Equivalent methods to analyse dynamic experiments in which the input function is noisy

Ronald H Huesman

Center for Functional Imaging, E O Lawrence Berkeley National Laboratory, University of California, Berkeley, CA 94720, USA

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Abstract. A comparison is made between two methods of parameter estimation for analysis of 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. Statistical uncertainties in the model-predicted values significantly change the nature of the fitting process and the quality of the results. The initial method 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. The second method introduces additional parameters to describe the input function, and adds terms to the weighted sum of squares which comprise the criterion. Instead of only 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. The two methods have different theoretical bases and appear to optimize different criteria, but it is shown here that they are equivalent to one another. The criterion which they minimize is the same under certain matrix invertibility constraints, which must be satisfied to ensure the stability of either method.

1. Introduction

In 1986 Huesman and Mazoyer (Huesman and Mazoyer 1986, 1987) developed a method to analyse 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 considering the noise in the input function was the ability to estimate accurately the covariance matrix of the parameter estimates.

In 1991 Chiao (Chiao 1991, Chiao *et al* 1994), and, independently, Chen (Chen *et al* 1991), suggested another method to analyse data with a noisy input function. The

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method developed by Chiao and Chen introduces additional parameters to describe the input function. It also adds terms to the weighted sum of squares which comprise the criterion. Instead of only 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 (Chen 1993) 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

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

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

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

Lower case bold characters indicate vectors, upper 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, $\boldsymbol{\rho}$. Note that the covariance matrix of the residuals changes with the parameters because $\Phi_{\rho\rho}$ is a function of H which is in turn a function of $\boldsymbol{k}$.

If we denote the solution to the minimization of equation (6) by $\hat{\boldsymbol{k}}$, it was shown by Monte Carlo simulation (Huesman and Mazoyer 1987) that the moments of the distribution of $\chi_1^2(\hat{\boldsymbol{k}})$ are consistent with a χ^2–distribution with $(n - \ell)$ degrees of freedom, where ℓ is the dimension of the parameter vector $\boldsymbol{k}$. It was also shown by Monte Carlo simulation (Huesman and Mazoyer 1987) that 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, i.e.:

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

The distribution of the values of $\hat{\boldsymbol{k}}$ and the estimation of their covariance matrix by equation (9) are expected if the data are normally distributed and the criterion is twice the negative logarithm of the likelihood function.

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

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

Note 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 equation (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 equation (15) is inserted in equation (13) we get

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

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

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

where

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

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

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

and

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

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

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

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 Henderson and Searle (1981).

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

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

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

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

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

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

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

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

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

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

Using the identity $(I + AB)^{-1}A = A(I + BA)^{-1}$, for which a derivation is given in Henderson and Searle (1981), we can write

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

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

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

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

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

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 equation (32) into equation (31) and equation (31) into equation (28) we finally get

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

And therefore we have shown that minimization of equation (13) is equivalent to minimization of equation (6) when the inverses of the matrices $(C'\Phi_{zz}^{-1}C)$ and $\Phi_{\rho\rho}$ exist.

The existence of the inverse of either of the matrices $(C'\Phi_{zz}^{-1}C)$ and $\Phi_{\rho\rho}$ implies the existence of the inverse of the other. This can be seen by rewriting equation (29) and equation (32):

$$\begin{aligned} C'\Phi_{zz}^{-1}C &= \Phi_{xx}^{-1} + (\phi_{xy} + H'\phi_{yy})\phi_{yy}^{-1}(\phi_{xy} + H'\phi_{yy})' \\ &= \Phi_{xx}^{-1}\left[I + \Phi_{xx}(\phi_{xy} + H'\phi_{yy})\phi_{yy}^{-1}(\phi_{xy} + H'\phi_{yy})'\right] \end{aligned} \tag{34}$$

$$\begin{aligned} \Phi_{\rho\rho} &= \phi_{yy}^{-1} + (\phi_{xy}\phi_{yy}^{-1} + H')'\Phi_{xx}(\phi_{xy}\phi_{yy}^{-1} + H') \\ &= \left[I + \phi_{yy}^{-1}(\phi_{xy} + H'\phi_{yy})'\Phi_{xx}(\phi_{xy} + H'\phi_{yy})\right]\phi_{yy}^{-1}\,. \end{aligned} \tag{35}$$

The terms in the square brackets of equation (34) and equation (35) can be expressed as $(I + AB)$ and $(I + BA)$ respectively, and therefore their determinants are equal (Henderson and Searle, 1981). Since Φ_{xx} and ϕ_{yy} are invertible, the matrices $(C'\Phi_{zz}^{-1}C)$ and $\Phi_{\rho\rho}$ either both have inverses or neither has an inverse. These matrices are functions of the compartmental parameters, $\boldsymbol{k}$, but not of the input function parameters, $\boldsymbol{a}$. Values of $\boldsymbol{k}$ for which the matrices are not invertible are easily avoided in the iterative process of minimizing the criterion of equation (6).

6. Discussion

We have shown that the two methods considered in this paper which analyse dynamic experiments in which the input function is noisy are equivalent to one another. The criterion which they minimize is the same under certain matrix invertibility constraints, which, if not satisfied, render both methods unstable. 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 led us to a better understanding 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 equation (26) into equation (15):

$$\begin{aligned} \hat{\boldsymbol{a}}(\boldsymbol{k}) &= (C'\Phi_{zz}^{-1}C)^{-1}C'\Phi_{zz}^{-1}\boldsymbol{z} \\ &= \boldsymbol{x} + (C'\Phi_{zz}^{-1}C)^{-1}(\phi_{xy} + H'\phi_{yy})(\boldsymbol{y} - H\boldsymbol{x})\,. \end{aligned} \tag{36}$$

This can also be rewritten by substituting equation (32) into equation (30) and equation (30) into equation (36):

$$\begin{aligned} \hat{\boldsymbol{a}}(\boldsymbol{k}) &= \boldsymbol{x} + (\Phi_{xx}H' - \Phi_{xy})\left(\Phi_{yy} - \Phi_{xy}'H' - H\Phi_{xy} + H\Phi_{xx}H'\right)^{-1}(\boldsymbol{y} - H\boldsymbol{x}) \\ &= \boldsymbol{x} + (\Phi_{xx}H' - \Phi_{xy})\Phi_{\rho\rho}^{-1}\boldsymbol{\rho}\,. \end{aligned} \tag{37}$$

Computational efficiency compels us to minimize equation (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 equation (37). The covariance matrix of the compartmental parameter estimates $\hat{\boldsymbol{k}}$ is estimated using equation (9).

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