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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

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

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

$$\frac{dQ^m(t)}{dt} = k_1^m A^1(t) - k_2^m Q^m(t), \qquad (2)$$

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:

$$Q^m(t) = k_1^m \int_0^t A^1(\tau) e^{-k_2^m(t-\tau)} d\tau. \qquad (3)$$

Total activity in volume m is given by

$$R^m(t) = f_v^m A^1(t) + Q^m(t), \qquad (4)$$

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

$$P_i(t) = \sum_{m=1}^{M_1} U_i^m(t) A^m(t) + \sum_{m=M_1+1}^{M} U_i^m(t) R^m(t), \qquad (5)$$

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 $t_L = T$:

$$p_{il} = \int_{t_{l-1}}^{t_l} P_i(t) dt. \qquad (6)$$

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 $[t_{l-1}, t_l]$, then the following approximation can be made:

$$p_{il} \approx \sum_{m=1}^{M_1} u_{il}^m \int_{t_{l-1}}^{t_l} A^m(t) dt + \sum_{m=M_1+1}^{M} u_{il}^m \int_{t_{l-1}}^{t_l} R^m(t) dt. \qquad (7)$$

Substituting (1), (3), and (4) into (7) and replacing the approximation with equality, one obtains the projection data model

$$p_{il} = \sum_{m=1}^{M_1} u_{il}^m \sum_{n=1}^{N} a_{mn} v_l^n + \sum_{m=M_1+1}^{M} u_{il}^m f_v^m \sum_{n=1}^{N} a_{1n} v_l^n$$
$$+ \sum_{m=M_1+1}^{M} u_{il}^m k_1^m \sum_{n=1}^{N} a_{1n} \tilde{v}_l^{mn}, \tag{8}$$

where the factors $v_l^n = \int_{t_{l-1}}^{t_l} V^n(\tau)d\tau$ and the factors $\tilde{v}_l^{mn} = \int_{t_{l-1}}^{t_l} \int_0^t V^n(\tau) e^{-k_2^m(t-\tau)} d\tau dt$ are integrals of unconvolved and convolved temporal B-spline basis functions, respectively, that can be evaluated quickly for equilength time intervals [7].

The projection data model given by (8) is nonlinear in the washout rate parameters k_2^m contained in the factors $\tilde{v}_l^{mn}$ 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_1^m and vascular fractions f_v^m are conditionally linear, given values for the k_2^m and the coefficients a_{1n} for the blood input function. Conversely, the a_{1n} are conditionally linear, given values for the k_2^m, k_1^m, and f_v^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:

$$\chi^2 = \sum_{i=1}^{I} \sum_{l=1}^{L} (p_{il}^* - p_{il})^2, \tag{9}$$

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

A. Iterative Search of the Nonlinear k_2^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_2^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_1^m and f_v^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 $\{jk; j = 1, \ldots, J; k = 1, \ldots, K\}$, 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

$$\alpha \mathbf{F}^1 \mathbf{a}_1 + \sum_{m=2}^{M_1} \mathbf{F}^m \mathbf{a}_m + \sum_{m=M_1+1}^{M} (f_v^m \mathbf{F}^m \mathbf{a}_1 + k_1^m \Lambda^m \mathbf{a}_1) = \mathbf{p}, \tag{10}$$

where $\mathbf{F}^m$ and Λ^m are $IJK \times N$ matrices whose $\{[i+(j-1)I+(k-1)IJ], n\}$th elements are $u_{ij}^m v_{jk}^n$ and $u_{ij}^m \tilde{v}_{jk}^{mn}$, respectively; $\mathbf{a}_m$ is an $N \times 1$ column vector whose nth element is a_{mn}; and $\mathbf{p}$ is an $IJK \times 1$ column vector whose $[i+(j-1)I+(k-1)IJ]$th element is p_{ijk}. The conditionally linear parameter α 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 α, dividing the f_v^m and k_1^m by α, and resetting α to one.

Equation (10) can be written more compactly as

$$\mathbf{G}\theta_g = \mathbf{p}, \tag{11}$$

where

$$\mathbf{G} = \begin{bmatrix} \mathbf{G}_1 & \mathbf{G}_2 & \mathbf{G}_3 \end{bmatrix}$$
$$\mathbf{G}_1 = \begin{bmatrix} \mathbf{F}^2 & \cdots & \mathbf{F}^{M_1} \end{bmatrix}$$
$$\mathbf{G}_2 = \begin{bmatrix} \mathbf{F}^1 \mathbf{a}_1 & \mathbf{F}^{M_1+1} \mathbf{a}_1 & \cdots & \mathbf{F}^M \mathbf{a}_1 \end{bmatrix}$$
$$\mathbf{G}_3 = \begin{bmatrix} \Lambda^{M_1+1} \mathbf{a}_1 & \cdots & \Lambda^M \mathbf{a}_1 \end{bmatrix}$$
$$\theta_g^{\mathrm{T}} = \begin{bmatrix} \mathbf{a}_2^{\mathrm{T}} & \cdots & \mathbf{a}_{M_1}^{\mathrm{T}} & \alpha & f_v^{M_1+1} & \cdots & f_v^M & k_1^{M_1+1} & \cdots & k_1^M \end{bmatrix}.$$

The least squares criterion (9) then becomes

$$\chi^2 = (\mathbf{p}^* - \mathbf{G}\theta_g)^{\mathrm{T}}(\mathbf{p}^* - \mathbf{G}\theta_g), \tag{12}$$

where $\mathbf{p}^*$ is an $IJK \times 1$ column vector whose $[i+(j-1)I+(k-1)IJ]$th element is p_{ijk}^*. The vector of values for the k_1^m, f_v^m, non-blood a_{mn}, and α that minimize χ^2 is

$$\hat{\theta}_g = (\mathbf{G}^{\mathrm{T}}\mathbf{G})^{-1}\mathbf{G}^{\mathrm{T}}\mathbf{p}^*. \tag{13}$$

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 $[(M_1-1)N+2M_2+1] \times [(M_1-1)N+2M_2+1]$ matrix $\mathbf{G}^{\mathrm{T}}\mathbf{G}$ can then be calculated by evaluating the following sums for the indicated blocks:

$$\begin{aligned} \mathbf{G}_1^{\mathrm{T}}\mathbf{G}_1 &: \sum_{j=1}^{J} \mu_j^{mm'} \nu_j^{nn'} \\ \mathbf{G}_1^{\mathrm{T}}\mathbf{G}_2 &: \sum_{j=1}^{J} \mu_j^{mm'} (\alpha_{12})_j^n \\ \mathbf{G}_1^{\mathrm{T}}\mathbf{G}_3 &: \sum_{j=1}^{J} \mu_j^{mm'} (\alpha_{13})_j^{mn} \\ \mathbf{G}_2^{\mathrm{T}}\mathbf{G}_2 &: \sum_{j=1}^{J} \mu_j^{mm'} (\alpha_{22})_j \\ \mathbf{G}_2^{\mathrm{T}}\mathbf{G}_3 &: \sum_{j=1}^{J} \mu_j^{mm'} (\alpha_{23})_j^m \\ \mathbf{G}_3^{\mathrm{T}}\mathbf{G}_3 &: \sum_{j=1}^{J} \mu_j^{mm'} (\alpha_{33})_j^{mm'}. \end{aligned} \tag{14}$$

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

TABLE I

INTERMEDIATE SUMS USEFUL FOR ACCELERATED COMPUTATION OF (13) AND (19)

Description	Sum	Index range	Number of multiply-and-adds
blood input function	$A^1_{jk} = \sum_{n=1}^N a_{1n} v^n_{jk}$	$j=1,\ldots,J$ $k=1,\ldots,K$	JKN
blood input convolved with $e^{-k^m_2 t}$	$\tilde{A}^{1m}_{jk} = \sum_{n=1}^N a_{1n} \tilde{v}^{mn}_{jk}$	$j=1,\ldots,J$ $k=1,\ldots,K$ $m=(M_1+1),\ldots,M$	JKM_2N
inner product of temporal spline basis functions n and n'	$\nu^{nn'}_j = \sum_{k=1}^K v^n_{jk} v^{n'}_{jk}$	$j=1,\ldots,J$ $n,n'=1,\ldots,N$	$JK\dfrac{N(N+1)}{2}$
inner product of convolved temporal spline mn and temporal spline n'	$\tilde{\nu}^{mnn'}_j = \sum_{k=1}^K \tilde{v}^{mn}_{jk} v^{n'}_{jk}$	$j=1,\ldots,J$ $m=(M_1+1),\ldots,M$ $n,n'=1,\ldots,N$	JKM_2N^2
inner product of convolved temporal splines mn and $m'n'$	$\tilde{\nu}^{mnm'n'}_j = \sum_{k=1}^K \tilde{v}^{mn}_{jk} \tilde{v}^{m'n'}_{jk}$	$j=1,\ldots,J$ $m,m'=(M_1+1),\ldots,M$ $n,n'=1,\ldots,N$	$JK\dfrac{M_2N(M_2N+1)}{2}$
inner product of blood input and temporal spline n	$(\alpha_{12})^n_j = \sum_{k=1}^K A^1_{jk} v^n_{jk}$ $= \sum_{n'=1}^N a_{1n'}\nu^{nn'}_j$	$j=1,\ldots,J$ $n=1,\ldots,N$	JKN or JN^2
inner product of convolved blood function m and temporal spline n	$(\alpha_{13})^{mn}_j = \sum_{k=1}^K \tilde{A}^{1m}_{jk} v^n_{jk}$ $= \sum_{n'=1}^N a_{1n'}\tilde{\nu}^{mnn'}_j$	$j=1,\ldots,J$ $m=(M_1+1),\ldots,M$ $n=1,\ldots,N$	JKM_2N or JM_2N^2
inner product of blood input and itself	$(\alpha_{22})_j = \sum_{k=1}^K A^1_{jk} A^1_{jk}$ $= \sum_{n=1}^N a_{1n}(\alpha_{12})^n_j$	$j=1,\ldots,J$	JK or JN
inner product of convolved blood function m and blood input	$(\alpha_{23})^m_j = \sum_{k=1}^K \tilde{A}^{1m}_{jk} A^1_{jk}$ $= \sum_{n=1}^N a_{1n}(\alpha_{13})^{mn}_j$	$j=1,\ldots,J$ $m=(M_1+1),\ldots,M$	JKM_2 or JM_2N
inner product of convolved blood functions m and m'	$(\alpha_{33})^{mm'}_j = \sum_{k=1}^K \tilde{A}^{1m}_{jk} \tilde{A}^{1m'}_{jk}$ $= \sum_{n=1}^N a_{1n} \sum_{n'=1}^N a_{1n'} \tilde{\nu}^{mnm'n'}_j$	$j=1,\ldots,J$ $m,m'=(M_1+1),\ldots,M$	$JK\dfrac{M_2(M_2+1)}{2}$ or $J\dfrac{M_2(M_2+1)}{2}N(N+1)$
inner product of spatial projection functions m and m'	$\mu^{mm'}_j = \sum_{i=1}^I u^m_{ij} u^{m'}_{ij}$	$j=1,\ldots,J$ $m,m'=1,\ldots,M$	$IJ\dfrac{M(M+1)}{2}$
inner product of spatial projection function m and projection data	$\varphi^m_{jk} = \sum_{i=1}^I u^m_{ij} p^*_{ijk}$	$j=1,\ldots,J$ $k=1,\ldots,K$ $m=1,\ldots,M$	$IJKM$
inner product of spatial projection function m and spatial sum of vascular projections	$(\beta_{12})^m_j = \sum_{m'=M_1+1}^M f^{m'}_v \mu^{m'm}_j$	$j=1,\ldots,J$ $m=1,\ldots,M$	JM_2M
inner product of spatiotemporal projection function mn and spatial sum of uptake projections for spline n'	$(\beta_{13})^{mnn'}_j = \sum_{m'=M_1+1}^M k^{m'}_1 \mu^{m'm}_j \tilde{\nu}^{m'n'n}_j$	$j=1,\ldots,J$ $m=1,\ldots,M_1$ $n,n'=1,\ldots,N$	$2JM_1M_2N^2$ multiplies $JM_1M_2N^2$ adds
inner product of spatial sum of vascular projections and itself	$(\beta_{22})_j = \sum_{m=M_1+1}^M f^m_v (\beta_{12})^m_j$	$j=1,\ldots,J$	JM_2
inner product of spatial sums of vascular projections for spline n and uptake projections for spline n'	$(\beta_{23})^{nn'}_j = \sum_{m'=M_1+1}^M k^{m'}_1 (\beta_{12})^{m'}_j \tilde{\nu}^{m'n'n}_j$	$j=1,\ldots,J$ $n,n'=1,\ldots,N$	$2JM_2N^2$ multiplies JM_2N^2 adds
inner product of spatial sums of uptake projections for splines n and n'	$(\beta_{33})^{nn'}_j = \sum_{m=M_1+1}^M \left[k^m_1 \times \sum_{m'=M_1+1}^M k^{m'}_1 \mu^{mm'}_j \tilde{\nu}^{mm'nn'}_j \right]$	$j=1,\ldots,J$ $n,n'=1,\ldots,N$	$JM_2(2M_2+1)\dfrac{N(N-1)}{2}$ mults $JM_2(M_2+1)\dfrac{N(N-1)}{2}$ adds

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^1_{jk} and $\tilde{A}^{1m}_{jk}$ 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 $\mu^{mm'}_j$. 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 $\mathbf{G}^T\mathbf{G}$. 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 $M_1 \gg M_2$ (i.e., when most of the time-

activity curves are modeled with N splines), to a factor of about $4K$ when $M_1 = 1$ (i.e., when compartmental models with two conditionally linear parameters are used for all curves except the blood input function).

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

$$\mathbf{G}^T_1\mathbf{p}^* : \sum_{j=1}^J \sum_{k=1}^K \varphi^m_{jk} v^n_{jk}$$
$$\mathbf{G}^T_2\mathbf{p}^* : \sum_{j=1}^J \sum_{k=1}^K \varphi^m_{jk} A^1_{jk} \qquad (15)$$
$$\mathbf{G}^T_3\mathbf{p}^* : \sum_{j=1}^J \sum_{k=1}^K \varphi^m_{jk} \tilde{A}^{1m}_{jk},$$

where the factors φ_{jk}^m are defined in Table I. Compared to straightforward matrix multiplication of $\mathbf{G}^T\mathbf{p}^*$, this reduces computation by a factor of about $((M_1 - 1)N + 2M_2)/(M_1 + M_2)$ (i.e., the average number of linear and conditionally linear parameters per segmented volume).

The system of equations $\mathbf{G}^T\mathbf{G}\hat{\theta}_g = \mathbf{G}^T\mathbf{p}^*$ can then be solved relatively quickly for the parameters $\hat{\theta}_g$, with the use of the Cholesky decomposition of $\mathbf{G}^T\mathbf{G}$ [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

$$\left[\mathbf{F}^1 + \sum_{m=M_1+1}^{M} (f_v^m \mathbf{F}^m + k_1^m \Lambda^m) \right] \mathbf{a}_1 + \sum_{m=2}^{M_1} \mathbf{F}^m \mathbf{a}_m = \mathbf{p} \tag{16}$$

and then write (16) more compactly as

$$\mathbf{H}\theta_h = \mathbf{p}, \tag{17}$$

where

$$\mathbf{H} = \begin{bmatrix} \mathbf{H}_1 & \mathbf{G}_1 \end{bmatrix}$$
$$\mathbf{H}_1 = \mathbf{H}_{11} + \mathbf{H}_{12} + \mathbf{H}_{13}$$
$$\mathbf{H}_{11} = \mathbf{F}^1$$
$$\mathbf{H}_{12} = \sum_{m=M_1+1}^{M} f_v^m \mathbf{F}^m$$
$$\mathbf{H}_{13} = \sum_{m=M_1+1}^{M} k_1^m \Lambda^m$$
$$\theta_h^T = \begin{bmatrix} \mathbf{a}_1^T & \mathbf{a}_2^T & \cdots & \mathbf{a}_{M_1}^T \end{bmatrix}.$$

The least squares criterion (9) then becomes

$$\chi^2 = (\mathbf{p}^* - \mathbf{H}\theta_h)^T(\mathbf{p}^* - \mathbf{H}\theta_h), \tag{18}$$

and the vector of values for the a_{mn} that minimize χ^2 is

$$\hat{\theta}_h = (\mathbf{H}^T\mathbf{H})^{-1}\mathbf{H}^T\mathbf{p}^*. \tag{19}$$

One can accelerate computation of blocks of the symmetric $M_1N \times M_1N$ matrix $\mathbf{H}^T\mathbf{H}$ as follows. The symmetric $N \times N$ block $\mathbf{H}_1^T\mathbf{H}_1$ is the sum of the following matrices and the transposes of $\mathbf{H}_{11}^T\mathbf{H}_{12}$, $\mathbf{H}_{11}^T\mathbf{H}_{13}$, and $\mathbf{H}_{12}^T\mathbf{H}_{13}$:

$$
\begin{aligned}
\mathbf{H}_{11}^T\mathbf{H}_{11} &: \sum_{j=1}^{J} \mu_j^{11} \nu_j^{nn'} \\
\mathbf{H}_{11}^T\mathbf{H}_{12} &: \sum_{j=1}^{J} (\beta_{12})_j^1 \nu_j^{nn'} \\
\mathbf{H}_{11}^T\mathbf{H}_{13} &: \sum_{j=1}^{J} (\beta_{13})_j^{1nn'} \\
\mathbf{H}_{12}^T\mathbf{H}_{12} &: \sum_{j=1}^{J} (\beta_{22})_j \nu_j^{nn'} \\
\mathbf{H}_{12}^T\mathbf{H}_{13} &: \sum_{j=1}^{J} (\beta_{23})_j^{nn'} \\
\mathbf{H}_{13}^T\mathbf{H}_{13} &: \sum_{j=1}^{J} (\beta_{33})_j^{nn'},
\end{aligned}
\tag{20}
$$

where the factors $(\beta_{rs})_j$ are defined in Table I. The asymmetric $N \times (M_1 - 1)N$ block $\mathbf{H}_1^T\mathbf{G}_1$ is the sum of the matrices

$$
\begin{aligned}
\mathbf{H}_{11}^T\mathbf{G}_1 &: \sum_{j=1}^{J} \mu_j^{m1} \nu_j^{nn'} \\
\mathbf{H}_{12}^T\mathbf{G}_1 &: \sum_{j=1}^{J} (\beta_{12})_j^m \nu_j^{nn'} \\
\mathbf{H}_{13}^T\mathbf{G}_1 &: \sum_{j=1}^{J} (\beta_{13})_j^{mnn'}.
\end{aligned}
\tag{21}
$$

The symmetric $(M_1 - 1)N \times (M_1 - 1)N$ block $\mathbf{G}_1^T\mathbf{G}_1$ has elements given by the first sum in (14).

The use of straightforward matrix multiplication requires about $2IJKM_2N$ multiply-and-adds to calculate $\mathbf{H}_1$, followed by about $IJK(M_1N)^2/2$ multiply-and-adds to calculate $\mathbf{H}^T\mathbf{H}$. For small M_2 and $M_1 \gg M_2$, most of the overhead for the accelerated computation lies in calculating the intermediate sums $\mu_j^{mm'}$ and the speedup is by a factor of about KN^2. For small M_1 and $M_2 \gg M_1$, there is significant additional overhead in calculating the intermediate sums $\tilde{\nu}_j^{mnm'n'}$ and the speedup is reduced to a factor of about $KN^2[I/(I + KN^2)][4/(M_2N)]$.

Computation of blocks of the $M_1N \times 1$ column vector $\mathbf{H}^T\mathbf{p}^*$ can also be accelerated. The $N \times 1$ block $\mathbf{H}_1^T\mathbf{p}^*$ is the sum of the following vectors:

$$
\begin{aligned}
\mathbf{H}_{11}^T\mathbf{p}^* &: \sum_{j=1}^{J} \sum_{k=1}^{K} \varphi_{jk}^1 v_{jk}^n \\
\mathbf{H}_{12}^T\mathbf{p}^* &: \sum_{j=1}^{J} \sum_{k=1}^{K} \left[\sum_{m=M_1+1}^{M} f_v^m \varphi_{jk}^m \right] v_{jk}^n \\
\mathbf{H}_{13}^T\mathbf{p}^* &: \sum_{j=1}^{J} \sum_{k=1}^{K} \left[\sum_{m=M_1+1}^{M} k_1^m \varphi_{jk}^m \tilde{v}_{jk}^{mn} \right].
\end{aligned}
\tag{22}
$$

The $(M_1 - 1)N \times 1$ block $\mathbf{G}_1^T\mathbf{p}^*$ has elements given by the first sum in (15). Compared to straightforward matrix multiplication of $\mathbf{H}^T\mathbf{p}^*$, 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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