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March 1996

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Equivalent Methods to Analyze Dynamic Experiments in Which the Input Function is Noisy

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Recycled Paper

Equivalent Methods to Analyze Dynamic Experiments in Which the Input Function Is Noisy *

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March 14, 1996

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1 Introduction

In 1986 Huesman and Mazoyer [1, 2] developed a method to analyze dynamic experiments in which the input function is noisy. Noise in the input function leads to uncertainties in the calculated model predicted values, and therefore the covariance matrix of the residuals is a function of the model parameters. These statistical uncertainties in the model predicted values significantly change the nature of the fitting process and the quality of the results. The method developed by Huesman and Mazoyer uses a weighted least-squares criterion where the weighting matrix is the inverse of the full covariance matrix of the residuals, incorporating both the noise in the output data and the noise in the input function. The methodology was applied to dynamic emission tomography studies of the heart, where the blood (input) and tissue (output) tracer concentrations at each time are derived from two regions of interest in the same tomographic section. Even though only marginal reduction of variance and bias was shown, the demonstrated advantage of consideration of the noise in the input function was the ability to accurately estimate the covariance matrix of the parameter estimates.

In 1991 Chiao [3, 4] and independently Chen [5] suggested another method to analyze data with a noisy input function. The method developed by Chiao and Chen introduces

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additional parameters to describe the input function. It also adds terms to the weighted sum of squares which comprise the criterion. Instead of just summing the weighted terms to account for differences between the model and the output function, there is a second set of terms to account for the differences between the model and the input function. In this formulation, the model predicts the expected input function as well as the output function.

There had been conjecture in our laboratory on how the solutions from these two methods compare, and in 1993 Chen [6] showed that under very restrictive conditions the results of the two methods are the same. The subject of the present work is a proof that under very general conditions, the results of the two methods are indeed the same.

2 Formulation of the Problem

Let $\boldsymbol{x}$ denote the measured input function of dimension m, and $\boldsymbol{y}$ correspond to the measured output function of dimension n. Let $\boldsymbol{a}$ be a vector of m parameters, one for each point of the input function. Then,

$$\boldsymbol{x} = \boldsymbol{a} + \boldsymbol{e}_x , \tag{1}$$

$$\boldsymbol{y} = H\boldsymbol{a} + \boldsymbol{e}_y . \tag{2}$$

The $n \times m$ model matrix H is a function of the compartmental parameters $\boldsymbol{k}$. The expectation-zero noise vectors $\boldsymbol{e}_x$ and $\boldsymbol{e}_y$ are defined such that

$$\left\langle \boldsymbol{e}_x \boldsymbol{e}_x' \right\rangle = \Phi_{xx} , \tag{3}$$

$$\left\langle \boldsymbol{e}_y \boldsymbol{e}_y' \right\rangle = \Phi_{yy} , \tag{4}$$

$$\left\langle \boldsymbol{e}_x \boldsymbol{e}_y' \right\rangle = \Phi_{xy} . \tag{5}$$

Lower case bold characters indicate vectors, upper case case characters represent matrices, prime indicates transpose, and angle brackets indicate expectation.

3 Method of Huesman and Mazoyer

The original formulation of Huesman and Mazoyer minimizes the function

$$\chi_1^2(\boldsymbol{k}) = \boldsymbol{\rho}' \Phi_{\rho\rho}^{-1} \boldsymbol{\rho} , \tag{6}$$

where

$$\boldsymbol{\rho} = \boldsymbol{y} - H\boldsymbol{x} \tag{7}$$

is the vector of residuals, and

$$\Phi_{\rho\rho} = \Phi_{yy} - \Phi_{xy}' H' - H\Phi_{xy} + H\Phi_{xx}H' \tag{8}$$

is the covariance matrix of the output residual vector, $\boldsymbol{\rho}$. Notice that the covariance matrix of the residuals changes with the parameters, because $\Phi_{\rho\rho}$ is a function of the matrix H which is in turn a function of the compartmental parameters, $\boldsymbol{k}$.

If we denote the solution to the minimization of eq(6) by $\hat{\boldsymbol{k}}$, it was shown in [2] that $\chi_1^2(\hat{\boldsymbol{k}})$ is distributed like a χ^2–distribution with $(n-\ell)$ degrees of freedom, where ℓ is the dimension of the parameter vector $\boldsymbol{k}$. An estimate of the covariance matrix of the resulting parameters $\hat{\boldsymbol{k}}$ is given by the inverse of half the second derivative matrix of the criterion evaluated at the minimum

$$\left[\frac{1}{2}\frac{\partial^2\chi_1^2(\boldsymbol{k})}{\partial\boldsymbol{k}^2}\right]^{-1}_{\boldsymbol{k}=\hat{\boldsymbol{k}}} . \tag{9}$$

4 Method of Chiao and Chen

The formulation of Chiao and Chen treats the elements of the vector $\boldsymbol{a}$ as additional parameters to be estimated, and therefore it also considers elements of the residuals of the input function vector as part of the weighted sum of squares criterion. In order to form a single vector containing both the input and the output data vectors, let the vector $\boldsymbol{z}$ of dimension $m+n$ be defined by

$$\boldsymbol{z} = \begin{pmatrix} \boldsymbol{x} \\ \boldsymbol{y} \end{pmatrix} . \tag{10}$$

The new combined residual is given by

$$\boldsymbol{z} - C\boldsymbol{a} , \tag{11}$$

where the matrix C consists of

$$C = \begin{pmatrix} I \\ H \end{pmatrix} , \tag{12}$$

and I is the $m \times m$ identity matrix. The criterion function used for estimating $\boldsymbol{a}$ and $\boldsymbol{k}$ is

$$\chi_2^2(\boldsymbol{k},\boldsymbol{a}) = (\boldsymbol{z} - C\boldsymbol{a})'\Phi_{zz}^{-1}(\boldsymbol{z} - C\boldsymbol{a}) , \tag{13}$$

where Φ_{zz} is the covariance matrix of the vector $\boldsymbol{z}$ and is given by

$$\Phi_{zz} = \begin{pmatrix} \Phi_{xx} & \Phi_{xy} \\ \Phi'_{xy} & \Phi_{yy} \end{pmatrix} . \tag{14}$$

Notice that in this case the covariance matrix of the residuals is simply the covariance matrix of the data vector $\boldsymbol{z}$, since the expression $C\boldsymbol{a}$ is not a random variable. This is the normal situation in weighted least squares estimation. This method avoids the complications of a noisy input function by fitting its parameters and treating it as data like the output. The disadvantage is that more parameters, sometimes called nuisance parameters, must be estimated.

5 Equivalence of the Methods

To show that the two methods described above are equivalent, we notice that we can first estimate the input function parameters $\boldsymbol{a}$ for arbitrary values of the compartmental parameters $\boldsymbol{k}$. Minimizing eq(13) with respect to $\boldsymbol{a}$ (for fixed $\boldsymbol{k}$) gives

$$\hat{\boldsymbol{a}}(\boldsymbol{k}) = (C'\Phi_{zz}^{-1}C)^{-1}C'\Phi_{zz}^{-1}\boldsymbol{z} \ , \tag{15}$$

and if eq(15) is inserted in eq(13) we get

$$\begin{aligned} \chi_2^2(\boldsymbol{k}) &= \chi_2^2(\boldsymbol{k}, \hat{\boldsymbol{a}}(\boldsymbol{k})) \\ &= \boldsymbol{z}' \left[I - C(C'\Phi_{zz}^{-1}C)^{-1}C'\Phi_{zz}^{-1}\right]' \Phi_{zz}^{-1} \left[I - C(C'\Phi_{zz}^{-1}C)^{-1}C'\Phi_{zz}^{-1}\right] \boldsymbol{z} \\ &= \boldsymbol{z}' \left[\Phi_{zz}^{-1} - \Phi_{zz}^{-1}C(C'\Phi_{zz}^{-1}C)^{-1}C'\Phi_{zz}^{-1}\right] \boldsymbol{z} \ . \end{aligned} \tag{16}$$

We now partition the matrix Φ_{zz}^{-1} as we have partitioned Φ_{zz} above:

$$\Phi_{zz}^{-1} = \begin{pmatrix} \phi_{xx} & \phi_{xy} \\ \phi'_{xy} & \phi_{yy} \end{pmatrix} , \tag{17}$$

where

$$\phi_{xx} = (\Phi_{xx} - \Phi_{xy}\Phi_{yy}^{-1}\Phi'_{xy})^{-1} = \Phi_{xx}^{-1} + \Phi_{xx}^{-1}\Phi_{xy}(\Phi_{yy} - \Phi'_{xy}\Phi_{xx}^{-1}\Phi_{xy})^{-1}\Phi'_{xy}\Phi_{xx}^{-1} \ , \tag{18}$$

$$\phi_{yy} = (\Phi_{yy} - \Phi'_{xy}\Phi_{xx}^{-1}\Phi_{xy})^{-1} = \Phi_{yy}^{-1} + \Phi_{yy}^{-1}\Phi'_{xy}(\Phi_{xx} - \Phi_{xy}\Phi_{yy}^{-1}\Phi'_{xy})^{-1}\Phi_{xy}\Phi_{yy}^{-1} \ , \tag{19}$$

$$\phi_{xy} = -\Phi_{xx}^{-1}\Phi_{xy}(\Phi_{yy} - \Phi'_{xy}\Phi_{xx}^{-1}\Phi_{xy})^{-1} = -(\Phi_{xx} - \Phi_{xy}\Phi_{yy}^{-1}\Phi'_{xy})^{-1}\Phi_{xy}\Phi_{yy}^{-1} \ , \tag{20}$$

and

$$\Phi_{xx} = (\phi_{xx} - \phi_{xy}\phi_{yy}^{-1}\phi'_{xy})^{-1} = \phi_{xx}^{-1} + \phi_{xx}^{-1}\phi_{xy}(\phi_{yy} - \phi'_{xy}\phi_{xx}^{-1}\phi_{xy})^{-1}\phi'_{xy}\phi_{xx}^{-1} \ , \tag{21}$$

$$\Phi_{yy} = (\phi_{yy} - \phi'_{xy}\phi_{xx}^{-1}\phi_{xy})^{-1} = \phi_{yy}^{-1} + \phi_{yy}^{-1}\phi'_{xy}(\phi_{xx} - \phi_{xy}\phi_{yy}^{-1}\phi'_{xy})^{-1}\phi_{xy}\phi_{yy}^{-1} \ , \tag{22}$$

$$\Phi_{xy} = -\phi_{xx}^{-1}\phi_{xy}(\phi_{yy} - \phi'_{xy}\phi_{xx}^{-1}\phi_{xy})^{-1} = -(\phi_{xx} - \phi_{xy}\phi_{yy}^{-1}\phi'_{xy})^{-1}\phi_{xy}\phi_{yy}^{-1} \ . \tag{23}$$

Equations (14) and (17) show similar partitioning of positive definite symmetric matrices which are inverses of each other. Derivations of the expressions given above for the relationships between the components of these matrices can be found in [7].

The various parts of eq(16) can be expressed in terms of the submatrices of Φ_{zz}^{-1}:

$$\begin{aligned} \boldsymbol{z}'\Phi_{zz}^{-1}\boldsymbol{z} &= \begin{pmatrix} \boldsymbol{x}' & \boldsymbol{y}' \end{pmatrix} \begin{pmatrix} \phi_{xx} & \phi_{xy} \\ \phi'_{xy} & \phi_{yy} \end{pmatrix} \begin{pmatrix} \boldsymbol{x} \\ \boldsymbol{y} \end{pmatrix} \\ &= \boldsymbol{x}'\phi_{xx}\boldsymbol{x} + \boldsymbol{x}'\phi_{xy}\boldsymbol{y} + \boldsymbol{y}'\phi'_{xy}\boldsymbol{x} + \boldsymbol{y}'\phi_{yy}\boldsymbol{y} \ , \end{aligned} \tag{24}$$

$$\begin{aligned} C'\Phi_{zz}^{-1}C &= \begin{pmatrix} I & H' \end{pmatrix} \begin{pmatrix} \phi_{xx} & \phi_{xy} \\ \phi'_{xy} & \phi_{yy} \end{pmatrix} \begin{pmatrix} I \\ H \end{pmatrix} \\ &= \phi_{xx} + H'\phi'_{xy} + \phi_{xy}H + H'\phi_{yy}H \ , \end{aligned} \tag{25}$$

$$
\begin{aligned}
C'\Phi_{zz}^{-1}\boldsymbol{z} &= \begin{pmatrix} I & H' \end{pmatrix} \begin{pmatrix} \phi_{xx} & \phi_{xy} \\ \phi'_{xy} & \phi_{yy} \end{pmatrix} \begin{pmatrix} \boldsymbol{x} \\ \boldsymbol{y} \end{pmatrix} \\
&= \phi_{xx}\boldsymbol{x} + \phi_{xy}\boldsymbol{y} + H'\phi'_{xy}\boldsymbol{x} + H'\phi_{yy}\boldsymbol{y} \\
&= (\phi_{xx} + H'\phi'_{xy} + \phi_{xy}H + H'\phi_{yy}H)\boldsymbol{x} + (\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x}) \\
&= C'\Phi_{zz}^{-1}C\boldsymbol{x} + (\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x}) \,. \qquad (26)
\end{aligned}
$$

We substitute eq(24) and eq(26) into eq(16) giving

$$
\begin{aligned}
\chi_2^2(\boldsymbol{k}) &= \boldsymbol{x}'\phi_{xx}\boldsymbol{x} + \boldsymbol{x}'\phi_{xy}\boldsymbol{y} + \boldsymbol{y}'\phi'_{xy}\boldsymbol{x} + \boldsymbol{y}'\phi_{yy}\boldsymbol{y} \\
&\quad - \left[C'\Phi_{zz}^{-1}C\boldsymbol{x} + (\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x})\right]' (C'\Phi_{zz}^{-1}C)^{-1} \\
&\quad \left[C'\Phi_{zz}^{-1}C\boldsymbol{x} + (\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x})\right] \\
&= \boldsymbol{x}'\phi_{xx}\boldsymbol{x} + \boldsymbol{x}'\phi_{xy}\boldsymbol{y} + \boldsymbol{y}'\phi'_{xy}\boldsymbol{x} + \boldsymbol{y}'\phi_{yy}\boldsymbol{y} - \boldsymbol{x}'C'\Phi_{zz}^{-1}C\boldsymbol{x} \\
&\quad - \boldsymbol{x}'(\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x}) - (\boldsymbol{y} - H\boldsymbol{x})'(\phi_{xy} + H'\phi_{yy})'\boldsymbol{x} \\
&\quad - (\boldsymbol{y} - H\boldsymbol{x})'(\phi_{xy} + H'\phi_{yy})'(C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x}) \,. \qquad (27)
\end{aligned}
$$

Substituting eq(25) into eq(27) and collecting terms gives

$$
\begin{aligned}
\chi_2^2(\boldsymbol{k}) &= \boldsymbol{x}'\phi_{xx}\boldsymbol{x} + \boldsymbol{x}'\phi_{xy}\boldsymbol{y} + \boldsymbol{y}'\phi'_{xy}\boldsymbol{x} + \boldsymbol{y}'\phi_{yy}\boldsymbol{y} \\
&\quad - \boldsymbol{x}'\phi_{xx}\boldsymbol{x} - \boldsymbol{x}'H'\phi'_{xy}\boldsymbol{x} - \boldsymbol{x}'\phi_{xy}H\boldsymbol{x} - \boldsymbol{x}'H'\phi_{yy}H\boldsymbol{x} \\
&\quad - \boldsymbol{x}'\phi_{xy}\boldsymbol{y} + \boldsymbol{x}'\phi_{xy}H\boldsymbol{x} - \boldsymbol{x}'H'\phi_{yy}\boldsymbol{y} + \boldsymbol{x}'H'\phi_{yy}H\boldsymbol{x} \\
&\quad - \boldsymbol{y}'\phi'_{xy}\boldsymbol{x} - \boldsymbol{y}'\phi_{yy}H\boldsymbol{x} + \boldsymbol{x}'H'\phi'_{xy}\boldsymbol{x} + \boldsymbol{x}'H'\phi_{yy}H\boldsymbol{x} \\
&\quad - (\boldsymbol{y} - H\boldsymbol{x})'(\phi_{xy} + H'\phi_{yy})'(C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x}) \\
&= \boldsymbol{y}'\phi_{yy}\boldsymbol{y} - \boldsymbol{x}'H'\phi_{yy}\boldsymbol{y} - \boldsymbol{y}'\phi_{yy}H\boldsymbol{x} + \boldsymbol{x}'H'\phi_{yy}H\boldsymbol{x} \\
&\quad - (\boldsymbol{y} - H\boldsymbol{x})'(\phi_{xy} + H'\phi_{yy})'(C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x}) \\
&= (\boldsymbol{y} - H\boldsymbol{x})' \left[\phi_{yy} - (\phi_{xy} + H'\phi_{yy})'(C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy} + H'\phi_{yy})\right] (\boldsymbol{y} - H\boldsymbol{x} \,.) \qquad (28)
\end{aligned}
$$

We now investigate the square bracket at the bottom of eq(28) by regrouping terms in the expression for $(C'\Phi_{zz}^{-1}C)$ given by eq(25):

$$
\begin{aligned}
C'\Phi_{zz}^{-1}C &= \phi_{xx} + H'\phi'_{xy} + \phi_{xy}H + H'\phi_{yy}H \\
&= \phi_{xx} - \phi_{xy}\phi_{yy}^{-1}\phi'_{xy} + (\phi_{xy} + H'\phi_{yy})\phi_{yy}^{-1}(\phi_{xy} + H'\phi_{yy})' \\
&= \Phi_{xx}^{-1} + (\phi_{xy} + H'\phi_{yy})\phi_{yy}^{-1}(\phi_{xy} + H'\phi_{yy})' \,. \qquad (29)
\end{aligned}
$$

Using the identity $(I + AB)^{-1}A = A(I + BA)^{-1}$, for which a derivation is given in [7], we can write

$$
\begin{aligned}
(C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy}+H'\phi_{yy}) = & \\
& \left[\Phi_{xx}^{-1}+(\phi_{xy}+H'\phi_{yy})\phi_{yy}^{-1}(\phi_{xy}+H'\phi_{yy})'\right]^{-1}(\phi_{xy}+H'\phi_{yy}) \\
= & \ \Phi_{xx}\left[I+(\phi_{xy}+H'\phi_{yy})\phi_{yy}^{-1}(\phi_{xy}+H'\phi_{yy})'\Phi_{xx}\right]^{-1}(\phi_{xy}+H'\phi_{yy}) \\
= & \ \Phi_{xx}(\phi_{xy}+H'\phi_{yy})\left[I+\phi_{yy}^{-1}(\phi_{xy}+H'\phi_{yy})'\Phi_{xx}(\phi_{xy}+H'\phi_{yy})\right]^{-1} \\
= & \ \Phi_{xx}(\phi_{xy}\phi_{yy}^{-1}+H')\left[\phi_{yy}^{-1}+(\phi_{xy}\phi_{yy}^{-1}+H')'\Phi_{xx}(\phi_{xy}\phi_{yy}^{-1}+H')\right]^{-1} . \qquad (30)
\end{aligned}
$$

Multiplying eq(30) on the left by $(\phi_{xy}+H'\phi_{yy})'$ we get

$$
\begin{aligned}
(\phi_{xy}+H'\phi_{yy})'(C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy}+H'\phi_{yy}) = & \\
& \phi_{yy}(\phi_{xy}\phi_{yy}^{-1}+H')'\Phi_{xx}(\phi_{xy}\phi_{yy}^{-1}+H')\left[\phi_{yy}^{-1}+(\phi_{xy}\phi_{yy}^{-1}+H')'\Phi_{xx}(\phi_{xy}\phi_{yy}^{-1}+H')\right]^{-1} \\
= & \ \phi_{yy}-\left[\phi_{yy}^{-1}+(\phi_{xy}\phi_{yy}^{-1}+H')'\Phi_{xx}(\phi_{xy}\phi_{yy}^{-1}+H')\right]^{-1} . \qquad (31)
\end{aligned}
$$

The term which requires inversion in eq(30) and eq(31) can be simplified to

$$
\begin{aligned}
\phi_{yy}^{-1}+(\phi_{xy}\phi_{yy}^{-1}+H')'\Phi_{xx}(\phi_{xy}\phi_{yy}^{-1}+H') = & \\
& \Phi_{yy}-\Phi_{xy}'\Phi_{xx}^{-1}\Phi_{xy}+(H'-\Phi_{xx}^{-1}\Phi_{xy})'\Phi_{xx}(H'-\Phi_{xx}^{-1}\Phi_{xy}) \\
= & \ \Phi_{yy}-\Phi_{xy}'H'-H\Phi_{xy}+H\Phi_{xx}H'=\Phi_{\rho\rho} , \qquad (32)
\end{aligned}
$$

which is the covariance matrix of the residual vector given by $\boldsymbol{\rho}=(\boldsymbol{y}-H\boldsymbol{x})$ which we have denoted by $\Phi_{\rho\rho}$. After substituting eq(32) into eq(31) and eq(31) into eq(28) we finally get

$$
\begin{aligned}
\chi_2^2(\boldsymbol{k}) &= (\boldsymbol{y}-H\boldsymbol{x})'\left(\Phi_{yy}-\Phi_{xy}'H'-H\Phi_{xy}+H\Phi_{xx}H'\right)^{-1}(\boldsymbol{y}-H\boldsymbol{x}) \\
&= \boldsymbol{\rho}'\Phi_{\rho\rho}^{-1}\boldsymbol{\rho} \\
&= \chi_1^2(\boldsymbol{k}) . \qquad (33)
\end{aligned}
$$

And therefore we have shown that eq(13) is equivalent to eq(6) when the inverses of the matrices $(C'\Phi_{zz}^{-1}C)$ and $\Phi_{\rho\rho}$ exist. It can also be shown that the existence of the inverse of one of these matrices implies the existence of the inverse of the other.

6 Discussion

We have shown that the two methods considered in this paper which analyze dynamic experiments in which the input function is noisy are equivalent to one another. The method of Chiao and Chen has the advantage of a relatively straightforward theoretical basis, but the function to be minimized has many more parameters to estimate than the initial method of Huesman and Mazoyer.

The method of Chiao and Chen has lead us to a better understand of how the input function parameters are adjusted in order to obtain the minimized criterion value. The resulting input function parameters can be found by substituting eq(26) into eq(15)

$$\begin{aligned}\hat{\boldsymbol{a}}(\boldsymbol{k}) &= (C'\Phi_{zz}^{-1}C)^{-1}C'\Phi_{zz}^{-1}\boldsymbol{z} \\ &= \boldsymbol{x} + (C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x}) \ .\end{aligned} \tag{34}$$

This can also be rewritten by substituting eq(32) into eq(30) and eq(30) into eq(34):

$$\begin{aligned}\hat{\boldsymbol{a}}(\boldsymbol{k}) &= \boldsymbol{x} + (\Phi_{xx}H' - \Phi_{xy})\left(\Phi_{yy} - \Phi_{xy}'H' - H\Phi_{xy} + H\Phi_{xx}H'\right)^{-1}(\boldsymbol{y} - H\boldsymbol{x}) \\ &= \boldsymbol{x} + (\Phi_{xx}H' - \Phi_{xy})\Phi_{\rho\rho}^{-1}\boldsymbol{\rho} \ .\end{aligned} \tag{35}$$

Computational efficiency compels us to minimize eq(6) for the compartmental parameter estimates $\hat{\boldsymbol{k}}$, after which the resulting difference between the measured input function $\boldsymbol{x}$ and the estimated input function parameters $\hat{\boldsymbol{a}}(\hat{\boldsymbol{k}})$ can be calculated from eq(35). The covariance matrix of the compartmental parameter estimates $\hat{\boldsymbol{k}}$ is estimated using eq(9).

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