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A Robust State-Space Kinetics-Guided Framework for Dynamic PET Image Reconstruction

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Abstract

Dynamic PET image reconstruction is a challenging issue due to the low SNR and the large quantity of spatio-temporal data. We propose a robust state-space image reconstruction (SSIR) framework for activity reconstruction in dynamic PET. Unlike statistically-based frame-by-frame methods, tracer kinetic modeling is incorporated to provide physiological guidance for the reconstruction, harnessing the temporal information of the dynamic data. Dynamic reconstruction is formulated in a state-space representation, where a compartmental model describes the kinetic processes in a continuous-time system equation, and the imaging data is expressed in a discrete measurement equation. Tracer activity concentrations are treated as the state variables, and are estimated from the dynamic data. Sampled-data H_∞ filtering is adopted for robust estimation. H_∞ filtering makes no assumptions on the system and measurement statistics, and guarantees bounded estimation error for finite-energy disturbances, leading to robust performance for dynamic data with low SNR and/or errors. This alternative reconstruction approach could help to deal with unpredictable situations in imaging (e.g. data corruption from failed detector blocks) or inaccurate noise models. Experiments on synthetic phantom and patient PET data are performed to demonstrate feasibility of the SSIR framework, and to explore its potential advantages over frame-by-frame statistical reconstruction approaches.

1. Introduction

Positron emission tomography (PET) measures the spatiotemporal distribution of metabolically active compounds in living tissue (Phelps 2000). Dynamic PET imaging involves a sequence of contiguous acquisitions or list mode acquisition. From dynamic PET data, we can reconstruct the spatial distribution of radioactivity over time, and/or estimate physiological parameters of the imaged tissue. The focus of this paper is on reconstructing activity images, and the term ‘dynamic PET reconstruction’ is used exclusively for activity reconstruction unless otherwise specified.

Conventionally, dynamic PET reconstruction is accomplished by reconstructing activity images *independently* at individual frames, using static image reconstruction methods (Leahy & Qi 2000, Lewitt & Matej 2003). Since the number of photons per time bin (or ‘frame’) is reduced with increased temporal resolution in dynamic imaging, these methods may lead to very noisy images, thus imposing a limitation on the temporal resolution of the scanner and its ability to capture kinetic changes. Moreover, most statistical reconstruction methods are based on an assumption of a Poisson measurement distribution, which is invalidated if preprocessing steps are applied to PET data. In particular, after corrections for attenuation and random and scattered coincidences, it is difficult to describe the data distribution with one certain model.

The most straightforward approach to improving PET image SNR with noisy data is to include the noise and bias effects of attenuation and random and scattered coincidences in the scanner model (Qi et al. 1998, Iatrou et al. 2004). With the added time dimension of dynamic imaging, several methods have been proposed to reduce noise through the use of prior temporal knowledge, such as imposing temporal smoothing in the reconstruction (Waldge et al. 2004, Taek-Soo et al. 2005). Alternatively, principal component analysis (PCA) can be used to transform the dynamic PET data in the temporal domain for noise reduction (Kao et al. 1997) or data decomposition (Wernick et al. 1999). Another approach is to use temporal basis functions, which can be a B-spline model (Nichols et al. 2002, Li et al. 2007), or can be adaptively determined from activity images (Matthews et al. 1997).

Tracer kinetic models, which are developed to quantify the underlying biological processes based on dynamic PET images (Carson & Cobelli 2001, Cobelli et al. 2000), can themselves be used as prior physiological knowledge in the reconstruction process. Several studies have used kinetic models as temporal priors for dynamic SPECT (Kadrmas & Gullberg 2001) or PET (Reader et al. 2006) reconstruction. These methods perform a post-reconstruction temporal smoothing based on a kinetic model, and have noise reduction effects on conventional reconstruction. However, it is also possible to include kinetic modeling directly in the reconstruction process. In such 4D PET reconstruction, parametric images can be directly reconstructed from dynamic PET data (Tsoumpas et al. 2008a, Tsoumpas et al. 2008b, Rahmim et al. 2009, Kamasak et al. 2005, Wang et al. 2008).

Here we propose a state-space image reconstruction (SSIR) method for dynamic PET reconstruction. We consider the PET data as observations of the underlying kinetic processes, and formulate the reconstruction problem in a state-space representation. The compartmental model serves as a continuous-time system equation, and the imaging data is expressed as discrete sampling of the system states in a measurement equation. Tracer activity concentrations in kinetic models are treated as the state variables, which are to be estimated from the dynamic data. Dynamic PET reconstruction becomes a state estimation problem in this SSIR framework. We apply a robust H_∞ filtering strategy for the estimation, with the motivation that this is a robust approach in unpredictable situations (e.g. complicated data statistics, failed detector blocks, or inaccurate scatter/attenuation corrections).

H_∞ filtering, which has its origins in robust control (Doyle et al. 1989), minimizes the maximum estimation error over all noise disturbances that lead to the same observations, and guarantees bounded estimation error for all finite-energy disturbances (Nagpal & Khargonekar 1991). Unlike statistically-principled reconstruction methods, the filter requires no prior knowledge of noise statistics (Shaked & Theodor 1992). It is thus particularly suitable for PET image reconstruction in situations when precorrections are performed leading to unknown and poorly modeled data statistics and/or when unknown errors exist in the data (such failed detector blocks, erroneous data corrections, etc). The robustness of H_∞ filtering has been shown for static PET image reconstruction (Liu et al. 2005). Based on our previous efforts (Tong & Shi 2007), we formulate *dynamic* PET reconstruction in a *hybrid* paradigm of continuous kinetics and discrete measurements based on tracer kinetic modeling. With this formulation, a *sampled-data* filtering solution (Sun et al. 1993) is needed to tackle the incompatibility of system and measurements. This SSIR framework assumes known kinetic parameters from population distributions (Graham et al. 2002, Muzi et al. 2005). These parameters are not considered accurate for a specific subject, and the discrepancy is modeled in the kinetic system uncertainty. Through the H_∞ filtering strategy, this *general* prior model is coupled with the *patient-specific* PET data to provide estimates for a specific subject.

In the following sections, we present the theoretical basis of our method, followed by experiments with simulations and patient data to show proof-of-principal of the SSIR framework.

2. Methodology

In our SSIR framework, tracer activity concentration are treated as the state variables, and are estimated from dynamic data through a robust filtering strategy. The framework consists of four key components: (1) a tracer kinetic model describing kinetic changes; (2) an imaging model which relates tracer activity to dynamic PET data; (3) a state-space formulation of the reconstruction problem; (4) a robust filtering solution. Each of the four components is presented in the following subsections.

2.1. Two-Tissue Compartmental Modeling of PET Tracer Kinetics

We adopt a two-tissue compartment model to describe the radiotracer kinetic processes. This model is commonly used to describe the uptake and retention of an analog of glucose, fluorodeoxyglucose (FDG) (Carson & Cobelli 2001). The structure of the model is illustrated in Figure 1, where C_P is the arterial concentration of nonmetabolized tracer in plasma, C_E is the concentration of nonmetabolized tracer in tissue, C_M is the concentration of the radioisotope-labeled metabolic products in tissue, and the kinetic parameters k_1 , k_2 , k_3 , k_4 (min^{-1}) are first-order rate constants specifying the the tracer exchange rates between compartments.

By applying the model in Figure 1 to all voxels and assuming a space-invariant tracer delivery C_P , the kinetic process for any voxel i ($i = 1, \dots, N$) is governed by the following differential equation (Cobelli et al. 2000):

$$\begin{bmatrix} \dot{C}_{Ei}(t) \\ \dot{C}_{Mi}(t) \end{bmatrix} = \begin{bmatrix} -(k_{2i}+k_{3i}) & k_{4i} \\ k_{3i} & -k_{4i} \end{bmatrix} \begin{bmatrix} C_{Ei}(t) \\ C_{Mi}(t) \end{bmatrix} + \begin{bmatrix} k_{1i} \\ 0 \end{bmatrix} C_P(t) \quad (1)$$

with the subscript i denoting different voxel locations. The above kinetic equation can be expressed in a compact notation as:

$$\frac{dx_i(t)}{dt} = a_i x_i(t) + b_i C_P(t) \quad (2)$$

where $x_i(t) = [C_{Ei}(t) \ C_{Mi}(t)]^T$, $a_i = \begin{bmatrix} -(k_{2i}+k_{3i}) & k_{4i} \\ k_{3i} & -k_{4i} \end{bmatrix}$, $b_i = [k_{1i} \ 0]^T$. The input $C_P(t)$ is assumed to be known here; in practice, $C_P(t)$ can be measured directly from arterial plasma samples during the imaging procedure (Phelps 2004), or estimated from imaged volumes that consist primarily of blood (Wong et al. 2001). The total tissue radioactivity concentration, $C_{Ti}(t)$, which directly generates the PET measurements through positron emission, can be expressed as:

$$C_{Ti}(t) = (1 - V_{Bi})[C_{Ei}(t) + C_{Mi}(t)] + V_{Bi}C_{WB}(t) \quad (3)$$

where V_{Bi} is the vascular volume fraction at voxel i , and $C_{WB}(t)$ is the radioactivity concentration in whole blood (i.e. plasma plus blood cells plus other particulate matter). Since V_{Bi} is difficult to measure in practice and for computational simplicity (Carson &

Cobelli 2001, Kamasak et al. 2005), $C_{Ti}(t)$ is simplified in this paper as the sum of the concentrations of nonmetabolized and metabolized tracer at that voxel location:

$$C_{Ti}(t) = C_{Ei}(t) + C_{Mi}(t) = \begin{bmatrix} 1 & 1 \end{bmatrix} x_i(t) \quad (4)$$

2.2. Imaging Model for Dynamic PET Data

In dynamic imaging, the k th scan ($k = 1, \dots, K$) attempts to measure the accumulation of the total concentration of radioactivity on the scanning time interval $[t_{k-1}, t_k]$, so the measured activity in scan k for voxel i ($i = 1, \dots, N$) is expressed as:

$$\lambda_{ik} = \int_{t_{k-1}}^{t_k} C_{Ti}(t) dt = \int_{t_{k-1}}^{t_k} \begin{bmatrix} 1 & 1 \end{bmatrix} x_i(t) dt \quad (5)$$

The activity image of the k th scan Λ_k is $\Lambda_k = [\lambda_{1k}, \lambda_{2k}, \dots, \lambda_{Nk}]^T$.

In PET imaging, the true coincidences are contaminated by the random coincidence and the scattered coincidence events. The raw data $y_k^{(p)}$ is measured by coincidence detection using a prompt time window with mean $E[y_k^{(p)}] = D\Lambda_k + r_k + s_k$, where D is the imaging matrix, r_k is mean of the random coincidence events, s_k is mean of the scattered coincidence events, and $E[\cdot]$ denotes the mathematical expectation. Prompt coincidence events $y_k^{(p)}$ are Poisson distributed (Nichols et al. 2002), and maximum-likelihood-based reconstruction methods are built on this assumption. In practice, however, pre-corrections can alter the data distribution and make it difficult to model the data statistics *a priori*. In our work, we model the corrected data y_k in a measurement equation as:

$$y_k = D\Lambda_k + g_k \quad (6)$$

where y_k is an $M \times 1$ vector with M being the number of the detector pairs, and the measurement noise g_k is to account for the unknown measurement errors during the imaging. Note that we do not assume any specific distribution of the corrected data y_k .

2.3. State-Space Formulation for Dynamic PET Reconstruction

Equations (2) and (6) form a state-space-like representation for the dynamic PET reconstruction problem. However, the temporal integration in equation (5) hinders direct application of filtering strategies. One simplification method is to assume that $C_{Ti}(t)$ piecewise constant during each scan (Kamasak et al. 2005), but this approximation becomes less accurate for long scan intervals or rapidly changing radioactive concentrations. Thus we convert the problem into a standard state-space representation.

2.3.1. Step 1: Constructing the State Equation via Time Integration—

For each voxel i , let $f_i(t) = \int_0^t x_i(\tau) d\tau$ ($f_i(t)$ is a 2×1 vector), equation (2) can then be integrated to generate an equivalent form as:

$$\frac{df_i(t)}{dt} = a_i f_i(t) + b_i \tilde{C}_p(t) \quad (7)$$

with $\tilde{C}_p(t) = \int_0^t C_p(\tau) d\tau$, and the measured activity in equation (5) can be written as:

$$\lambda_{ik} = [1 \quad 1] [f_i(t_k) - f_i(t_{k-1})] \quad (8)$$

Defining the state vector $F(t) = [f_1(t)^T, f_2(t)^T, \dots, f_N(t)^T]^T$ (a $2N \times 1$ vector), and also introducing a system noise term $\tilde{v}(t)$, the system kinetic equation for all voxels can be constructed from equation (7) as:

$$\frac{dF(t)}{dt} = AF(t) + B \tilde{C}_p(t) + \tilde{v}(t) \quad (9)$$

where the system matrix A is a $2N \times 2N$ block diagonal matrix with blocks a_i , the input gain B is of size $2N \times 1$ as $B = [b_1^T, b_2^T, \dots, b_N^T]^T$, and $\tilde{v}(t)$ is to account for the uncertainties in tracer kinetics coming from input disturbances and modeling errors. The activity image Λ_k can then be expressed as:

$$\Lambda_k = \tilde{T} [F(t_k) - F(t_{k-1})] \quad (10)$$

where the $N \times 2N$ transformation matrix $\tilde{T}$ is block diagonal with each block being $[1 \quad 1]$.

Equation (9) describes the radiotracer kinetic process, which incorporates prior physiological knowledge into the reconstruction.

2.3.2. Step 2: Deriving the Measurement Equation—Defining the new

measurements $z_k = \sum_{l=1}^k y_l$, the new measurement equation can be derived from equations (6) and (10) as

$$z_k = D \tilde{T} F(t_k) + e_k = L F(t_k) + e_k \quad (11)$$

where $L = D \tilde{T}$ is the measurement matrix, and e_k is the measurement noise after the transform with $e_k = \sum_{l=1}^k g_l$.

Equations (9) and (11) form the standard state-space representation, where equation (9) describes the *continuous-time* radiotracer kinetic process, and equation (11) models the transformed PET data as *discrete sampling* of the system states. The system noise $\tilde{v}(t)$ can include modeling errors, so kinetic parameters do not need to be known exactly. By coupling this general model with patient-specific measurements z_k , we can obtain subject-specific estimates of the state variables $F(t)$, and calculate the reconstructed activity images Λ_k using equation (10). In this way, the dynamic PET reconstruction problem has been formulated as a state estimation problem.

2.4. Sampled-Data H_∞ Filtering for Dynamic PET Reconstruction

We apply the sampled-data H_∞ filter to the estimation problem in equations (9) and (11). First, sampled-data filtering is used to tackle the incompatibility between continuous states and discrete measurements. Second, the mini-max H_∞ estimation criterion is adopted to deal with the imperfect knowledge of PET data statistics. We present the formulation of the H_∞ criterion and the filtering algorithm in the following.

The formulation of the H_∞ criterion involves the definition of a filtering performance measure J and a noise reduction level γ . We follow the formulation presented in (Sun et al. 1993). Define the performance measure of the sampled-data H_∞ filter, J , as:

$$J = \frac{\|F(t) - \hat{F}(t)\|_{W_1(t)}^2}{\|\tilde{v}(t)\|_{W_2(t)^{-1}}^2 + \|e_k\|_{W_3(k)^{-1}}^2 + \|F_0 - \hat{F}_0\|_{P_0^{-1}}^2} \quad (12)$$

with $\hat{F}_\lambda(t)$ denoting the estimate of $F(t)$. The notation $\|x\|_G^2$ is defined as the square of the weighted (by G) L_2 norm of x , i.e. $\|x\|_G^2 = x^T G x$. Here, $W_1(t)$, $W_2(t)$, $W_3(k)$ and P_0 are the weighting matrices for the estimation error, the process noise, the measurement noise, and the initial estimate, respectively, and $\hat{n}_0$ is the initial state estimate. Thus, J is the value of the estimation error relative to the values of the process noise, the measurement noise, and the uncertainty in the initial state.

Recall γ is the prescribed noise reduction level. The H_∞ criterion is defined as

$$\sup J \leq \gamma^2 \quad (13)$$

where the supremum is taken over all possible disturbances and initial states that determine J through equation (12). Equation (13) defines the mini-max H_∞ criterion. Given $\gamma > 0$, the sampled-data H_∞ filter will search all possible estimates $\hat{n}(t)$ such that the optimal estimate of $F(t)$ has bounded estimation error even in the worst-case scenario. Equation (13) guarantees the bounded estimation error over all possible disturbances of finite energy, regardless of the noise statistics and/or data errors. As a result, the filter is robust to disturbances and variations and is well suited to conditions when system disturbances and data uncertainties have highly complicated statistics and can not be known exactly, as is the case in PET image reconstruction with erroneous data corrections.

Under the formulation of equation (13), the sampled-data H_∞ filtering algorithm was derived and presented in (Sun et al. 1993), but their algorithm does not include weighting matrices in the performance measure J . In robust control and estimation, weighting matrices can be incorporated to achieve performance trade-offs (Shen & Deng 1997). In our work, we include weighting matrices $W_1(t)$, $W_2(t)$, $W_3(k)$ in J as defined in equation (12), and accordingly modify the filtering equations developed in (Sun et al. 1993). The filtering algorithm for our hybrid paradigm of equations (9) and (11) is given as follows:

$$\frac{d\hat{F}(t)}{dt} = A\hat{F}(t) + B\tilde{C}_p(t) \quad (14)$$

$$\hat{F}(t_k) = \hat{F}(t_k^-) + P(t_k)L^T W_3(k)^{-1} [z_k - L\hat{F}(t_k^-)] \quad (15)$$

where $\hat{F}(t_k^-) = \lim_{\varepsilon \rightarrow 0} \hat{F}(t_k - \varepsilon)$, and $P(t_k)$ is the stabilizing solution to the following Riccati equation (Reid 1972) with jumps:

$$\frac{dP(t)}{dt} = AP(t) + P(t)A^T + \frac{P(t)W_1(t)P(t)}{\gamma^2} + W_2(t) \quad (16)$$

$$P(t_k) = P(t_k^-) [I + L^T W_3(k)^{-1} L P(t_k^-)]^{-1} \quad (17)$$

with the initial condition $P(0) = P_0$.

The filter given above can be understood in an intuitive manner. Between observation time instants when the PET data are collected, the state estimate is propagated according to the continuous kinetics described by equation (14), and the state prediction $\widehat{F}(t_k^-)$ is obtained by solving this differential equation on the scan interval $[t_{k-1}, t_k]$, with the previous state estimate $\widehat{n}(t_{k-1})$ as the initial condition of the differential equation. Then at the observation time $t = t_k$, the new measurement z_k is used to update the estimate in equation (15) with the filter gain being $P(t_k)L^T W_3(k)^{-1}$. $P(t_k^-)$ is obtained by solving the Riccati differential equation (16) with $P(t_{k-1})$ as the initial condition, and is then updated through equation (17) to generate $P(t_k)$.

The complete sampled-data H_∞ filtering algorithm is summarized in Algorithm 1 below. The non-negativity constraint is enforced not in the filtering steps, but rather in a post-processing step. When generating the activity image Λ_k using equation (10), negative activity values are replaced with zero.

2.5. Computational Issues of the Reconstruction Framework

2.5.1. Numerical Issues and Sequential Processing—Equation (16) is a matrix Riccati differential equation. It contains movable singularities and can cause stability problems when standard Runge-Kutta methods (Dormand & Prince 1980) are applied. Möbius schemes (Schiff & Shnider 1999) can integrate accurately through the singularities, and are thus adopted in our implementation.

For large data sets, calculation in the update equations (15) and (17) may exceed computer memory limits. A sequential processing method, which is similar to block-iterative schemes (Hudson & Larkin 1994) and sequential Kalman filter (Bar-Shalom et al. 2001), is proposed here to alleviate the computational burden.

The measurement data z_k is partitioned into M_0 blocks of equal size as:

$$z_k = [z_k^{(1)T}, z_k^{(2)T}, \dots, z_k^{(M_0)T}]^T \quad (18)$$

Correspondingly, the measurement matrix L and the measurement noise e_k are partitioned as: $L = [L^{(1)T}, L^{(2)T}, \dots, L^{(M_0)T}]^T$ and $e_k = [e_k^{(1)T}, e_k^{(2)T}, \dots, e_k^{(M_0)T}]^T$.

After obtaining the predictions $\widehat{F}(t_k^-)$ and $P(t_k^-)$ from equations (14) and (16), each block of measurements $z_k^{(m)}$, $m = 1, 2, \dots, M_0$ is used *sequentially* to update the state estimate:

$$\widehat{F}^{(m)}(t_k) = \widehat{F}^{(m-1)}(t_k) + P^{(m)}(t_k) L^{(m)T} W_3^{(m)}(k)^{-1} [z_k^{(m)} - L^{(m)} \widehat{F}^{(m-1)}(t_k)] \quad (19)$$

$$P^{(m)}(t_k) = P^{(m-1)}(t_k) [I + L^{(m)T} W_3^{(m)}(k)^{-1} L^{(m)} P^{(m-1)}(t_k)]^{-1} \quad (20)$$

where $\widehat{F}^{(0)}(t_k) = \widehat{F}(t_k^-)$, $P^{(0)}(t_k) = (t_k^-)$, and the final estimate for time t_k is obtained with $\hat{n}(t_k) = \hat{n}^{(M0)}(t_k)$, $P(t_k) = P^{(M0)}(t_k)$.

2.5.2. Parameter Setting in Sampled-Data H_∞ Filtering—The following filtering parameters need to be determined: the initial estimate $\hat{n}(0)$ and $P(0)$, the weighting matrices $W_1(t)$, $W_2(t)$, $W_3(k)$ and the noise reduction level γ . Although no closed-form answers exist for parameter selection, we used the following guidelines.

In our implementation, $\hat{n}(0)$ is set based on prior knowledge of tracer kinetics, with $P(0)$ reflecting uncertainty in $\hat{n}_0$. Since there is no radioactivity at time $t = 0$, we set $\hat{n}_0 = 0$, and assign P_0 a small value. In H_∞ filtering, the error bound γ is related to the accuracy level the filter could achieve. In general, a lower γ leads to lower estimation error, but being too low will not guarantee that the Riccati differential equation (16) has a positive definite solution, which is an important assumption in deriving the H_∞ filtering equations. Note γ is not exactly the same as the estimation error; rather, it is the upper bound of estimation errors given all possible disturbances of finite energy. For a sampled-data system, there is no closed-form equations to calculate γ . Through simulations we observe that the filter achieves the best performance for γ in the range of 0.7 – 0.8. The weighting matrices $W_1(t)$, $W_2(t)$, $W_3(k)$ should be positive definite matrices and are related to confidence measures.

Statistical properties of the randoms-corrected PET data y_k can be used to set $W_3(k)$ and $W_2(t)$. The mean and the variance of y_k are: $E[y_k] = y_k^{(mean)}$, $\text{Var}^{(diag)}[y_k] = y_k^{(mean)} + 2r_k$, where $\text{Var}^{(diag)}[\]$ denotes diagonal elements of the covariance matrix of y_k , and $y_k^{(mean)} = D\Lambda_k + s_k$.

Since $z_k = \sum_{l=1}^k y_l$ (Section 2.3) and y_l collected at different imaging frames are independent to each other, the mean and the variance of z_k are:

$$E[z_k] = \sum_{l=1}^k E[y_l], \quad \text{Var}^{(diag)}[z_k] = \sum_{l=1}^k \text{Var}^{(diag)}[y_l].$$

In equation (12), $W_3(k)$ is the weighting matrix for the measurement noise e_k , so it is related to the uncertainty in data z_k . We set $W_3(k)$ to be a diagonal matrix (as data from different detector pairs are uncorrelated), with the diagonal elements proportional to $\text{Var}^{(diag)}[z_k]$. Similarly, $W_2(t)$ reflects the uncertainty in $\tilde{v}(t)$, which can not be modeled *a priori*. In our implementation, $W_2(t)$ is set to be a scaling of $W_3(k)$. Note we only use the mean and the variance of PET data here. No further assumption on the data distribution is made as in conventional statistical reconstruction.

3. Experiments

3.1. Simulation Experiments

Simulation experiments were conducted to test proof-of-principle of the SSIR framework. Figure 2(a) shows a schematic representation of the Zubal thorax phantom (digitized at 32×32 pixels), which has 3 regions of interest (ROIs). Kinetic parameters from previous studies (Li et al. 1998) were used to simulate kinetic changes in these ROIs (Table 1), and the corresponding time activity curves are shown in Figure 2(b). The plasma function $C_P(t)$ was generated using (Wong et al. 2001): $C_P(t) = (A_1 t - A_2 - A_3)e^{a_1 t} + A_2 e^{a_2 t} + A_3 e^{a_3 t}$, with $A_1 = 851.12 \mu\text{Ci/mL/min}$, $A_2 = 20.81 \mu\text{Ci/mL}$, $A_3 = 21.88 \mu\text{Ci/mL}$, $a_1 = -4.13 \text{min}^{-1}$, $a_2 = -0.01 \text{min}^{-1}$, and $a_3 = -0.12 \text{min}^{-1}$.

A sinogram sequence y_k was generated with equations (5) and (6). The total scan time was 60min, divided into 18 frames ($4 \times 0.5\text{min}$, $4 \times 2\text{min}$, $10 \times 5\text{min}$). We simulated 2 random event levels (30% and 50% of the total events per scan). We also simulated 2 prompt event levels (10^5 and 10^7 for the entire data set).

Given the above data sets with different prompt and random event levels, our task is to reconstruct the 18 activity images based on tracer kinetic models. As we discussed in Section 2.3, kinetic parameters are not known *a priori* for a specific subject or tissue region, so information from previous studies has to be used instead. To simulate this model mismatch, we performed two types of recovery. In the ‘perfect model’ case, the parameters in recovery were the same as those in data generation. In the ‘disturbed model’ case, 10% noise was added to the parameters in data generation. Both the SSIR strategy and the maximum likelihood shifted Poisson (ML-SP) reconstruction (proposed for randoms-corrected data in (Yavuz & Fessler 1998)) were applied. The ML-SP reconstruction was performed independently at each of the 18 time frames. For the ML-SP algorithm, we used 30 and 10 iterations for high and low count cases respectively.

3.1.1. Simulation of Spatial Model Mismatch—The SSIR method requires prior knowledge on tissue segmentation, and such information can be obtained from structural imaging like CT data. In practice, we may not have accurate tissue classification, especially for pathological regions invisible on CT images. We used simulations to test how the SSIR strategy performs under this type of model mismatch.

In the Zubal phantom, a square of 4×4 pixels in ROIc was associated with different kinetic behavior ($k_1 = 0.38\text{min}^{-1}$, $k_2 = 1.05\text{min}^{-1}$, $k_3 = 0.14\text{min}^{-1}$, $k_4 = 0.01\text{min}^{-1}$) to simulate pathology (Figure 2(c)). We used inaccurate tissue classification information in the reconstruction. Only kinetic information of ROIa, ROIb, and ROIc is used, and no information of the pathological region is included in the kinetic model. Correspondingly, the kinetic model in reconstruction contains no information of the pathological region, and is mismatched to the pathological data set. Other settings in the experiment (imaging schedule, input function, imaging matrix, etc.) were kept unchanged. Both the SSIR method and the ML-SP algorithm were applied to this pathological data set.

3.2. Application to Patient Data

We applied the SSIR framework to measured PET data from a locally advanced breast cancer patient. A female patient with a tumor in her right breast received an FDG PET scan before neoadjuvant chemotherapy. Dynamic imaging was performed for 60 min (1-min preinjection frame, $4 \times 20\text{s}$, $4 \times 40\text{s}$, $4 \times 1\text{min}$, $4 \times 3\text{min}$, $8 \times 5\text{min}$). The patient was scanned on a GE Advance PET scanner (Waukesha, WI) using 2D acquisition. The data was corrected for attenuation, random coincidences, scatter coincidences, and deadtime.

Several preparation steps were needed for the reconstruction. First, the blood time-activity curve $C_p(t)$ was estimated from the scanner reconstruction results (Mankoff et al. 2002). Another important step is to assign proper kinetic parameters to different regions. We performed an initial OSEM reconstruction, and segmented the image into left and right breast tissue regions and one thorax region. For this study, we assigned one set of kinetic parameters to the entire breast region ($k_1 = 0.07\text{min}^{-1}$, $k_2 = 0.12\text{min}^{-1}$, $k_3 = 0.01\text{min}^{-1}$, $k_4 = 0$) representative of normal breast tissue based on (Tseng et al. 2004). We assigned another set of parameters to the entire thorax region ($k_1 = 0.12\text{min}^{-1}$, $k_2 = 0.31\text{min}^{-1}$, $k_3 = 0.01\text{min}^{-1}$, $k_4 = 0.02\text{min}^{-1}$) based on (Dimitrakopoulou-Strauss et al. 2001).

The general kinetic model is mismatched with the specific patient data set: no information of the pathological region is included and one set of parameters is used for the whole thorax

region and whole breast. This experiment evaluates how the SSIR strategy performs in cases where only limited or inaccurate prior information on tissue classification and kinetic parameters is available.

To test the robustness of the strategies to measurement errors, we also performed reconstruction on an incomplete data set. One portion (a strip in the sinogram, shown in Figure 3) of the data was discarded to simulate the failure of two adjacent detector blocks.

Images were reconstructed to a grid of 64×64 pixels, using the SSIR method and the OSEM algorithm. We adopted the sequential processing scheme for the SSIR method. We used 3 iterations with 28 subsets for the OSEM algorithm. The OSEM reconstruction was performed independently at each of the 25 time frames. For both reconstruction methods, a 10-mm FWHM Gaussian filter was applied to the reconstructed images.

4. Results

4.1. Results from Simulation Experiments

The computation time for 18 time frames in the SSIR strategy was 33 minutes, on a 3.4 GHz machine with 3 GB memory. Figure 4 shows the ground truth and estimated activity images at time frames #4, #12 for the perfect model reconstruction from 30% randoms rate data. While ML-SP can give reasonable estimates for the high-count case in figure 4(d), it fails for the low-count case (Figure 4(b)). In contrast, with the guidance of the compartment model, the SSIR strategy generates improved results (Figure 4(c)(e)), illustrating the benefits of a physiologically meaningful framework. Moreover, as the H_∞ criterion guarantees bounded estimation error, the SSIR performance is acceptable even for the low count case (Figure 4(c)).

Figure 5 shows the results for the disturbed model reconstruction from low count level. Not surprisingly, ML-SP fails for all low count cases due to the low SNR and violation of the Poisson assumption. In contrast, despite the mismatched kinetic model (10% disturbance on parameters), the SSIR method can still reliably and accurately estimate the activity images.

Table 2 provides a quantitative comparison of the strategies for 4 data sets (2 count levels $\times$ 2 random event levels) and 2 prior models (perfect model and disturbed model). The reconstruction results are evaluated using relative bias and mean squared error (MSE)

defined as $\text{bias}_{rel} = \frac{1}{N} \sum_{i=1}^N |\lambda_{ik} - \hat{\lambda}_{ik}| / \lambda_{ik}$, $\text{MSE} = \frac{1}{N} \sum_{i=1}^N (\lambda_{ik} - \hat{\lambda}_{ik})^2 / \lambda_{ik}^2$. The bias and MSE are then averaged over the 18 frames of reconstruction. From Table 2, we can see that the SSIR method provides stable and accurate reconstruction results for different counts and noise levels.

Figure 6 shows the results from the simulated pathological data set. The ML-SP method produces noisy results, and it is difficult to visually identify any of the features in the images. Despite the spatial model mismatch, the SSIR strategy generates accurate reconstruction for the 3 ROIs and reasonable recovery of the pathological region.

4.2. Results from Patient Data

Results from the complete patient data are presented in Figure 7. Both conventional OSEM and the SSIR method can resolve the lesion in the patient's right breast. Time activity curves (TAC) of different tissue regions are shown in Figure 9. The SSIR method provides less noisy and smoother TAC than OSEM reconstruction. Although we used one set of kinetic parameters for the whole thorax region, TACs from background tissue and liver are different. This indicates that the H_∞ filter does not over-constrain the solution to the prior

kinetic model. Noise in the reconstructed images is quantified with the coefficient of variation (COV) in a uniform region (the liver region), and the results are presented in Table 3. COV_{average} is the coefficient of variation in the liver averaged over all 25 frames, and COV_{static} is the coefficient of variation in the liver for images summed from frame 21 to 25 (i.e. the last 25min in the imaging). From Table 3, the SSIR results are less noisy than the OSEM results, with COV_{average} reduced by 26%, and COV_{static} reduced by 20%.

Results from the incomplete data set are presented in Figure 8. An artifact is observed in the OSEM results, where part of the right breast and the lesion can not be resolved. The SSIR strategy generates results with fewer artifacts. The difference between results from incomplete and complete data is quantified through a pixel-to-pixel comparison of the images in Figure 7 and 8. The relative difference at each pixel is calculated, and then averaged over all pixels and frames. The difference is 25.6% for OSEM results, and 14.2% for SSIR results. This effect is also illustrated in Figure 9. For OSEM results, the lesion time activity curve reconstructed from incomplete data deviates greatly from the complete data result. For SSIR results, activity curves from incomplete data are similar to those from complete data, even though only population-based kinetics was used.

5. Discussion

We have developed a state-space framework for dynamic PET reconstruction. One motivation for our approach is to generate high-quality dynamic activity images, which one could read individually at each frame for applications such as quality assurance or movies of dynamic images (Morris et al. 2010). Another application is to improve kinetic parameter estimation. With the constraints of a relatively simple kinetic model (e.g. two-tissue compartment model), our method can generate less noisy dynamic images, leading to potentially more accurate kinetic parameter estimation. These dynamic activity images could also be used for parameter estimation of more complex models, such as axially distributed models (Muzic & Sidel 2003), which are often too sensitive for PET data with high noise levels.

The proposed reconstruction method relies on simple assumptions of the tracer kinetics to constrain the image estimates. Since image reconstruction is often performed before kinetic parameter estimation, one concern for our method is the lack of accurate kinetic parameters before reconstruction. We have tested how the SSIR framework performs under different types of model disturbances. For patient data, one set of kinetic parameters ($k_1 = 0.07\text{min}^{-1}$, $k_2 = 0.12\text{min}^{-1}$, $k_3 = 0.01\text{min}^{-1}$, $k_4 = 0$) representative of normal breast tissue was used for the whole breast region. From (Tseng et al. 2004), the average kinetic parameters for lesion tissue (from a study of 14 patients with locally advanced breast cancer) are $k_1 = 0.16\text{min}^{-1}$, $k_2 = 0.30\text{min}^{-1}$, $k_3 = 0.04\text{min}^{-1}$, $k_4 = 0$. So the parameters we used in SSIR (the normal tissue parameters) contain 56%–75% difference from the lesion parameters. Still, SSIR can recover the lesion in the patients right breast. Similarly for simulation of spatial model mismatch in Section 3.1.1, the assumed kinetic parameters ($k_1 = 0.78\text{min}^{-1}$, $k_2 = 1.16\text{min}^{-1}$, $k_3 = 0.11\text{min}^{-1}$, $k_4 = 0.03\text{min}^{-1}$) contain 11%–200% difference from the actual parameters ($k_1 = 0.38\text{min}^{-1}$, $k_2 = 1.05\text{min}^{-1}$, $k_3 = 0.14\text{min}^{-1}$, $k_4 = 0.01\text{min}^{-1}$) for the pathological region, and the region can still be recovered. We show that this approach is fairly robust to inexact knowledge of kinetics, including parameter disturbances and crude/inaccurate prior models. Another logical concern is that we may over-constrain the dynamic images with the *a priori* knowledge. The patient TACs demonstrate that this method allows for deviations from the constraining kinetics. H_∞ filtering can combine the general prior model (with mismatch) and the subject-specific PET data, and generate an optimal solution under the mini-max criterion.

From simulation results, we show that the SSIR strategy has the potential to generate more accurate and precise reconstruction results than convention OSEM for different count and noise levels (shown in Figure 4 and 5 and Table 2). The improved performance of the SSIR method comes from two aspects. First, kinetic models (*even imperfect ones*) help to guide the reconstruction; the framework uses more prior knowledge than frame-by-frame reconstruction methods. In the temporal domain, tracer kinetics enforces smoothness. In the spatial domain, pixels in the same tissue region are assigned the same kinetic parameters, and hence have similar activity in reconstruction. Second, the H_∞ criterion guarantees bounded estimation error, so it has robust performance for data with low SNR and unknown statistics. Results from patient experiments have further demonstrated the advantages of the SSIR framework. The SSIR method can provide less noisy images and TACs (Table 3 and Figure 9). We also present an example of its robustness to data disturbances (Figure 8).

The experimental results show proof-of-principal of the SSIR framework, rather than a full comparison with maximum likelihood (ML) based methods. When accurate system modeling and exact knowledge of data statistics are available, 4D ML-based methods (with temporal modeling) may be a better choice (Nichols et al. 2002, Kamasak et al. 2005). Due to the complexity of a full comparison, such a study is beyond the scope of this paper. One observation is that the SSIR method has better performance in low count case than in high count case under the disturbed model (Table 2). The SSIR framework guarantees bounded estimation error. Within the error bound, estimates may not have the minimum mean squared error (but are still of high fidelity due to the error bound). This is different from other estimators that minimize the average estimation error under certain statistical assumptions. Such statistical assumptions may be incorrect in practice, particularly for non-routine circumstances (e.g. unforeseen data errors, prototype systems, or new protocols/ tracers) where accurate data corrections are often not available. In these situations, the SSIR method has advantages over ML-based algorithms since it requires minimal assumptions on data statistics. The extreme case of this is missing data due to failed detector blocks. In this case, OSEM reconstruction has errors in the noise model, and the result has artifacts in the right breast. In contrast, the SSIR method still has robust performance under such condition.

One potential improvement for the SSIR framework is to incorporate subject-specific information to guide the reconstruction. A possible solution is to obtain such information from the integration of different data sources. An example is to obtain tissue classification information from CT or MRI images. Another solution is to estimate the kinetic parameters along with the activity variables, which can be realized through joint or sequential estimation of the parameters and the state variables. For joint estimation, the kinetic parameters are included in the state variables, and the reconstruction becomes a non-linear system estimation problem. For sequential estimation, kinetic parameters are fixed during the estimation of activity variables, and then updated after activity reconstruction is completed. Also the framework could be extended to direct parametric image reconstruction, with the estimation formulated as a system identification problem.

The SSIR method can also be extended for list-mode PET data, and such an extension would include the following changes in the problem formulation. For list-mode data, the measured counts are a scaling of the emitted counts, so the time integration step in equation (5) is no longer needed. The state-space representation will consist of a continuous-time kinetic equation and a continuous-time measurement equation. Continuous-time H_∞ filter proposed in (Nagpal & Khargonekar 1991) can be used to estimate the activity distribution. However, solving the filtering differential equations on a fine time scale would be computationally intensive.

6. Conclusion

We have developed a tracer-kinetics-guided state-space image reconstruction (SSIR) framework for reconstructing activity images from dynamic PET data. Using a state-space representation, we formulate the reconstruction problem as a state estimation problem, and apply sampled-data H_∞ filtering for solution. H_∞ filtering makes no assumptions on the system and measurement statistics, and guarantees bounded estimation error for all finite-energy disturbances. This robust feature has the potential to accommodate unknown statistics in the PET data and unpredictable errors in the image acquisition (e.g. failed detector blocks or erroneous scatter/attenuation corrections). Tracer kinetics guide the reconstruction algorithm, constraining the reconstructed images to physiologically realistic solutions and leading to potentially more accurate and precise dynamic PET images. We demonstrate the efficacy of the proposed SSIR framework with simulated and measured PET data sets, showing robust performance for low count data.

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Figure 1.
Two-tissue compartment model with four kinetic parameters.

Figure 2.

(a): Zubal thorax phantom with multiple tissue regions indicated by different colors. (b): Time activity curves for three distinct tissue regions in Zubal thorax phantom. (c): Zubal thorax phantom with a 16-pixel pathological region simulated in ROIc.

Figure 3. Sinogram of the target slice at frame 22 of patient data. (a): Complete sinogram. (b): Sinogram with one portion discarded, corresponding to two adjacent failed detector blocks.

Figure 4.

Reconstructed activity images with perfect model from 30% random coincidence rate data at frames #4, #12 (top to bottom) of 18 frames. (a): ground truth. (b): ML-SP results for low counts. (c): SSIR results for low counts. (d): ML-SP results for high counts. (e): SSIR results for high counts and color scale.

Figure 5. Reconstructed activity images with disturbed model from low counts data at frames #4, #12 (top to bottom) of 18 frames. (a): ground truth. (b): ML-SP results for low random coincidence rate. (c): SSIR results for low random coincidence rate. (d): ML-SP results for high random coincidence rate. (e): SSIR results for high random coincidence rate and color scale.

Figure 6. Reconstructed activity images at frames #1, #4 (top to bottom) for the data set with a simulated pathological region. (a): ground truth. (b): ML-SP results. (c): SSIR results and color scale.

Figure 7. Reconstructed activity images at time frames #5, #9, #13, #17, #21 of 25 frames for slice #21 of the patient data (complete data). Top: OSEM reconstruction results; bottom: SSIR reconstruction results. The two images at each frame have the same color scale. Breast lesion is indicated by arrows on images at frame #21.

Figure 8.

Reconstructed activity images at frames #5, #9, #13, #17, #21 of 25 frames for slice #21 of the patient data (incomplete block-missing data). Top: OSEM reconstruction results; bottom: SSIR reconstruction results. The two images at each frame have the same color scale.

Figure 9.
Time activity curve (TAC) in different tissue regions. (a): OSEM results; (b): SSIR results.

Table 1

Kinetic parameters for different tissue regions in Zubal thorax phantom.

Region	$k_1(\text{min}^{-1})$	$k_2(\text{min}^{-1})$	$k_3(\text{min}^{-1})$	$k_4(\text{min}^{-1})$
ROI a	0.56	2.75	0.45	0.01
ROI b	0.38	1.05	0.14	0.01
ROI c	0.78	1.16	0.11	0.03

Table 2

Analysis of estimated activity images for different data sets and different prior models (perfect model and disturbed model). RC rate stands for random coincidence event rate, and bias_{rel} denotes relative bias.

	Low Counts				High Counts			
	30%RC rate		50%RC rate		30%RC rate		50%RC rate	
	bias_{rel}	MSE	bias_{rel}	MSE	bias_{rel}	MSE	bias_{rel}	MSE
ML-SP	0.315	0.250	0.321	0.252	0.144	0.070	0.166	0.083
SSIR (perfect)	0.035	0.026	0.037	0.026	0.021	0.002	0.027	0.006
SSIR (disturbed)	0.045	0.003	0.045	0.003	0.061	0.005	0.084	0.009

Table 3

Noise analysis of reconstructed activity images from patient data, with $COV_{average}$ denoting coefficient of variation in the liver averaged over 25 frames, and COV_{static} denoting coefficient of variation in the liver for images summed from frame 21 to 25.

	Complete Data		Incomplete Data	
	$COV_{average}(\%)$	$COV_{static}(\%)$	$COV_{average}(\%)$	$COV_{static}(\%)$
OSEM	38.1	8.8	39.8	14.0
SSIR	28.7	7.1	30.2	11.7

Algorithm 1

Summary of the H_{∞} filtering algorithm

Generate matrices A and B with kinetic parameters from population studies (as in equation (9))

Set filtering parameters (details in Section 2.5.2)

for $k = 1$ to number of time bins **do**

 Calculate the state prediction $\hat{F}(t_k^-)$ by solving equation (14)

 Calculate $P(t_k^-)$ by solving equation (16)

 Calculate $P(t_k)$ through equation (17)

 Calculate the state estimate $\hat{n}(t_k)$ through equation (15)

 Generate the activity image Λ_k using equation (10)

end for