td>
<td>6.88</td>
<td>5.82</td>
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<td>12.16</td>
<td>10.63</td>
<td>18.96</td>
<td>16.11</td>
<td>9.02</td>
<td>7.60</td>
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<tr>
<td>5</td>
<td>14.48</td>
<td>12.91</td>
<td>22.40</td>
<td>19.52</td>
<td>11.06</td>
<td>9.46</td>
</tr>
<tr>
<td>6</td>
<td>16.43</td>
<td>14.82</td>
<td>25.11</td>
<td>22.23</td>
<td>12.96</td>
<td>11.17</td>
</tr>
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</table>
Table 3
The averaged percent errors in $\hat{k}_1 - \hat{k}_3$ and $\hat{K}$ from 28 parameter sets at all the six noise levels

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$\hat{k}_1$</th>
<th>$\hat{k}_2$</th>
<th>$\hat{k}_3$</th>
<th>$\hat{K}$</th>
</tr>
</thead>
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<td>OSS CSS</td>
<td>OSS CSS</td>
<td>OSS CSS</td>
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<tr>
<td>1</td>
<td>0.08 0.08</td>
<td>0.15 0.12</td>
<td>0.12 0.09</td>
<td>0.08 0.07</td>
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<tr>
<td>2</td>
<td>0.38 0.19</td>
<td>0.65 0.30</td>
<td>0.15 0.13</td>
<td>0.09 0.09</td>
</tr>
<tr>
<td>3</td>
<td>0.55 0.43</td>
<td>0.97 0.74</td>
<td>0.19 0.14</td>
<td>0.15 0.10</td>
</tr>
<tr>
<td>4</td>
<td>0.68 0.57</td>
<td>1.13 0.99</td>
<td>0.55 0.23</td>
<td>0.22 0.14</td>
</tr>
<tr>
<td>5</td>
<td>0.65 0.85</td>
<td>1.14 1.33</td>
<td>0.92 0.40</td>
<td>0.35 0.23</td>
</tr>
<tr>
<td>6</td>
<td>1.03 0.78</td>
<td>1.79 1.34</td>
<td>1.48 0.78</td>
<td>0.49 0.32</td>
</tr>
</tbody>
</table>

were chosen in the simulation conducted to investigate the effect of noise on parameter estimation using OSS.

Table 2 illustrates the averaged CV’s of $k_1 - k_3$ and $K$ from the 28 parameter sets at all the six noise levels used in simulation. As expected, the fluctuations (characterized by CV) in parameter estimates increase as the noise increases. The CV results for OSS are quite similar to those for CSS, indicating that parameter estimation using both OSS and CSS is similar as far as the effect of noise is concerned. The accuracy of parameter estimates is also quite similar for OSS and CSS at different noise level situations as illustrated in Table 3. Parameters can be estimated very accurately using OSS at different noise levels. Given the limited number of simulations, there is a very small amount of increase in biases (characterized by percentage errors) as the noise is getting higher. This increase, however, is by no means significant.

5. Discussion

A general algorithm for optimal sampling schedule design in the context where measurements are obtained based on accumulation, has been presented. This general algorithm can automatically find the minimum number of image frames and properly arrange them using the D-optimality criterion. The accumulative measurement characteristics is incorporated into the OSS design process by using the measurement variance structure given in Eq. (8), which takes both the length of the scanning interval and the value of the model output into account. Besides, to take the noise characteristics of PET measurement into consideration and to avoid low signal-to-noise ratio in the measurement, a lower bound is introduced to prevent intervals from becoming too short in the adjustment. The value of the lower bound is set before the optimization starts. In the current study, the value used is 10 s. However, different values can be used and it is only a matter of choice before the beginning of the optimization. Although, the adjusted/merged frames can be kept as they are, when the lower bound is reached, resulting in a large number of short-duration frames, the signal-to-noise ratio will be very low in these frames.

The number of intervals in an OSS design derived are dependent on the number of unknown model parameters, and generally it is equal to the number of unknown model parameters for a wide class of models [5]. The initial sampling schedule with which the algorithm starts is not important. In fact, sampling schedule with different number of intervals and distributions can be used as initial sampling schedules for the algorithm to start with. They will be finally adjusted and merged into an identical OSS design as long as the a priori parameter set is the same. The distribution of intervals in an OSS design found depends only on the study duration $[t_0, T]$ and the a priori model parameters used.

The three-parameter FDG model has been used as a case study to demonstrate the usefulness of the algorithm in finding OSS design for PET system. An OSS design consisting of three intervals for the three-parameter FDG model was obtained starting from a sampling schedule used in practice. As mentioned above, a different initial sampling schedule can be used and the same OSS design will
be obtained, given that the same set of averaged parameters are used. For the four- and five-parameter FDG models [19,20], we have demonstrated that four and five scanning intervals in the OSS design are adequate to generate good parameter estimates [21].

The validity of using the OSS design is investigated by computer simulation. It has been shown that the quality of parameter estimation with the use of OSS is very much comparable to that with the use of CSS in terms of the accuracy and precision of the estimated parameters (Tables 2 and 3, Figs. 7 and 8). The effect of measurement noise on parameter estimation using OSS is very similar to that of using CSS. The effect of intra-subject and inter-subject parameter variations on parameter estimation using the OSS design is also investigated. Twenty eight parameter sets obtained from three human subjects were used to represent a broad range of parameter variations (Fig. 5). It seems that the OSS design derived from the averaged parameter set (i.e. the population mean of the 28 sets) works quite well and the use of it is insensitive to different parameter variations in terms of the parameter estimates obtained. The CV's and percentage errors of the estimated parameters (Figs. 7 and 8) have demonstrated the consistent behavior of using the OSS design in parameter estimation. This robustness of parameter estimation with respect to intra-subject and inter-subject parameter variations is of particular importance for OSS to be used in practical applications and in the generation of parametric images.

There are a number of significant advantages of using the OSS approach. Firstly, the data storage space can be significantly reduced. For the three-parameter FDG model as demonstrated in the case study, the use of three scanning intervals in adequate to generate good parameter estimates. Compared with the use of 22 scanning intervals in a conventional sampling schedule, the storage space is reduced by more than 80%. The reduction of frame numbers is essential for the future diagnostically lossless data compression in the spatial domain [29], which can reduce the storage space by more than 95% and greatly facilitate the data retrieval, the on-line image database management, and the communications via Internet. Secondly, the data processing time can also be significantly reduced as fewer images (or measurements) mean shorter time in data analysis. For instance, the time required for data analysis can be reduced by 75% with the use of OSS, which is very important as medical imaging, is becoming more and more involved in scientific research and clinical diagnosis and the outcome of data analysis must be available promptly. The significance of the reduction in processing time can be even pronounced in the generation of functional images [25]. Thirdly, using the new modeling approach of OSS, fast sampling speed is not required to capture the peak value, which is very important for myocardial PET study where input function can be obtained non-invasively in the left-ventricle (LV) [30]. Fourthly, using traditional sampling schedule, we often end up with too many very noisy dynamic image frames on the computer screen. On the other hand, OSS can provide images that are easy for displaying in a multiple-plane manner, and that are more reliable and informative for clinical applications. And finally, there are additional potential benefits of applying the OSS approach to SPECT. In traditional full dynamic tomographic data acquisition, short frame times of sampling is often desired in order to have more accurate data for subsequent analysis. However, it can lead to severe bias in the reconstructed images due to high noise level and low count in short image frames. As the frame rate in dynamic SPECT is limited by the mechanical rotation speed of the detectors, high speed of sampling rate is impractical. With OSS, the minimum frame duration is substantially longer than with traditional full dynamic tomographic data acquisition. It allows SPECT to record data without fast rotation of detectors while maintaining parameter estimation accuracy as compared to those obtained from full dynamic data acquisition.

Although, the algorithm is developed to generate optimal sampling intervals so that the storage space needed for dynamic imaging data and the time required for data analysis can be greatly reduced, it can also be used to optimally arrange the distribution of the intervals in a sampling schedule based on the D-optimality criterion, if the merging operation is suppressed. If needed, lower and upper bounds for each interval can be intr-
duced and specified for this purpose. This application of the algorithm can be used to verify those sampling protocols commonly used in practice and can possibly help to improve the precision of the quantitative information extracted.

The current study presents an algorithm for optimal sampling schedule design for TTAC (i.e. the output function) only. The extension of the algorithm to the design of OSS for both PTAC and TTAC simultaneously in non-invasive dynamic cardiac PET studies is currently under development and the result will be reported separately.

6. Conclusions

We have developed a general optimal sampling schedule design algorithm for accumulative measurements, which fills the gap that the existing algorithms and software packages do not cover. Based upon the merging operation introduced, the algorithm can automatically find the minimum number of image frames required for parameter estimation and properly arrange them. Computer simulations based on real experimental data from dynamic brain FDG-PET studies have demonstrated the usefulness of the algorithm. With the use of the OSS design, the parameter estimation accuracy and precision are basically maintained while the number of image frames is greatly reduced, which leads to a significant reduction in image storage space and data processing time. The algorithm developed seems to be applicable to imaging systems such as PET, SPECT, and the like to provide the OSS design in order to greatly reduce the computer resources required without losing quality in parameter estimation.

Acknowledgements

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References


