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Fully 4-D Direct Joint Estimation of Compartmental Models and Blood Input Function from Dynamic SPECT Projections

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I. INTRODUCTION

COMPARTMENTAL model analysis of dynamic cardiac single photon emission computed tomography (SPECT) data can provide a quantitative measure of myocardial perfusion and can potentially provide better contrast between healthy and diseased tissue, compared to static images [1]. Compartmental analysis may also be useful for assessing tissue viability [2].

In previous work, we formulated a nonlinear estimation problem in which linear and conditionally linear parameters are estimated directly from projection data with the use of least squares, given iteratively estimated values for nonlinear washout parameters for one-compartment kinetic models for segmented volumes [3, 4]. This approach removes parameter bias generated by artifacts that appear in conventional image reconstructions because of projection data inconsistency and data truncation by cone beam collimators. The methods can be applied to any collimator or orbit geometry, provided that the acquired data yield qualitatively correct images that can be used to segment the entire projected field of view. To reduce the large computational burden associated with straightforward solution of the embedded linear least squares subproblem, we also developed an accelerated “semidirect” approach in which B-splines are first used to model smooth time-activity curves for segmented volumes, and then compartmental models are fit to the curves [5, 6].

In the present work, we generalize the semidirect methods to accelerate direct joint estimation of compartmental models for tissue volumes and B-spline time-activity curve models for the blood input function and other volumes that do not obey a compartmental model. We hypothesize that the additional temporal regularization provided by compartmental models will improve the accuracy and precision of uptake and washout parameters for small tissue volumes such as myocardial defects.

II. PROJECTION DATA MODEL

In the following model, the projected field of view is encompassed by \( M = M_1 + M_2 \) segmented volumes that contain spatially uniform activity distributions. Time-activity curves for volumes \( m = 1, \ldots, M_1 \) are modeled with the use of B-splines, and curves for volumes \( m = (M_1 + 1), \ldots, M \) are modeled with the use of compartments.

The spline model for the time-activity curve for volume \( m \) is

\[
A^m(t) = \sum_{n=1}^{N} a_{mn} V^n(t),
\]

where \( a_{mn} \) are model coefficients, \( V^n(t) \) are B-spline basis functions, and \( N \) is the number of basis functions. For convenience, the blood input volume is assigned index \( m = 1 \).

For the one-compartment kinetic model, the relationship between the blood input function, \( A^1(t) \), and the activity in the tissue in volume \( m \), \( Q^m(t) \), is modeled to be

\[
\frac{dQ^m(t)}{dt} = k_1^m A^1(t) - k_2^m Q^m(t),
\]

where \( k_1^m \) is the uptake rate parameter and \( k_2^m \) is the washout rate parameter. For initial conditions of zero, the tissue activity is the convolution of the blood input function with a single decaying exponential:

\[
Q^m(t) = k_1^m \int_0^t A^1(\tau) e^{-k_2^m(t-\tau)} d\tau.
\]

Total activity in volume \( m \) is given by

\[
R^m(t) = f_v^m A^1(t) + Q^m(t),
\]

where \( f_v^m \) is the fraction of vasculature in the volume.

The detected count rate at time \( t \) along ray \( i \) is modeled as

\[
P_i(t) = \sum_{m=1}^{M_1} U_i^m(t) A^m(t) + \sum_{m=M_1+1}^{M} U_i^m(t) R^m(t),
\]

where \( U_i^m(t) \) is the spatial projection along ray \( i \) of the indicator function for volume \( m \) and incorporates physical effects such as attenuation, geometric point response, and scatter.

The model for the projection data is obtained by integrating (5) over \( L \) contiguous time intervals that span the data acquisition from time \( t_0 = 0 \) to time \( t_L = T \):

\[
p_{il} = \int_{t_{i-1}}^{t_i} P_i(t) dt.
\]

If the time intervals are short enough so that each segmented volume projection function \( U_i^m(t) \) is approximated well by a piecewise constant function with amplitude \( u_{il}^m \) during time interval \( [t_{i-1}, t_i] \), then the following approximation can be made:

\[
p_{il} \approx \sum_{m=1}^{M_1} u_{il}^m \int_{t_{i-1}}^{t_i} A^m(t) dt + \sum_{m=M_1+1}^{M} u_{il}^m \int_{t_{i-1}}^{t_i} R^m(t) dt.
\]
Substituting (1), (3), and (4) into (7) and replacing the approximation with equality, one obtains the projection data model

\[ p_{il} = \sum_{m=1}^{M_l} u_{il}^m \sum_{n=1}^{N} a_{mn} v_{i}^n + \sum_{m=M_l+1}^{M} u_{il}^m f_{i}^m \sum_{n=1}^{N} a_{1n} \tilde{v}_{i}^{mn}, \]

where the factors \( v_{i}^n = \int_{t_i}^{\tau} V^n(\tau) d\tau \) and the factors \( \tilde{v}_{i}^{mn} = \int_{t_{il}}^{\tau} V^n(\tau) e^{-k^2(t-\tau)} dt \) are integrals of unconvolved and convolved temporal B-spline basis functions, respectively, that can be evaluated quickly for equal length time intervals [7].

The projection data model given by (8) is nonlinear in the washout rate parameters \( k_{ij}^m \) contained in the factors \( \tilde{v}_{i}^{mn} \) for volumes modeled with compartmental models, and is linear in the spline time-activity curve coefficients \( a_{mn} \) for the other non-blood-input volumes. The compartmental model uptake rate parameters \( k_{ij}^m \) and vascular fractions \( f_{i}^m \) are conditionally linear, given values for the \( k_{ij}^m \) and the coefficients \( a_{1n} \) for the blood input function. Conversely, the \( a_{1n} \) are conditionally linear, given values for the \( k_{ij}^m \), \( k_{in}^m \), and \( f_{i}^m \).

III. LEAST SQUARES CRITERION AND ITERATIVE MINIMIZATION ALGORITHM

The projection data model parameters can be estimated relatively quickly by minimizing the sum of squared differences between the measured and modeled projections:

\[ \chi^2 = \sum_{i=1}^{L} \sum_{l=1}^{L} (p_{il}^e - p_{il})^2, \]  

(9)

where \( p_{il}^e \) are the measured projections and \( L \) is the number of projection rays acquired simultaneously by the detector(s).

A. Iterative Search of the Nonlinear \( k_{ij}^m \) Parameter Space and Joint Estimation of Other Parameters

A modified Newton-Raphson minimization algorithm [8] can be used to iteratively search the space of nonlinear washout rate parameters \( k_{ij}^m \) for values that minimize (9), starting at values obtained from semidirect estimation. Holding the blood time-activity curve coefficients \( a_{1n} \) constant while searching the washout parameter space, one can jointly estimate all other parameters as described in Section III-B. At the expense of more computation one can also include the \( a_{1n} \) in the iterative search space, rather than hold the \( a_{1n} \) constant. Similarly, one can jointly estimate the blood curve and all other spline curve coefficients as described in Section III-C, while searching the washout parameter space and either holding constant or searching for the compartmental model parameters \( k_{ij}^m \) and \( f_{i}^m \).

Joint estimation of linear and conditionally linear parameters can be accelerated by up to three orders of magnitude for typical data acquisitions that use a multi-rotation circular (or other periodic) detector trajectory. In the following, the time index \( l = 1, \ldots, L \) is replaced with the indices \( \{ij; j = 1, \ldots, J; k = 1, \ldots, K\} \), where \( J \) is the number of angles per rotation and \( K \) is the number of rotations. The index \( k \) is dropped from the now-periodic spatial projection factors denoted by \( u_{ij}^m \).

B. Accelerated Linear Estimation of the \( k_{1}^m \), \( f_{v}^m \), and Non-Blood \( a_{mn} \), Given the \( k_{2}^m \) and Blood \( a_{1n} \)

To solve for values of the \( k_{1}^m \), \( f_{v}^m \), and non-blood \( a_{mn} \) that minimize (9), given values for the \( k_{2}^m \) and blood \( a_{1n} \), one can express (8) in matrix form as

\[ \alpha F^l a_1 + \sum_{m=2}^{M_l} F^m a_m + \sum_{m=M_l+1}^{M} (f_{v}^m F^m a_1 + k_{1}^m \Lambda^m a_1) = p, \]

(10)

where \( F^m \) and \( \Lambda^m \) are \( IJK \times N \) matrices whose \([i+(j-1)I+(k-1)J, n]^{th}\) elements are \( u_{ij}^m v_{j}^n \) and \( u_{ij}^m \tilde{v}_{i}^{mn} \), respectively; \( a_m \) is an \( N \times 1 \) column vector whose \( n^{th} \) element is \( a_{mn} \), and \( p \) is an \( IJK \times 1 \) column vector whose \([i+(j-1)I+(k-1)J, n]^{th}\) element is \( p_{ij} \). The conditionally linear parameter \( \alpha \) has been included to allow one to adjust the blood input amplitude while minimizing (9). One can then incorporate the adjusted amplitude into the original model parameters by multiplying the \( a_{1n} \) by \( \alpha \), dividing the \( f_{v}^m \) and \( k_{1}^m \) by \( \alpha \), and resetting \( \alpha \) to one.

Equation (10) can be written more compactly as

\[ G \theta_g = p, \]

(11)

where

\[ G = [G_1 \; G_2 \; G_3], \]

\[ G_1 = [F^2 \; \cdots \; F^M], \]

\[ G_2 = [F^1 a_1 \; F^{M+1} a_1 \; \cdots \; F^M a_1], \]

\[ G_3 = [\Lambda^{M+1} a_1 \; \cdots \; \Lambda^M a_1]. \]

The least squares criterion (9) then becomes

\[ \chi^2 = (p^* - G \theta_g) G^T (p^* - G \theta_g), \]

(12)

where \( p^* \) is an \( IJK \times 1 \) column vector whose \([i+(j-1)I+(k-1)J, n]^{th}\) element is \( p_{ij} \). The vector of values for the \( k_{1}^m \), \( f_{v}^m \), non-blood \( a_{mn} \), and \( \alpha \) that minimize \( \chi^2 \) is

\[ \hat{\theta}_g = (G^T G)^{-1} G^T p^*. \]

(13)

One can accelerate the computation of (13) by first calculating some of the intermediate sums shown in Table I. Elements in blocks of the symmetric \([M_1-1] N + 2 M_2 + 1 \times [M_1-1] N + 2 M_2 + 1\) matrix \( G^T G \) can then be calculated by evaluating the following sums for the indicated blocks:

\[ G_1^T G_1 : \sum_{j=1}^{J} \mu_{j}^{mm'} v_{j}^{nn'} \]

\[ G_1^T G_2 : \sum_{j=1}^{J} \mu_{j}^{mm'} (\alpha_{12})_j \]

\[ G_1^T G_3 : \sum_{j=1}^{J} \mu_{j}^{mm'} (\alpha_{13})_j \]

\[ G_2^T G_2 : \sum_{j=1}^{J} \mu_{j}^{mm'} (\alpha_{22})_j \]

\[ G_2^T G_3 : \sum_{j=1}^{J} \mu_{j}^{mm'} (\alpha_{23})_j \]

\[ G_3^T G_3 : \sum_{j=1}^{J} \mu_{j}^{mm'} (\alpha_{33})_j \]  

(14)

The factors \( \mu_{j}^{mm'} \) and \( (\alpha_{rs})_j \) are defined in Table I, where two sets of formulæ are given for computing the \((\alpha_{rs})_j\). The set
that uses summations over the rotation index \( k \) typically requires fewer operations: \( JK(N + M_2 + 1)(N + M_2 + 2)/2 \) multiply-and-adds, given the factors \( A_{jk}^T \) and \( A_{jk}^{Tm} \) defined in Table I.

For \( I \gg K[(N + M_2)/((M_1 + M_2)]^2 \), most of the overhead for the accelerated computation lies in calculating the intermediate sums \( \mu_{jk}^{m'm'} \). Thus, computation is reduced by a factor of about \( K[(M_1 - 1)N + 2M_2]/((M_1 + M_2)]^2 \), compared to straightforward matrix multiplication of \( G^T G \). This reduction corresponds to the number of rotations, \( K \), times the square of the average number of linear and conditionally linear parameters per segmented volume. Speedup ranges from a factor of about \( KN^2 \) when \( M_1 = 1 \) (i.e., when most of the time-activity curves are modeled with \( N \) splines), to a factor of about \( 4K \) when \( M_1 = 1 \).}

One can also accelerate computation of elements in blocks of the \( [(M_1 - 1)N + 2M_2 + 1] \times 1 \) column vector \( G^T p^* \) by evaluating the following sums for the indicated blocks:

\[
\begin{align*}
G^T_1 p^* &= \sum_{j=1}^{J} \sum_{k=1}^{K} \rho_{jk}^T v_{jk}^n \\
G^T_2 p^* &= \sum_{j=1}^{J} \sum_{k=1}^{K} \rho_{jk}^T A_{jk}^{Tm} \\
G^T_3 p^* &= \sum_{j=1}^{J} \sum_{k=1}^{K} \rho_{jk}^T A_{jk}, \\
\end{align*}
\]
and then write \((16)\) more compactly as
\[ G \tilde{\theta}_g = G^T p^* \] can then be solved relatively quickly for the parameters \(\tilde{\theta}_g\), with the use of the Cholesky decomposition of \(G^T G\) \([9]\).

C. Accelerated Linear Estimation of the Blood and Non-Blood \(a_{mn}\). Given the \(k_2^m, k_1^m\), and \(f_v^m\)

To solve for values of the \(a_{mn}\) that minimize (9), given values for the \(k_2^m, k_1^m,\) and \(f_v^m\), one can first express (8) in matrix form as
\[
\begin{align*}
F^1 &+ \sum_{m=M+1}^{M} (f_v^m F^m + k_1^mA^m) \begin{bmatrix} a_1 \end{bmatrix} + \sum_{m=2}^{M_1} F^m a_m = p \\
\end{align*}
\]
and then write (16) more compactly as
\[
H \tilde{\theta}_h = p, \tag{17}
\]
where
\[
\begin{align*}
H &= \begin{bmatrix} H_1 & G_1 \end{bmatrix} \\
H_1 &= H_{11} + H_{12} + H_{13} \\
H_{11} &= F^1 \\
H_{12} &= \sum_{m=M+1}^{M} f_v^m F^m \\
H_{13} &= \sum_{m=M+1}^{M} k_1^mA^m \\
\tilde{\theta}_h &= \begin{bmatrix} a_1^T & a_2^T & \cdots & a_{M_1}^T \end{bmatrix}.
\end{align*}
\]

The least squares criterion (9) then becomes
\[
\chi^2 = (p^* - H \tilde{\theta}_h)^T (p^* - H \tilde{\theta}_h), \tag{18}
\]
and the vector of values for the \(a_{mn}\) that minimize \(\chi^2\) is
\[
\tilde{\theta}_h = (H^T H)^{-1} H^T p^*. \tag{19}
\]

One can accelerate computation of blocks of the symmetric \(M_1 N \times M_1 N\) matrix \(H^T H\) as follows. The symmetric \(N \times N\) block \(H^T_j H_j\) is the sum of the following matrices and the transposes of \(H^T_j H_{12}, H^T_{12} H_j, H^T_{12} H_{13},\) and \(H^T_{12} H_{13}\):
\[
\begin{align*}
H^T_{11} H_{11} &= \sum_{j=1}^{J} J_{11}^n \nu_j^m \nu_j^m' \\
H^T_{11} H_{12} &= \sum_{j=1}^{J} (J_{12}^n \nu_j^m) \nu_j^m' \\
H^T_{11} H_{13} &= \sum_{j=1}^{J} (J_{13}^n \nu_j^m) \nu_j^m' \\
H^T_{12} H_{12} &= \sum_{j=1}^{J} J_{22}^n \nu_j^m \nu_j^m' \\
H^T_{12} H_{13} &= \sum_{j=1}^{J} J_{23}^n \nu_j^m \nu_j^m' \\
H^T_{13} H_{13} &= \sum_{j=1}^{J} J_{33}^n \nu_j^m \nu_j^m',
\end{align*}
\]
where the factors \((J_{ij}^n)\) are defined in Table I. The asymmetric \(N \times (M_1 - 1)N\) block \(H^T_j G_1\) is the sum of the matrices
\[
\begin{align*}
H^T_{11} G_1 &= \sum_{j=1}^{J} J_{11}^m \mu_j^m \nu_j^m \\
H^T_{12} G_1 &= \sum_{j=1}^{J} (J_{12}^m \nu_j^m) \nu_j^m' \\
H^T_{13} G_1 &= \sum_{j=1}^{J} (J_{13}^m \nu_j^m) \nu_j^m'.
\end{align*}
\]

The symmetric \((M_1 - 1)N \times (M_1 - 1)N\) block \(G_1^T G_1\) has elements given by the first sum in (14).

The use of straightforward matrix multiplication requires about \(2 M_2 M_1 N^2\) multiply-and-adds to calculate \(H_1\), followed by about \(4 M_1^2 N^2\) multiply-and-adds to calculate \(H^T H\). For small \(M_2\) and \(M_1 \gg M_2\), most of the overhead for the accelerated computation lies in calculating the intermediate sums \(\mu_{jnn'}^m\) and the speedup is by a factor of about \(NK^2\). For small \(M_1\) and \(M_2 \gg M_1\), there is significant additional overhead in calculating the intermediate sums \(\nu_{jnn'}\) and the speedup is reduced to a factor of about \(KN^2 [1/(1 + N^2)] [4/(M_2 N)]\).

Computation of blocks of the \(M_1 N \times 1\) column vector \(H^T p^*\) can also be accelerated. The \(N \times 1\) block \(H^T p^*\) is the sum of the following vectors:
\[
\begin{align*}
H^T_{11} p^* &= \sum_{j=1}^{J} \sum_{k=1}^{K} \mu_{jkk} v_j^k \\
H^T_{12} p^* &= \sum_{j=1}^{J} \sum_{k=1}^{K} \left( \sum_{m=M+1}^{M} f_v^m \nu_j^m \nu_j^m' \right) v_j^k \\
H^T_{13} p^* &= \sum_{j=1}^{J} \sum_{k=1}^{K} \left( \sum_{m=M+1}^{M} k_1^m \nu_j^m \nu_j^m' \right) v_j^k.
\end{align*}
\]

The \((M_1 - 1)N \times 1\) block \(G_1^T p^*\) has elements given by the first sum in (15). Compared to straightforward matrix multiplication of \(H^T p^*\), this reduces computation by a factor of about \(N\).

IV. FUTURE DIRECTIONS

Work is underway to implement these direct joint estimation methods. Various strategies for updating conditionally linear parameters will be investigated and the effects on convergence of the fit will be studied. The accuracy and precision of compartmental parameters obtained with the direct method will be compared to that obtained with the semidirect method.

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