Model Error Correction for Linear Methods of Reversible Radioligand Binding Measurements in PET Studies

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Abstract

Graphical analysis methods are widely used in positron emission tomography quantification because of their simplicity and model independence. But they may, particularly for reversible kinetics, lead to bias in the estimated parameters. The source of the bias is commonly attributed to noise in the data. Assuming a two-tissue compartmental model, we investigate the bias that originates from model error. This bias is an intrinsic property of the simplified linear models used for limited scan durations, and it is exaggerated by random noise and numerical quadrature error. Conditions are derived under which Logan’s graphical method either over- or under-estimates the distribution volume in the noise-free case. The bias caused by model error is quantified analytically. The presented analysis shows that the bias of graphical methods is inversely proportional to the dissociation rate. Furthermore, visual examination of the linearity of the Logan plot is not sufficient for guaranteeing that equilibrium has been reached. A new model which retains the elegant properties of graphical analysis methods is presented, along with a numerical algorithm for its solution. We perform simulations with the fibrillar amyloid β radioligand [11C] benzothiazole-aniline using published data from the University of Pittsburgh and Rotterdam groups. The results show that the proposed method significantly reduces the bias due to model error. Moreover, the results for data acquired over a 70 minutes scan duration are at least as good as those obtained using existing methods for data acquired over a 90 minutes scan duration.

Key words: Bias; graphical analysis; Logan plot; PET quantification; PIB; Alzheimer’s disease; distribution volume.
PACS: 82.20.Wt, 87.57.-s, 87.57.uk

1. Introduction

Graphical analysis (GA) has been routinely used for quantification of positron emission tomography (PET) radioligand measurements. The first GA method for measuring primarily tracer uptakes for irreversible kinetics was introduced by Patlak, [1, 2], and extended for measuring tracer distribution (accumulation) in reversible systems by Logan, [3]. These techniques have been utilized both with input data acquired from plasma measurements and using the time activity curve from a reference brain region. They have been used for calculation of tracer uptake rates, absolute distribution volumes (DV) and DV ratios (DVR), or, equivalently, for absolute and relative binding potentials (BP). They are widely used because of their inherent simplicity and general applicability regardless of the specific compartmental model.

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The well-known bias, particularly for reversible kinetics, in parameters estimated by GA is commonly attributed to noise in the data, \cite{4, 5, 6}, and therefore techniques to reduce the bias have concentrated on limiting the impact of the noise. These include (i) rearrangement of the underlying system of linear equations so as to reduce the impact of noise yielding the so-called multi-linear method (MA1), \cite{5}, and a second multi-linear approach (MA2), \cite{7}, (ii) preprocessing using the method of generalized linear least squares (GLLS), \cite{8}, yielding a hybrid GLLS-GA method, \cite{9}, (iii) use of the method of perpendicular least squares, \cite{10}, also known as total least squares (TLS), \cite{11}, (iv) likelihood estimation, \cite{12}, (v) Tikhonov regularization \cite{13}, (vi) principal component analysis, \cite{14}, and (vii) reformulating the method of Logan so as to reduce the noise in the denominator, \cite{15}. Here, we turn our attention to another important source of the bias: the model error which is implicit in GA approaches.

The bias associated with GA approaches has, we believe, three possible sources. The bias arising due to random noise is most often discussed, but errors may also be attributed to the use of numerical quadrature and an approximation of the underlying compartmental model. It is demonstrated in Section 2 that not only is bias an intrinsic property of the linear model for limited scan durations, which is exaggerated by noise, but also that it may be dominated by the effects of the model error. Indeed, numerical simulations, presented in Section 4, demonstrate that large bias can result even in the noise-free case. Conditions for over- or under-estimation of the DV due to model error and the extent of bias of the Logan plot are quantified analytically. These lead to the design of a bias correction method, Section 3, which still maintains the elegant simplicity of GA approaches. This bias reduction is achieved by the introduction of a simple nonlinear term in the model. While this approach adds some moderate computational expense, simulations reported in Section 4.3 for the fibrillar amyloid \( \beta \) radioligand \([11C]\) benzothiazole-aniline (Pittsburgh Compound-B [PIB]), \cite{16}, illustrate that it greatly reduces bias. Relevant observations are discussed in Section 5 and conclusions presented in Section 6.

2. Theory

2.1. Existing linear methods

For the measurement of DV, existing linear quantification methods for reversible radiotracers with a known input function, i.e. the unmetabolized tracer concentration in plasma, are based on the following linear approximation of the true kinetics developed by Logan, \cite{3}:

\[
\text{MA0 : } \int_0^t C_T(\tau)d\tau \approx DV \int_0^t C_p(\tau)d\tau - bC_T(t). \tag{1}
\]

Here \( C_T(t) \) is the measured tissue time activity curve (TTAC), \( C_p(t) \) is the input function, DV represents the distribution volume and quantity \( b \) is a constant. With known \( C_T(t) \) and \( C_p(t) \) we can solve for DV and \( b \) by the method of linear least squares. This model, which we denote by MA0 to distinguish it from MA1 and MA2 introduced in \cite{5}, approximately describes tracer behavior at equilibrium. Dividing through by \( C_T(t) \), showing that the DV is the linear slope and \(-b\) the intercept, yields the original Logan graphical analysis model, denoted here by Logan-GA,

\[
\text{Logan - GA : } \frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} \approx DV \frac{\int_0^t C_p(\tau)d\tau}{C_T(t)} - b, \tag{2}
\]

in which the DV and intercept \(-b\) are obtained by using linear least squares (LS) for the sampled version of (2). Although it is well-known that this model often leads to under-estimation of the DV it is still widely used in PET studies. An alternative formulation based on (11) is the so-called MA1,

\[
\text{MA1 : } C_T(t) \approx \frac{DV}{b} \int_0^t C_p(\tau)d\tau - \frac{1}{b} \int_0^t C_T(\tau)d\tau, \tag{3}
\]
for which the DV can again be obtained using LS \cite{3}. Recently another formulation, obtained by division in (1) by $C_p(t)$ instead of $C_T(t)$, has been developed by Zhou et al. \cite{15}. But, as noted by Varga et al in \cite{10} the noise appears in both the independent and dependent variables in (2) and thus TLS may be a more appropriate model than LS for obtaining the DV. Whereas it has been concluded through numerical experiments for tracer $^{[18]F}$FCWAY and $^{[11]C}$MDL 100,907, \cite{5}, that MA1 \cite{5} performs better than other linear methods, including Logan-GA \cite{2}, TLS and MA2 \cite{7,5}, none of these techniques explicitly deals with the inherent error due to the assumption of model MA0 \cite{11}. The focus here is thus examination of the model error specifically for Logan-GA and MA1, from which a new method for reduction of model error is designed.

2.2. Model error analysis

The general three-tissue compartmental model for the reversible radioligand binding kinetics of a given brain region or a voxel can be illustrated as follows, \cite{17,18}:

$$
\begin{array}{c}
C_p(t) \\
\downarrow \quad K_1 \\
C_F(t) \\
\downarrow \quad k_3 \\
C_N(t) \\
\downarrow \quad k_5 \\
C_{NS}(t) \\
\end{array}
\begin{array}{c}
C_F(t) \\
\downarrow \quad k_2 \\
C_S(t) \\
\downarrow \quad k_4 \\
C_{NS}(t) \\
\end{array}
$$

Figure 1: Three-tissue compartmental model of reversible radioligand binding dynamics.

Here $C_p(t)$ (kBq/ml) is the input function, i.e. the unmetabolized radiotracer concentration in plasma, and $C_F(t)$, $C_{NS}(t)$ and $C_S(t)$ (kBq/g) are free radioactivity, nonspecific bound and specific bound tracer concentrations, resp., and $K_1$ (ml/min/g) and $k_i$ (1/min), $i = 2, \cdots, 6$, are rate constants. The DV is related to the rate constants as follows \cite{19},

$$
DV = \frac{K_1}{k_2} (1 + \frac{k_3}{k_4} + \frac{k_5}{k_6}). \quad (4)
$$

The numerical implementation for estimating the unknown rate constants of the differential system illustrated in Figure 1 is difficult because three exponentials are involved in the solution of this system, \cite{18}. Specifically, without the inclusion of additional prior knowledge, the rate constants may be unidentifiable, \cite{20}. Fortunately, for most tracers it can safely be assumed that $C_{NS}$ and $C_F$ reach equilibrium rapidly for specific binding regions. Then it is appropriate to use a two-tissue four-parameter (2T-4k) model by binning $C_{NS}(t)$ and $C_F(t)$ to one compartment $C_{F+NS}(t) = C_F(t) + C_{NS}(t)$. This is equivalent to taking $k_5 = k_6 = 0$, and hence $C_{NS}(t) = 0$. On the other hand, for regions without specific binding activity, we know $C_S(t) = 0$ which is equivalent to taking $k_3 = k_4 = 0$, and it is again appropriate for most radioligands to bin $C_{NS}(t)$ and $C_F(t)$. The one-tissue compartmental model is then appropriate for regions without specific binding activity. For some tracers, however, for example the modeling of PIB in the cerebellar reference region, the best data fitting is obtained by using the 2T-4k model without binning $C_{NS}(t)$ and $C_F(t)$, \cite{21}. Assuming the latter, the DV is given by $K_1/k_2(1 + k_3/k_4)$, and $K_1/k_2(1 + k_5/k_6)$, for regions with and without specific binding activity, resp. Ignoring the notational differences between the two models, for regions with and without specific binding activity, they are both described by the same abstract mathematical 2T-4k model equations. Here, without loss of generality, we present the
2T-4k model equations for specific binding regions,

\[ \frac{dC_{F+NS}(t)}{dt} = K_1C_p(t) - (k_2 + k_3)C_{F+NS}(t) + k_4C_S(t) \]  
\[ \frac{dC_S(t)}{dt} = k_3C_{F+NS}(t) - k_4C_S(t). \]  

To obtain the equations appropriate for regions without specific binding activity, \( C_S(t) \) is replaced by \( C_{NS}(t) \) and \( k_3 \) and \( k_4 \) are interpreted as the association and dissociation parameters of regions without specific binding activity. To simplify the explanation \( C_S(t), k_3 \) and \( k_4 \) are used throughout for both regions with and without specific binding activity, with the assumption that \( C_S(t), k_3 \) and \( k_4 \) should automatically be replaced by \( C_{NS}(t), k_5 \) and \( k_6 \) respectively, when relevant.

The solution of the linear differential system (5)-(6) is given by

\[ C_{F+NS}(t) = (a_1e^{-\alpha_1t} + b_1e^{-\alpha_2t}) \otimes C_p(t) \]  
\[ C_S(t) = a_2(e^{-\alpha_1t} - e^{-\alpha_2t}) \otimes C_p(t) \]  

where \( \otimes \) represents the convolution operation,

\[ \alpha_{1,2} = (k_2 + k_3 + k_4 \mp \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4})/2, \]  
\[ a_1 = \frac{K_1(k_4 - \alpha_1)}{\alpha_2 - \alpha_1}, \quad b_1 = \frac{K_1(\alpha_2 - k_4)}{\alpha_2 - \alpha_1}, \quad \text{and} \quad a_2 = \frac{K_1k_3}{\alpha_2 - \alpha_1}. \]  

The overall concentration of radioactivity is

\[ C_T(t) = C_{F+NS}(t) + C_S(t) = ((a_1 + a_2)e^{-\alpha_1t} + (b_1 - a_2)e^{-\alpha_2t}) \otimes C_p(t). \]  

Integrating (5)-(6) and rearranging yields

\[ \int_0^t C_T(\tau)d\tau = \text{DV} \int_0^t C_p(\tau)d\tau - \frac{\frac{k_3 + k_4}{k_2k_3}C_{F+NS}(t)}{\frac{k_2 + k_3 + k_4}{k_2k_4}C_S(t)}, \]  
\[ = \text{DV} \int_0^t C_p(\tau)d\tau - \frac{k_3 + k_4}{k_2k_4}C_T(t) - \frac{1}{k_4}C_S(t). \]  

This is model (11) when \( C_S(t) \) is linearly proportional to \( C_T(t) \) for a time window within the scan duration of \( T \) minutes. The accuracy of linear methods based on (11) is thus dependent on the validity of the assumption that \( C_S(t) \) and \( C_{F+NS}(t) \) are approximately linearly proportional to \( C_T(t) \) over a time window within \([0,T]\). Logan observed that \( C_{F+NS}(t) \) and \( C_S(t) \) are roughly proportional to \( C_T(t) \), after some time point \( t^* \). If the assumption of linear proportionality breaks down for the given window, \([t^*,T]\), bias in the estimated uptake rate or DV will be introduced, as shown later in Section 4.3, due to the intrinsic model error of a GA method. Indeed, in Section 5.1 we show that, for the PIB radioligand on some regions with small \( k_4 \), there is no window within a 90 minutes scan duration where \( C_S(t) \) and \( C_T(t) \) are linearly proportional. This is despite the apparent good linearity, visually, of the Logan plot of \( \int_0^t C_T(\tau)d\tau/C_T(t) \) against \( \int_0^t C_p(\tau)d\tau/C_T(t) \). Waiting for equilibrium, which may take several hours, is impractical in terms of patient comfort, cost and measurement of radioactivities.

The limitation of the constant approximation can be analysed theoretically. Because \( \alpha_2 >> \alpha_1 > 0 \) and \( C_p(t) \) is very small for large time the convolution \( e^{-\alpha_2t} \otimes C_p(t) = \int_0^t e^{-\alpha_2(t-\tau)}C_p(\tau)d\tau \) is relatively small. We can safely assume that the ratio of \( e^{-\alpha_2t} \otimes C_p(t) \) to \( e^{-\alpha_1t} \otimes C_p(t) \) is roughly 0 for \( t > t^* \). Then \( C_S(t) \), see equation (13), is approximately proportional to \( e^{-\alpha_1t} \otimes C_p(t) \) for \( t > t^* \). In our tests with PIB, the neglected component \( a_2e^{-\alpha_2t} \otimes C_p(t) \) is less than 8% \( C_S(t) \) for \( t \geq 35 \text{ min}. \). On the other hand, this
is not the case for $C_{F+NS}(t)$, see equation (7), because $a_1$ and $b_1$ need not be of the same scale. For example, if $k_4 << k_2 + k_3$ we know $b_1/a_1 \approx (k_2 + k_3)/(2k_4)$ from (8), thus $b_1 >> a_1 > 0$. Specifically, $b_1 e^{-a_1 t} \otimes C_p(t)$ may not be small in relation to $a_1 e^{-a_1 t} \otimes C_p(t)$. Thus, it is not appropriate, as is assumed for the Logan-GA (2) and other linear methods derived from MA0, to approximate

$$\bar{s}(t) = \frac{k_3 + k_4}{k_2 k_4} \cdot \frac{C_{F+NS}(t)}{C_T(t)} + \frac{k_2 + k_3 + k_4}{k_2 k_4} \cdot \frac{C_S(t)}{C_T(t)},$$

(13)
as constant for $t \in [t^*, T]$. One may argue that if $(a_1 + a_2)/(b_1 - a_2)$ is close to 1 the term $e^{-a_2 t} \otimes C_p(t)$ in $C_T(t)$ could be ignored. Then the ratio of $C_T(t)$ to $C_S(t)$ would be close to constant after $t^*$, and the resulting estimates of the DV using Logan-GA (2) and MA1 (3) would be reasonable. While it is easy to verify that $(a_1 + a_2)/(b_1 - a_2)$ is positive and bounded above by one, this fraction need not be close to its upper bound. Indeed, for realistic test data, see Table 1, $0.05 \leq (a_1 + a_2)/(b_1 - a_2) \leq 0.65$. The simulations presented in Tables 2 and 3 validate that a small value of this fraction may cause a problem in the estimation of the DV using the linear Logan-GA and MA1 methods.

It is immediate using $C_T(t) = C_{F+NS}(t) + C_S(t)$, and positivity of both $C_{F+NS}(t)/C_T(t)$ and $C_S(t)/C_T(t)$, that $\bar{s}(t)$ is bounded above and below,

$$\frac{k_3 + k_4}{k_2 k_4} < \bar{s}(t) < \frac{k_2 + k_3 + k_4}{k_2 k_4} = \frac{k_3 + k_4}{k_2 k_4} + \frac{1}{k_4},$$

(14)
and $1/k_4$ determines the variation in $\bar{s}(t)$. If $k_4$ is small the bound is not tight and the DV estimated by Logan-GA, or a linear method derived from MA0, may not be accurate, see for example the regions of interest (ROIs) 1, 3 and 6 in the test examples reported in Table 1. We reiterate that, by the discussion above, the variation for ROI 6, within which no specific binding activity exist, is determined by $1/k_6$. This relationship between the size of $k_4$ and the bias in the Logan-GA estimate of the DV is illustrated in Figure 8 of Section 5.1 for the test data of Table 1.

2.3. Model error of Logan equation

The complete mathematical result for the model error of Logan-GA and MA0 is presented in the Appendix. Similar results, omitted here to save space, can be obtained for MA1. The main conclusion is that both Logan-GA and MA0 can lead to an over-estimation of the DV. This contrasts the standard view of these methods. We summarize in the following theorem, for which the main idea is to show that replacing (13) which occurs on the right hand side of (14) by a constant intercept $b$ introduces an error in the least squares solution for the DV which can be specifically quantified.

**Corollary 1.** Suppose Logan-GA, or respectively MA0, are used for noise-free data acquired for $n$ frames with frame time $t_i, i = 1, \cdots, n$ and $t^* = t_1$. Then, with $\bar{s}(t)$ as defined in (13), for each method the same conclusions are reached:

- The DV is over-estimated (under-estimated) if $\bar{s}(t), t \in [t_1,t_n]$, is a non-constant decreasing (increasing) function, and

- the DV is exact if $\bar{s}(t), t \in [t_1,t_n]$, is a constant function;

Let $DV_T$ be the true value of the DV, and define the variation of a function over $[t_1,t_n]$ by

$$V(x(t)) = \max_{t \in [t_1,t_n]} x(t) - \min_{t \in [t_1,t_n]} x(t).$$

(15)
Then the bias in $DV_L$ calculated by Logan-GA is bounded by
\[
|DV_L - DV_T| \leq \sum_{n-l+1}^{n}(n-l+1) \frac{n}{l}\sum_{i=1}^{l} p_i V(s(t)),
\]
where $p_i = \int_0^t C_p(\tau) d\tau / C_T(t_i)$.

This theorem is an immediate result of Lemma 3 and Corollary 3 in the Appendix for the vectors obtained from the sampling of the functions
\[
s(t) = \frac{k_3 + k_4}{k_2k_4} CF_{+NS}(t) + \frac{k_2 + k_3 + k_4}{k_2k_4} CS(t), \quad \text{and}
\]
\[
r(t) = \int_0^t C_T(\tau) d\tau, \quad \text{and} \quad r(t) = \int_0^t C_p(\tau) d\tau, \quad q(t) = C_T(t),
\]
at discrete time points $t = t_1, \ldots, t_n$. The relevant vectors are defined by $r = r/q, p = p/q, s = s/q,$ where the division corresponds to componentwise division. It is easy to check that all these vectors are positive vectors, $p, \bar{p}, r$ and $\bar{r}$ are non-constant increasing vectors and $q$ is decreasing. Thus all conditions for Lemma 3 and Corollary 3 are satisfied. Note that in the denominator of (16) the simplification $(n-l+1)\sum_{i=1}^{n}(p_i) - (\sum_{i=1}^{n} p_i)^2 = \sum_{i \neq j, i < j \leq n} (p_i - \bar{p}_j)^2$ is used. In the latter discussion we may use the variation (increasing or decreasing) of $\bar{C}_S(t)/C_T(t)$ instead of that of $\bar{s}(t)$ because
\[
\bar{s}(t) = \frac{k_3 + k_4}{k_2k_4} + \frac{1}{k_4} C_S(t)/C_T(t).
\]

It is not surprising that the properties of Logan-GA and MA0 are similar. Indeed, MA0 is none other than weighted Logan-GA with weights $C_T(t_i)$, which changes the noise structure in the variables. In contrast to the conventional under-estimation observations, it is surprising that the DV may be over-estimated. However, the over-estimation is indeed observed in the tests presented in Section 4.2 and 4.3. Inequality (16) indicates that Logan-type linear methods will work well for data for which $V(\bar{s})$ is flat. Unfortunately, $V(\bar{s})$ may become flat only for a late time interval. Thus our interest, in Section 4 is to better estimate the DV using a reasonable (practical) time window, which may include the window over which $C_S(t)/C_T(t)$ is still increasing. Our initial focus is on the modification of Logan-type methods. Then, in Section 4 we present numerical simulations using noise-free data which illustrate the difficulties with Logan-GA and MA1, and support the results of Theorem 3.

3. Methods

In the previous discussion we have seen the theoretical limitations of the Logan-GA and MA1 methods. Here we present a new model and associated algorithm which assists with reducing the bias in the estimation of the DV.

Observe that, $\alpha_2 >> \alpha_1$, implies that $C_S = a_2 e^{-\alpha_1 t} \otimes C(p(t) + \epsilon(t))$, where $\epsilon(t)$ can be ignored for $t > t^*$. Therefore, for $t > t^*$ (12) can be approximated by a new model as follows
\[
\int_0^t C_T(\tau) d\tau \approx DV \int_0^t C_p(\tau) d\tau - AC_T(t) - B e^{-\alpha_1 t} \otimes C_p(t),
\]
where $A = (k_3 + k_4)/k_2k_4$ and $B = a_2/k_4$. This suggests new algorithms should be developed for estimation of parameters DV, $A$, $B$ and $\alpha_1$. Here, a new approach, based on the basis function method (BFM) in [22], in which $\alpha_1$ is discretized, is given by the following Algorithm.
Algorithm 1. Given $C_p(t_i)$ and $C_T(t_i)$ for $i = 1, \cdots, n$ and $t^* = t_1$, the DV is estimated by performing the following steps.

1. Calculate DV and intercept $-b$, using Logan-GA.
2. Set $\alpha_1^{\min} = 0.001$ and $\alpha_1^{\max} = \min(1, 2/b)$ if $b > 0$ otherwise $\alpha_1^{\max} = 1$.
3. Form discretization $\alpha_1^{(j)}$, $j = 1 : 100$ for $\alpha_1$, with equal spacing logarithmically between $\alpha_1^{\min}$ and $\alpha_1^{\max}$.
4. For each $j$ solve the linear LS problem, i.e. cast it as a multiple linear regression problem with $\int_0^t C_T(\tau) d\tau$ as the dependent variable.

$$DV \int_0^t C_p(\tau) d\tau - AC_T(t) - B \int_0^t e^{-\alpha_1^{(j)} \tau} C_p(t - \tau) d\tau \approx \int_0^t C_T(\tau) d\tau$$

with data at $t_i$, $i = l, \cdots, n$, to give values $DV^{(j)}$, $A^{(j)}$ and $B^{(j)}$.
5. Determine $\alpha_1^{(j^*)}$ for which residual is minimum over all $j$. Set DV, $A$ and $B$ to be $DV^{(j^*)}$, $A^{(j^*)}$ and $B^{(j^*)}$, resp.

Remarks:

1. The interval for $\alpha_1$ is determined as follows: First the lower bound 0.001 for $\alpha_1$ is suitable for most tracers, but could be reduced appropriately. This lower bound is not the same as that on $\theta$ used in BFM, in which $\theta$ is required to be greater than the decay constant of the isotope, [22]. Second by point (2) of Corollary 3 in the Appendix A, $b$ should be positive and near the average value of $\bar{s}(t)$, where, by (14), $k_1 + k_3 + k_4 < \bar{s}(t) < \frac{k_2 + k_3 + k_4}{k_2 k_4}$. On the other hand, $\frac{k_2 + k_3 + k_4}{k_2 k_4} \approx \frac{1}{\alpha_1}$ if $4k_2 k_4$ is small relative to $(k_2 + k_3 + k_4)^2$. Thus, $\alpha_1$ is linked with $b$ through $\bar{s}(t)$. This is used to give the estimate of the upper bound on $\alpha_1$. Practically, it is possible that the Logan-GA may yield an intercept $b < 0$, then we set $\alpha_1^{\max} = 1$.
2. Numerically, because $\int_0^t C_p(\tau) d\tau$ is much larger than both $C_T(t)$ and $C_S(t)$ for $t > t^*$, the estimate of DV is much more robust to noise in the formulation, including both model and random noise effects, than are the estimates of $A$ and $B$. Therefore, while $A$ and $B$ may not be good estimates of $(k_3 + k_4)/(k_2 k_4)$ and $a_2/k_4$, resp. for noisy data, the estimate of DV will still be acceptable. Consequently, it is possible that Logan-GA and MA0 will produce reasonable estimates for DV, even when the model error is non negligible.
3. The algorithm can be accelerated by employing a coarse-to-fine multigrid strategy. The coarser level grid provides bounds for the fine level grid. The grid resolution can be gradually refined until the required accuracy is satisfied.

4. Experimental Results

We present a series of simulations which first validate the theoretical analysis of Section 2 for noise-free data, and then numerical experiments which contrast the performance of Algorithm 1 with Logan-GA, MA1 and nonlinear kinetic analysis (KA) algorithms for noisy data.

4.1. Simulated Noise-Free Data

We assume the radioligand binding system is well modeled by the 2T-4k compartmental model and focus the analysis on the bias in the estimated DV which can be attributed to the simplification of the 2T-4k model. For the simulation we use representative kinetic parameters for brain studies with the PIB tracer. These kinetic parameters, detailed in Table I are adopted from published clinical data, [21, 22].
The simulated regions include the posterior cingulate (PCG), cerebellum (Cere) and a combination of cortical regions (Cort). The kinetic parameters of each ROI are also associated with the subject medical condition, namely normal controls (NC) and Alzheimer’s Disease (AD) diagnosed subjects. The kinetic parameters for the first seven ROIs are from [21] while the last four are from [22]. Rate constants for ROIs 5 to 11 are directly adopted from the published literature, while those for ROIs 1 to 4 are rebuilt from information provided in [21]. The values for ROIs 1 to 4 and 8 to 11 represent average values for each group, while those for ROIs 5 and 6 are derived from one AD subject and those for ROI 7 from another AD subject.

Table 1: Rate constants for eleven ROIs, including PCG, Cere, and Cort, for AD and NC adopted from [21, 23]. For ROIs 6, 7, 10 and 11 no specific binding activity is assumed, i.e. $k_3 = k_4 = 0$, $DV = K_1/k_2(1+k_3/k_6)$; while for ROIs 1 to 5, 8 and 9 we assume that the free and nonspecific compartments rapidly reach equilibrium, i.e. $k_5 = k_6 = 0$, $DV = K_1/k_2(1+k_3/k_4)$. Coefficients $a_1, b_1$ and $a_2$ are defined in (9). The values for ROIs 1 to 4 and 8 to 11 represent average values for each group, while those for ROIs 5 and 6 are derived from one AD subject and those for ROI 7 from another AD subject.

| ROI/Group | Area | $K_1$  | $k_2$  | $k_3$  | $k_4$  | $k_5$  | $k_6$  | $DV$  |
|-----------|------|--------|--------|--------|--------|--------|--------|-------|
| 1/NC      | Cort | 0.250  | 0.152  | 0.015  | 0.0106 | 0      | 0      | 3.9722 | 0.11 |
| 2/AD      | Cort | 0.220  | 0.113  | 0.056  | 0.023  | 0      | 0      | 6.6872 | 0.65 |
| 3/NC      | PCG  | 0.250  | 0.150  | 0.015  | 0.0106 | 0      | 0      | 4.0252 | 0.11 |
| 4/AD      | PCG  | 0.220  | 0.100  | 0.050  | 0.017  | 0      | 0      | 8.6706 | 0.63 |
| 5/AD      | PCG  | 0.262  | 0.121  | 0.044  | 0.015  | 0      | 0      | 8.5168 | 0.44 |
| 6/AD      | Cere | 0.273  | 0.144  | 0      | 0      | 0.007  | 0.005  | 4.5500 | 0.05 |
| 7/AD      | Cere | 0.333  | 0.172  | 0      | 0      | 0.029  | 0.042  | 3.2728 | 0.26 |
| 8/NC      | Cort | 0.250  | 0.140  | 0.020  | 0.018  | 0      | 0      | 3.7480 | 0.18 |
| 9/AD      | Cort | 0.220  | 0.110  | 0.050  | 0.025  | 0      | 0      | 5.9841 | 0.63 |
| 10/NC     | Cere | 0.270  | 0.140  | 0      | 0      | 0.020  | 0.026  | 3.4353 | 0.20 |
| 11/AD     | Cere | 0.260  | 0.130  | 0      | 0      | 0.020  | 0.025  | 3.5810 | 0.22 |

The noise-free decay-corrected input function is adapted from the plasma measurements for a NC subject as presented in Figure 3(A) of [21]. Using the data from that figure we convert to kBq/ml under the assumption of a 100kg body mass, and obtain the functional representation for $C_p(t) = u(t)$, (kBq/ml), which is illustrated in Figure 2

$$u(t) = \begin{cases} 0 & t \in [0, 0.3] \\ 407.4933(t - 0.3) & t \in [0.3, 0.6] \\ -436.6t + 384.208 & t \in [0.6, 0.76] \\ 46.6747(t + 0.24)^{-2.2560} + 5.7173(t + 0.24)^{-0.5644} & t \geq 0.76 \end{cases} \quad (19)$$

Using this input function and the eleven data sets given in Table 1 eleven noise-free TTACS, $C_T(t)$ (kBq/ml), are generated using the 2T-4k model. The scanning protocol, consistent with that adopted in [21], has frame durations, $\Delta t_i$, measured in minutes, $4 \times 0.25, 8 \times 0.5, 9 \times 1, 2 \times 3, 8 \times 5$ and $3 \times 10$. The last eight frames, which fall in the window from 35 to 90 minutes, are chosen for the time window over which we assume that equilibrium is achieved. A scan duration of 90 minutes is common for most PIB-PET dynamic studies, [24].

4.2. Examples of over-estimation for Logan-GA and MA1

Theorem 1 predicts that the DV will be over-estimated when $\bar{s}$ decreases. This is validated for data for the simulated ROIs. The estimates of the DV, for scan durations $T = 90$ minutes with $t^* = 35$ minutes, and $T = 240$ minutes with $t^* = 100$ minutes, are reported in Table 2. The extended time window
is generated by adding 15 frames each of 10 minutes length. Indeed, the over-estimation predicted in Theorem 1 is confirmed for ROI 7, for which the decrease of $C_S(t)/C_T(t)$ and, hence $s$ after 35 minutes, is clearly illustrated in Figure 6. Moreover, $C_S(t)/C_T(t)$ is decreasing after 100 minutes for all ROIs except ROI 6, see Figure 6(b), and in all but this case the values of DV are over-estimated. We note that $s$ is nearly flat on the selected windows, $[t^*, T]$ for the cases in which the over-estimation of DV is small. These results further validate the conclusions of Theorem 1. Additionally, the use of the long scan duration of 240 minutes leads to estimates with less overall bias because the variation in $C_S(t)/C_T(t)$ is smaller over $[100\text{min.}, 240\text{min.}]$ than over the earlier window. Equivalently, as given by (16), a small variation in $s$ guarantees a small error in the estimated DV. Clearly, linear methods based on the MA0 model work well during the equilibrium phase. Unfortunately, this equilibrium may be reached too late for practical application, see for example ROI 6 in Figure 6(b), for which approximate equilibrium is not reached until 3 hours. The results with 90 minutes scan duration show that better estimates are obtained for larger $(a_1 + a_2)/(b_1 - a_2)$, which consistently supports the analysis in Section 2.2.

In these simulations the accurate data and integrals are used so as to assure that the results are not impacted by use of a low accuracy numerical quadrature but instead are focused on the effects of the model error of Logan-GA and MA1. It is interesting to note, however, that the error introduced by the numerical quadrature always lowers the estimate of the DV, see Section 5.2. Moreover, the noise from other sources may have a similar impact. This is a topic for future research.

4.3. Algorithm Performance for Noise-Free Data

We contrast the performance of Algorithm 1 with Logan-GA, MA1 and KA for noise-free data. The use of a long scan duration (up to 90 minutes) is to assure that equilibrium is achieved as needed for GA methods. For a method for which the bias due to model error is not impacted by the need for equilibrium, a shorter scan duration is preferred. For the results presented in Table 3 the DV is calculated for the noise-free case over a scan duration of just 70 minutes with $t^* = 35$ minutes. Accurate integrals are used so as to focus the conclusions on the impact of the model error.

The KA solutions were obtained using two different optimization algorithms for the solution of the highly nonlinear problem, the interior point and the Marquardt-Levenberg methods, Matlab® functions fmincon and lsqnonlin, resp. In order to provide the most fair comparison the results presented are
Table 2: The DV calculated using Logan-GA and MA1 with noise-free data and accurate integrals. DV is calculated for scan durations $T = 90$ minutes with $t^* = 35$ minutes, and $T = 240$ minutes with $t^* = 100$ minutes. The percentage bias is listed in parentheses.

| ROI ID | True DV | 35-90 min | 100-240 min |
|--------|---------|-----------|-------------|
|        | Logan-GA | MA1       | Logan-GA    | MA1       |
| 1      | 3.9722  | 3.549(-10.65%) | 3.542(-10.84%) | 3.981(0.22%) | 3.977(0.12%) |
| 2      | 6.6872  | 6.585(-1.53%)  | 6.577(-1.65%)  | 6.709(0.33%) | 6.709(0.33%) |
| 3      | 4.0252  | 3.599(-10.73%) | 3.586(-10.92%) | 4.034(0.22%) | 4.030(0.11%) |
| 4      | 8.6706  | 8.342(-3.79%)  | 8.331(-3.92%)  | 8.687(0.19%) | 8.685(0.16%) |
| 5      | 8.5168  | 8.129(-4.55%)  | 8.117(-4.69%)  | 8.536(0.23%) | 8.533(0.19%) |
| 6      | 4.5500  | 3.204(-29.58%) | 3.208(-29.50%) | 4.281(-5.91%) | 4.273(-6.10%) |
| 7      | 3.2728  | 3.300(0.82%)   | 3.298(0.76%)   | 3.286(0.41%) | 3.288(0.45%) |
| 8      | 3.7480  | 3.635(-3.01%)  | 3.625(-3.28%)  | 3.780(0.84%) | 3.779(0.84%) |
| 9      | 5.9841  | 5.910(-1.23%)  | 5.902(-1.37%)  | 6.007(0.38%) | 6.007(0.39%) |
| 10     | 3.4353  | 3.416(-0.57%)  | 3.408(-0.78%)  | 3.462(0.77%) | 3.463(0.80%) |
| 11     | 3.5810  | 3.552(-0.81%)  | 3.544(-1.04%)  | 3.608(0.75%) | 3.609(0.79%) |

for fmincon, which gave the better solutions. The KA solution is very dependent on provision of a good initial value. If the initial values of $k_3$ and $k_4$ are taken very close to their true values, the estimate of the DV may be nearly perfect. Here we use initial values for $K_1$, $k_2$, $k_3$ and $k_4$ set to [0.2, 0.1, 0.01, 0.001].

For Logan-GA and MA1, solutions were also calculated for the scan duration of $T = 90$ minutes with $t^* = 35$ minutes as illustrated in Table 2. The KA results, not given, which do not require the attainment of equilibrium were comparable for both scan durations as expected. This independence with respect to the requirement of attainment of equilibrium was also observed for Algorithm 1 except for ROI 6. In this case the neglected part in model (17) is relatively large as compared to that for the other ROIs, i.e. the ratio of $e^{-\alpha_2 t} \otimes C_p(t)$ to $e^{-\alpha_1 t} \otimes C_p(t)$ for ROI 6 is greater than that for the other ROIs. A significant reduction in the bias for ROI 6 from $-12.71%$ (70 min.) to $-7.39%$ (90 min.) was observed. It is clear, by comparing the results with those in Table 2 that Algorithm 1 for a scan duration of just 70 minutes is much more accurate for the calculation of the DV than are Logan-GA and MA1 using scan durations of 90 minutes.

Table 3: DV calculated by Logan-GA, MA1, KA and Algorithm 1 for a 70 minutes scan duration with $t^* = 35$ minutes. In each case the percentage bias is listed in parentheses.

| ROI ID | Logan-GA | MA1 | KA | Algorithm 1 |
|--------|----------|-----|----|-------------|
| 1      | 3.395(-14.54%) | 3.392(-14.61%) | 3.928(-1.12%) | 4.014(1.05%) |
| 2      | 6.511(-2.64%)  | 6.506(-2.71%)  | 6.552(-2.02%) | 6.777(1.34%) |
| 3      | 3.436(-14.65%) | 3.433(-14.71%) | 3.982(-1.08%) | 4.066(1.00%) |
| 4      | 8.163(-5.86%)  | 8.157(-5.92%)  | 8.535(-1.56%) | 8.743(0.83%) |
| 5      | 7.931(-6.88%)  | 7.925(-6.95%)  | 8.383(-1.57%) | 8.530(0.16%) |
| 6      | 3.004(-33.97%) | 3.007(-33.92%) | 4.675(2.74%)  | 3.972(-12.71%) |
| 7      | 3.293(0.63%)   | 3.292(0.58%)   | 3.188(-2.59%) | 3.277(0.12%) |
| 8      | 3.555(-5.15%)  | 3.549(-5.30%)  | 3.679(-1.84%) | 3.784(0.95%) |
| 9      | 5.847(-2.28%)  | 5.842(-2.37%)  | 5.859(-2.10%) | 6.008(0.40%) |
| 10     | 3.376(-1.73%)  | 3.371(-1.87%)  | 3.361(-2.17%) | 3.451(0.47%) |
| 11     | 3.506(-2.09%)  | 3.501(-2.24%)  | 3.505(-2.11%) | 3.585(0.10%) |

In contrasting the results with respect to only the bias in the calculation of the DV it is clear that Algorithm 1 leads to significantly more robust solutions than Logan-GA1 and MA1 for noise-free data.
On the other hand, the KA approach can lead to very good solutions, comparable and perhaps marginally better than Algorithm 1. For ROI 6, for which the KA solution is significantly better, we recall that the solution depends on the initial values of the parameters. Changing the initial $k_6$ to 0.01, the resulting bias in the DV of ROI 6 calculated by KA is increased to 31.75%. On the other hand, Algorithm 1 is not dependent on specifying initial values, and is thus more computationally robust.

### 4.4. Experimental Design for Noisy Data

While the results with noise-free data support the use of Algorithm 1, it is more critical to assess its performance for noise-contaminated simulations. The experimental evaluation for noisy data is based on the noise-free input $u(t)$ and noise-free output $C_T(t)$, one output TTAC for each of the eleven parameter sets given in Table 1. Noise contamination of the input function and these TTACs is obtained as follows.

#### 4.4.1. The Noise-Contaminated TTAC Data

For a given noise-free decay-corrected concentration TTAC, $C_T(t)$, Gaussian ($G(0, \sigma(C_T(t)))$) noise at each time point $t_i$ is modeled using the approach in [9, 10, 5]. The standard deviation in the noise at each time point $t_i$, depends on the frame time interval $\Delta t_i$ in seconds, the tracer decay constant $\lambda$ (0.034 for $^{11}C$) and a scale factor $Sc$

$$\sigma(C_T(t_i)) = Sc \sqrt{\frac{C_T(t_i)e^{\lambda t_i}}{\Delta t_i}}.$$  \hspace{1cm} (20)

The resulting coefficients of variation $CV_T$ (ratio $\sigma(C_T(t_i))$ to $C_T(t_i)$), for scale factors 1 and 2, are illustrated in Figure 3.

#### 4.4.2. The Noise-Contaminated Input Function

The noise in the input function can be attributed to two sources, system and random noise. Although the random $\gamma$-ray emission follows a Poisson distribution, we use the limiting result that a large mean Poisson distribution is approximately Gaussian to model this randomness as Gaussian. Thus both sources are modeled as Gaussian but with different variance. Consider first the following model for determining
the randomness of the $\gamma$-ray emissions. Suppose a $\mu$ ml blood sample is placed in a $\gamma$-ray well counter which has efficiency $e$ and the measured counts over $\Delta w_i$ seconds are $n(t_i)$. Then the measured decay corrected concentration (kBq/ml) is

$$C_p(t_i) = \frac{n(t_i)e^{\lambda t_i}}{1000\Delta w_i\mu e},$$

where 1000 is a normalization factor to convert the counts to “kilo” counts. Then, assuming that the mean of $C_p(t_i)$ (or its true value) is $u(t_i)$ as given in [19], the standard deviation in the measurement of $C_p(t_i)$ due to random effects is $\sigma_R(C_p(t_i)) = \sqrt{u(t_i)e^{\lambda t_i}/(1000\Delta w_i\mu e)}$. The coefficient of variation, $CV_R = \sigma_R(C_p(t_i))/u(t_i)$, which results from this random noise is shown in Figure 2. It is assumed in the experiments that each blood sample has volume $\mu = 0.5ml$, the count duration is $\Delta w_i = 100$ seconds and the well counter efficiency is $e = 50\%$. Then, denoting the coefficient of variation due to system noise by $CV_S$, the noise-contaminated input is given by

$$C_p(t_i) = u(t_i)(1 + (CV_R + CV_S)\eta_i),$$

(21)

where $\eta_i$ is selected from a standard normal distribution $(G(0, 1))$, and in the simulations we use $CV_S = 0.05$, see Figure 2.

4.5. Experimental Results for Noisy Data

Two hundred random noise realizations are generated for each input-TTAC pair, and for each noise level ($Sc = 1, 2$). The distribution volume is calculated for each experimental pair using Logan-GA, MA1, KA and Algorithm I. In each case two scan durations are considered, 70 and 90 minutes respectively, and $t^* = 35$ minutes. Unlike the noise-free case, the numerical quadrature for $\int_0^t C_p(\tau)d\tau$ uses only the samples at scan points $C_p(t_i)$.

We present histograms for the percentage relative error of the bias $100(DV_{est} - DV_T)/DV_T$ in order to provide a comprehensive contrast of the methods. Figure 4 shows the histograms for all eleven ROIs, with the range of the error for each method indicated in the legend. The figures (a)-(b) are for scan windows of 90 minutes, for noise scale factors $Sc = 1$ and $Sc = 2$ while (c)-(d) are for scan windows of 70 minutes. Figure 5 provides equivalent information for a representative cortical region ROI 3. It is clear that the distributions of the relative errors for KA and MA1 are far from normal; KA has a significant positive tail while Logan-GA has strong negative bias. MA1 has unacceptably long tails except for the case of low noise with long scan duration, i.e. $Sc = 1$ with 90 minutes scan duration. On the other hand, the histogram for Algorithm I is close to a Gaussian random distribution; the mean is near zero and the distribution is approximately symmetric. Moreover, Algorithm I performs well, and is only outperformed marginally by MA1 for the lower noise and longer time window case. On the other hand, there are some situations, particularly for MA1, in which the relative error is less than $-100\%$; in other words, the calculated DVs are negative. Such unsuccessful results occur only for the higher noise level ($Sc = 2$).

While there was only one such occurrence for the Logan-GA (70 min. with ROI 9), there were 40 such occurrences for MA1, 33 for the shorter time interval of 70 minutes (ROIs 1, 3, 4, 5, 6, 8 and 9) and 7 for the longer interval of 90 minutes, (ROIs 1 and 6). The reason for the negative DV for MA1 is discussed in Section 5.3. From the results for the higher noise $Sc = 2$ we conclude that Algorithm I using the shorter 70 minutes scan duration outperforms the other algorithms, even in comparison to their results for the longer scan duration.

Obviously Algorithm I is more expensive computationally than Logan-GA and MA1. In the simulations, the average CPU time, in seconds, per TTAC was 0.00083, 0.00057, 12.2 and 0.0036, for Logan-GA, MA1, KA and Algorithm I, respectively. The high cost of the KA results from the requirement to use a nonlinear algorithm. Because the KA requires a good initial estimate for the parameters the cost is variable for each TTAC; it is dependent on whether the supplied initial value is a good initial estimate.
Figure 4: Histograms for normalized error (in percentage), $100(DV_{est} - DV_T)/DV_T$, of the results for all eleven ROIs and four methods. The error ranges are presented in the legends.
Figure 5: Histograms for normalized error (in percentage), 100(DV_{est} - DV_T)/DV_T, of the results for ROI 3 and four methods. The error ranges are presented in the legends.
Figure 6: $C_S(t)/C_T(t)$ against time for all test ROIs except ROIs 3, 5 and 11 for the first 90 minutes (a) and 720 minutes (b). Dotted vertical lines are plotted at time $t^* = 35$ minutes (a) and $t^* = 100$ minutes (b). The curves for ROIs 3, 5 and 11 are similar to those for ROIs 1, 4 and 10 resp.

Indeed the KA results take from 8 to 25 seconds, while the costs using the other methods are virtually TTAC independent.

5. Discussion

5.1. Equilibrium Behavior and Dependence on the Size of $k_4$

The graphical analysis methods of Logan-type rely on the assumption that the ratio $C_S(t)$ to $C_T(t)$ is approximately constant within a chosen window $[t^*, T]$. This ratio is plotted against time for the simulated data for ROIs 1 to 11 in Figure 6(a) It is clear that the ratios for ROIs 1, 3 and 6 have not reached equilibrium even by 90 minutes. These are the three data sets with the largest bias reported in Section 4.2 and with smallest $k_4$ (resp. $k_0$). It is certain that equilibrium is eventually reached. These curves first increase to a peak at about 120 minutes for ROIs 1 and 3 and at about 180 minutes for ROI 6 and then decrease before reaching approximately constant values (Figure 6(b)). On the other hand, increasing the scan duration to more than two hours is not practical. Moreover, as illustrated in Figure 7, using the linearity of $\int_0^t C_T(\tau) d\tau / C_T(t)$ versus $\int_0^t C_T(\tau) d\tau / C_p(t)$ to verify whether equilibrium has been reached may be misleading. For example, it would appear that all eleven data sets have achieved equilibrium after roughly 35 minutes. The arrow in Figure 7 points to the marker corresponding to the data calculated at the middle point of the frame from 35 to 40 minutes.

We illustrate the relation between the bias in the estimate of DV calculated by Logan-GA and $k_4$ in Figure 8. As discussed in Section 2.2, a small value of $k_4$ may cause a large variation in $\bar{s}(t)$. This graph verifies that the magnitude of the bias decreases as $k_4$ increases, further verifying that large bias in DV may arise purely due to modeling assumptions in the absence of noise in the data.

5.2. The effects of quadrature error

Both Logan-GA and MA1, (2) and (3) resp., require the calculation of integrals $\int_0^t C_T(\tau) d\tau$ and $\int_0^t C_p(\tau) d\tau$. Assume the noise-free measurements $C_T(t_i)$ are derived from the integral over the $i$th frame duration. Thus we can easily recover its integral without introducing error while quadrature error for calculation of $\int_0^t C_p(\tau) d\tau$ due to using a limited number of plasma samples is unavoidable. The accuracy
Figure 7: $\int_0^t C_T(\tau) d\tau / C_T(t)$ (y-axis) against $\int_0^t C_p(\tau) d\tau / C_T(t)$ (x-axis) for all test ROIs except ROIs 3, 5 and 11 for the first 90 minutes. The last eight points correspond to the time interval 35 to 90 minutes. The curves for ROIs 3, 5 and 11 are similar to those for ROIs 1, 4 and 10 resp.. The arrow points to the first frame falling in this interval for ROI 6.

Figure 8: The bias in the Logan-GA estimation of the DV against the value of $k_4$ for the eleven ROIs, assuming noise-free data, a scan duration of 90 minutes and $t^* = 35$ minutes. The specific data pairs $(k_4, \text{bias})$ are, for ROIs 1 to 11, respectively, $(0.0106, -0.4231)$, $(0.0230, -0.1024)$, $(0.0106, -0.4318)$, $(0.0170, -0.3286)$, $(0.0150, -0.3874)$, $(0.0050, -1.3459)$, $(0.0420, 0.0267)$, $(0.0182, -0.1130)$, $(0.0251, -0.0736)$, $(0.0256, -0.0195)$, and $(0.0253, -0.0288)$. 

16
of the numerical quadrature impacts the accuracy of the parameter estimates. Note that we classify the noise effects as another source of bias in DV.

We recalculate the DV for the experiments reported in Section 4.2, but now using numerical quadrature for calculation of \( \int_0^t C_p(\tau) d\tau \) with data sampled one time point per time frame. The bias for each ROI of the estimated DV using 90 minutes scan data with \( t^* = 35 \) minutes is \(-11.83\%\), \(-2.99\%\), \(-11.91\%\), \(-4.88\%\), \(-5.64\%\), \(-30.49\%\), \(-1.22\%\), \(-4.61\%\), \(-2.81\%\), \(-2.40\%\) and \(-2.63\%\) when calculated using Logan-GA, and \(-12.02\%\), \(-3.10\%\), \(-12.10\%\), \(-5.01\%\), \(-5.77\%\), \(-30.42\%\), \(-1.28\%\), \(-4.87\%\), \(-2.93\%\), \(-2.61\%\) and \(-2.86\%\) calculated using MA1. It is interesting to note that the DV calculated for ROI 7 is no longer an over-estimate. This does not contradict the result of Theorem 1, which predicts that the DV for ROI 7 will be over-estimated due to model error, provided that the other aspects of the calculation are accurate. Now using a less accurate quadrature the negative bias due to quadrature error canceled the positive bias due to the model error. Indeed, for all eleven test cases the impact of the less accurate quadrature is to shift the bias down, i.e. it is more negative as compared to the equivalent more accurate calculations shown in Table 2.

5.3. Bias and classification between AD and NC subjects

In the eleven simulated ROIs, large under-estimation of the DV calculated by Logan-GA and MA1 is observed for ROIs 1 (NC Cort), 3 (NC PCG) and 6 (AD Cere). A lower value of the DV in the cortical regions of NCs and in the cerebellum for AD subjects will result in under-estimation of the DVR for NCs and over-estimation of the DVR for AD subjects when the cerebellum is used as the reference region for the DVR calculation. Thus, the difference between AD and NC can be artificially enhanced, and viewed as a positive outcome associated with the bias of Logan-GA and MA1. This conclusion, however, can not be generalized. It is unknown whether it is always the case that AD/NC have small/large \( k_6 \) in cerebellar regions and relatively large/small \( k_4 \) in cortical regions. Confirmation of these assertions would suggest, based on the discussion in Sections 2.2 and 5.1, that the DVR is over-estimated for AD subjects and under-estimated for healthy subjects (also see Figure 8). In addition, more subtle differences, such as the ones between mild cognitive impairment (MCI) and NC, or among NC with differential genetic risk for AD, may make the effects of bias much less predictable. Consequently, we evaluate the quantification methods based on their bias because the goal of these methods is to estimate the DV as accurately as possible.

5.4. When does MA1 fail?

As noted in Section 4.5, MA1 generates some results with negative DVs. Such results are reported as unsuccessful in Ichise’s original paper [5]. Careful study of these results shows that the negative DVs arise when \(-1/b\) has the wrong sign. For most radioligand binding studies \(1/b\) is a small positive number because \(b > (k_3 + k_4)/(k_2k_4)\), which is usually larger than 10, see Remark (1) of Algorithm 1. Thus a small error in the estimate of \(-1/b\) due to large noise in the data may change its sign. This in turn impacts the sign of the estimate of the DV.

6. Conclusions

In this article, we quantified the model error in estimating distribution volume using graphical analysis methods. We described the conditions under which the DV is either over- or under-estimated, and quantified the bias caused by model error. We validated our findings through simulations with noise-free data. To reduce the impact of model error, we added a simple nonlinear term to the fundamental linear model MA0, and presented a new algorithm for its solution. Simulations with noisy data demonstrate that the new algorithm is cost-effective and robust even for shorter scan durations. For PIB-PET studies, the new method using shorter scan data (70 minutes) outperforms, or is at least as good as, Logan-GA, MA1.
Lemma 1. (Chebyshev’s sum inequality \([25]\)) Given real numbers 
\[ a_1 \geq a_2 \geq \cdots \geq a_n \text{ and } b_1 \geq b_2 \geq \cdots \geq b_n, \]
then
\[ \frac{1}{n} \sum_{k=1}^{n} a_k b_k \geq \left( \frac{1}{n} \sum_{k=1}^{n} a_k \right) \left( \frac{1}{n} \sum_{k=1}^{n} b_k \right). \]  
(22)

Similarly, if \( a_1 \geq a_2 \geq \cdots \geq a_n \text{ and } b_1 \leq b_2 \leq \cdots \leq b_n, \) then
\[ \frac{1}{n} \sum_{k=1}^{n} a_k b_k \leq \left( \frac{1}{n} \sum_{k=1}^{n} a_k \right) \left( \frac{1}{n} \sum_{k=1}^{n} b_k \right). \]  
(23)

In the above Chebyshev’s sum inequalities the numbers are not required to be positive and the equality is true if and only if one of the two vectors, \( a \) or \( b \), is a constant vector. If \( a \) and \( b \) are positive vectors, the Chebyshev’s sum inequalities can be expressed as \( a^T b \geq \frac{1}{n}||a||_1 ||b||_1 \) and \( a^T b \leq \frac{1}{n}||a||_1 ||b||_1 \).

Lemma 2. If \( p, q \) and \( s \) are positive real vectors, of which \( p \) is an increasing vector and \( q \) is a decreasing vector, then
1. \( ||q||_2^2 p^T s - p^T q q^T s \geq 0 \) if \( s/q \) is a non-constant increasing vector. The inequality is strict if \( p \) is strictly increasing.
2. \( ||q||_2^2 p^T s - p^T q q^T s \leq 0 \) if \( s/q \) is a non-constant decreasing vector. The inequality is strict if \( p \) is strictly increasing.
3. \( ||q||_2^2 p^T s - p^T q q^T s = 0 \) if \( s/q \) is a constant vector.
4. \( ||p||_2^2 q^T s - p^T q p^T s \geq 0 \) if \( s/p \) is a non-constant decreasing vector. The inequality is strict if \( p \) is strictly increasing.
5. \( ||p||_2^2 q^T s - p^T q p^T s \leq 0 \) if \( s/p \) is a non-constant increasing vector. The inequality is strict if \( p \) is strictly increasing.
6. \( \|\mathbf{p}\|^2\mathbf{q}^T\mathbf{s} - \mathbf{p}^T\mathbf{q}\mathbf{p}^T\mathbf{s} = 0 \) if \( \mathbf{s}/\mathbf{p} \) is a constant vector.

\textbf{Proof.} We only prove the first case. The proof for the other items follows similarly. We use mathematical induction. For the lowest dimension \( n = 2 \),

\[
\|\mathbf{q}\|^2\mathbf{p}^T\mathbf{s} - \mathbf{p}^T\mathbf{q}\mathbf{p}^T\mathbf{s} = (q_1^2 + q_2^2)(p_1s_1 + p_2s_2) - (p_1q_1 + p_2q_2)(q_1s_1 + q_2s_2) \\
= q_1^2p_2s_2 + q_2^2p_1s_1 - p_1q_1q_2s_2 - p_2q_2q_1s_1 \\
= (q_1s_2 - q_2s_1)(q_1p_2 - q_2p_1) \\
= (q_1p_2 - q_2p_1)((q_1q_2)(\frac{s_2}{q_2} - \frac{s_1}{q_1}) \\
\geq 0.
\]

The last reduction follows from the monotonicity of \( \mathbf{p}, \mathbf{q} \), which implies \( q_1p_2 - q_2p_1 \geq 0 \), and the non-constant increasing assumption of \( \mathbf{s}/\mathbf{q} \), which guarantees \( \frac{s_2}{q_2} - \frac{s_1}{q_1} > 0 \). When \( \mathbf{p} \) is strictly increasing \( q_1p_2 - q_2p_1 > 0 \). Under this condition \( \|\mathbf{q}\|^2\mathbf{p}^T\mathbf{s} - \mathbf{p}^T\mathbf{q}\mathbf{p}^T\mathbf{s} > 0 \) for \( n = 2 \). Assuming the inequality \( \|\mathbf{q}\|^2\mathbf{p}^T\mathbf{s} - \mathbf{p}^T\mathbf{q}\mathbf{p}^T\mathbf{s} \geq 0 \) is true for dimension \( n = i \), i.e.

\[
\sum_{k=1}^{i} q_k^2 \sum_{k=1}^{i} p_k s_k - \sum_{k=1}^{i} p_k q_k \sum_{k=1}^{i} q_k s_k \geq 0,
\]

then for \( n = i + 1 \)

\[
\|\mathbf{q}\|^2\mathbf{p}^T\mathbf{s} - \mathbf{p}^T\mathbf{q}\mathbf{p}^T\mathbf{s} = (\sum_{k=1}^{i} q_k^2 + q_{i+1}^2)(\sum_{k=1}^{i} p_k s_k + p_{i+1}s_{i+1}) - (\sum_{k=1}^{i} p_k q_k + p_{i+1}q_{i+1})(\sum_{k=1}^{i} q_k s_k + q_{i+1}s_{i+1}) \\
= (\sum_{k=1}^{i} q_k^2 \sum_{k=1}^{i} p_k s_k - \sum_{k=1}^{i} p_k q_k \sum_{k=1}^{i} q_k s_k) \\
+ (p_{i+1}s_{i+1})\sum_{k=1}^{i} q_k^2 - q_{i+1}s_{i+1}\sum_{k=1}^{i} p_k q_k + (q_{i+1}^2 \sum_{k=1}^{i} p_k s_k - p_{i+1}q_{i+1}\sum_{k=1}^{i} q_k s_k) \\
\geq 0 + s_{i+1}\sum_{k=1}^{i} q_k (q_k p_{i+1} - p_k q_{i+1}) + q_{i+1}\sum_{k=1}^{i} s_k (q_{i+1} p_k - p_{i+1} q_k) \\
= \sum_{k=1}^{i} (q_k p_{i+1} - p_k q_{i+1})(q_k s_{i+1} - q_{i+1} s_k) \\
= \sum_{k=1}^{i} ((q_k p_{i+1} - p_k q_{i+1})(q_k q_{i+1})) \left( \frac{s_{i+1}}{q_{i+1}} - \frac{s_k}{q_k} \right) \\
\geq 0.
\]

The last reduction is based on the monotonicity of \( \mathbf{p}, \mathbf{q} \) and \( \mathbf{s}/\mathbf{q} \). When \( \mathbf{p} \) is strictly increasing \( q_k p_{i+1} - p_k q_{i+1} > 0 \) \( \text{for all} \ k \leq i \) the inequality will be strict because at least one of the terms \( \frac{s_{i+1}}{q_{i+1}} - \frac{s_k}{q_k} \), \( k = 1, \cdots, i \), is positive based on the monotonicity condition. The result thus follows by induction for all integers \( n \geq 2 \).

The following corollary now follows immediately by observing that \( \mathbf{s}/\mathbf{q} \) increases when \( \mathbf{s} \) increases and \( \mathbf{s}/\mathbf{p} \) decreases when \( \mathbf{s} \) decreases.
Corollary 2. If \( p, q \) and \( s \) are positive real vectors, of which \( p \) is a strictly increasing vector and \( q \) is a decreasing vector, then

1. \( \|p\|_2^2q^Ts - p^Tqp^Ts > 0 \) if \( s \) is a decreasing vector.
2. \( \|q\|_2^2p^Ts - p^Tqq^Ts > 0 \) if \( s \) is an increasing vector.

Lemma 3. If \( p, q, r \) and \( s \) are positive real vectors, of which \( p \) is strictly increasing, \( q \) is decreasing, and \( p, r, s \) and \( x^* \) satisfy \( px^* - s = r \); and \([\hat{x}, \hat{b}] = \text{argmin} \|px - bq - r\|_2^2\); then

1. the estimated solution \( \hat{x} \) and exact solution \( x^* \) are related by
   - \( \hat{x} > x^* \) if \( s/q \) is a non-constant decreasing vector,
   - \( \hat{x} < x^* \) if \( s/q \) is a non-constant increasing vector,
   - \( \hat{x} = x^* \) if \( s/q \) is a constant vector;
2. the following inequality is true without any monotonicity assumptions:
   \[
   |\hat{x} - x^*| \leq \frac{p^Tq\|q\|_2^2}{\|p\|_2^2\|q\|_2^2 - (p^Tq)^2} V(s). \tag{24}
   \]
3. the sign of the intercept \( \hat{b} \) is determined as follows:
   - \( \hat{b} > 0 \) if \( s/p \) is a non-constant decreasing vector,
   - \( \hat{b} < 0 \) if \( s/p \) is a non-constant increasing vector,
   - \( \hat{b} = 0 \) if \( s/p \) is a constant vector;
4. given \( x = x^* \), the LS solution of \( px - bq \approx r \) for \( b = q^Ts/\|q\|_2^2 \);
5. given \( b = q^Ts/\|q\|_2^2 \), the LS solution of \( px - bq \approx r \) for \( x \) and the true solution \( x^* \) have the same relationship as stated in the first conclusion of this theorem.

Proof. It is easy to verify that the LS solution of \( px - bq \approx r \) is

\[
\hat{x} = \frac{\|q\|_2^2p^Tr - p^Tqq^Tr}{\|p\|_2^2\|q\|_2^2 - (p^Tq)^2}, \quad \hat{b} = -\frac{\|p\|_2^2q^Tr + p^Tqq^Tr}{\|p\|_2^2\|q\|_2^2 - (p^Tq)^2}.
\]

The proof then follows as outlined below:

1. Replace \( r \) in the expression for \( \hat{x} \) with \( px^* - s \). Then
   \[
   \hat{x} = \frac{\|q\|_2^2p^T(px^* - s) - p^Tqq^T(px^* - s)}{\|p\|_2^2\|q\|_2^2 - (p^Tq)^2} = x^* + \frac{p^Tqq^Ts - \|q\|_2^2p^Ts}{\|p\|_2^2\|q\|_2^2 - (p^Tq)^2}, \tag{25}
   \]
   and the results immediately follow from Lemma 2 \( 1 \)- \( 3 \) and the fact \( \|p\|_2\|q\|_2 > p^Tq \) when \( p \) is not linear proportional to \( q \).
2. Because
   \[
   p^Tqq^Ts - \|q\|_2^2p^Ts = p^Tq(q \circ q)^Ts - \|q\|_2^2(p \circ q)^Ts \leq p^Tq\|q\|_2^2\max_i(s_i) - \|q\|_2^2p^Tq \cdot \min_i(s_i) = p^Tq\|q\|_2^2(\max_i(s_i) - \min_i(s_i)),
   \]

22
and similarly
\[ \mathbf{p}^T \mathbf{q} \mathbf{q}^T \mathbf{s} - \|\mathbf{q}\|_2^2 \mathbf{p}^T \mathbf{s} \geq \mathbf{p}^T \mathbf{q} \|\mathbf{q}\|_2^2 (\min_i (\bar{s}_i) - \max_i (\bar{s}_i)). \]

We have
\[ |\mathbf{p}^T \mathbf{q} \mathbf{q}^T \mathbf{s} - \|\mathbf{q}\|_2^2 \mathbf{p}^T \mathbf{s}| \leq \mathbf{p}^T \mathbf{q} \|\mathbf{q}\|_2^2 (\min_i (\bar{s}_i) - \max_i (\bar{s}_i)). \]

Using the fact \( \|\mathbf{p}\|_2^2 \|\mathbf{q}\|_2^2 - (\mathbf{p}^T \mathbf{q})^2 > 0 \) and (25), we conclude the inequality is true.

3. Again we replace \( \mathbf{r} \) with \( \mathbf{p}x^* - \mathbf{s} \), then the expression for \( \hat{\mathbf{b}} \) becomes
\[
\hat{\mathbf{b}} = \frac{-\|\mathbf{p}\|_2^2 \mathbf{q}^T (\mathbf{p}x^* - \mathbf{s}) + \mathbf{p}^T \mathbf{q} \mathbf{p}^T (\mathbf{p}x^* - \mathbf{s})}{\|\mathbf{p}\|_2^2 \|\mathbf{q}\|_2^2 - (\mathbf{p}^T \mathbf{q})^2} = \frac{\|\mathbf{p}\|_2^2 \mathbf{q}^T \mathbf{s} - \mathbf{p}^T \mathbf{q} \mathbf{p}^T \mathbf{s}}{\|\mathbf{p}\|_2^2 \|\mathbf{q}\|_2^2 - (\mathbf{p}^T \mathbf{q})^2}.
\]

The results immediately follow from Lemma 2 and the fact \( \|\mathbf{p}\|_2 \|\mathbf{q}\|_2 > \mathbf{p}^T \mathbf{q} \) when \( \mathbf{p} \) and \( \mathbf{q} \) do not have the same direction.

4. This result is easily verified.

5. Given \( \hat{\mathbf{b}} = \mathbf{q}^T \mathbf{s}/\|\mathbf{q}\|_2^2 \), the LS solution of \( \mathbf{p}x - \hat{\mathbf{b}} \mathbf{q} \approx \mathbf{r} \) for \( x \) is
\[
\hat{x} = \frac{1}{\|\mathbf{p}\|_2^2} \mathbf{p}^T (\mathbf{q}\hat{\mathbf{b}} + \mathbf{r}) = \frac{1}{\|\mathbf{p}\|_2^2} (\mathbf{p}^T \mathbf{q} \|\mathbf{q}\|_2^2 \mathbf{s} + \mathbf{p}^T (\mathbf{p}x^* - \mathbf{s})) = x^* + \frac{\mathbf{p}^T \mathbf{q} \|\mathbf{q}\|_2^2 \mathbf{s} - \|\mathbf{q}\|_2^2 \mathbf{p}^T \mathbf{s}}{\|\mathbf{p}\|_2^2 \|\mathbf{q}\|_2^2}.
\]

The results now follow from Lemma 2.

\( \square \)

We now transform the exact equation to \( \mathbf{p}/\mathbf{q}x^* - \mathbf{s}/\mathbf{q} = \mathbf{r}/\mathbf{q} \) and rewrite the results using vectors \( \hat{\mathbf{p}} = \mathbf{p}/\mathbf{q}, \hat{\mathbf{s}} = \mathbf{s}/\mathbf{q} \) and \( \hat{\mathbf{r}} = \mathbf{r}/\mathbf{q} \). Correspondingly, we find the LS solution of \( \hat{\mathbf{p}}x - \mathbf{e}\hat{\mathbf{b}} \approx \hat{\mathbf{r}} \) for \( \mathbf{e} = (1, 1, \ldots, 1)^T \).

**Corollary 3.** If \( \hat{\mathbf{p}}, \hat{\mathbf{r}} \) and \( \hat{\mathbf{s}} \) are positive, of which \( \hat{\mathbf{p}} \) is strictly increasing, \( \hat{\mathbf{p}}, \hat{\mathbf{r}}, \hat{\mathbf{s}} \) and \( x^* \) satisfy \( \hat{\mathbf{p}}x^* - \hat{\mathbf{s}} = \hat{\mathbf{r}} \); and \( [\hat{x}, \hat{b}] = \text{argmin} \|\hat{\mathbf{p}}x - \mathbf{e}\hat{\mathbf{b}} - \hat{\mathbf{r}}\|_2^2 \), then

1. the estimated solution \( \hat{x} \) and the exact solution \( x^* \) are related by
   - \( \hat{x} > x^* \) if \( \hat{\mathbf{s}} \) is a non-constant decreasing vector,
   - \( \hat{x} < x^* \) if \( \hat{\mathbf{s}} \) is a non-constant increasing vector,
   - \( \hat{x} = x^* \) if \( \hat{\mathbf{s}} \) is a constant vector;

Moreover, the following inequality is true without any monotonicity assumptions.
\[
|\hat{x} - x^*| \leq \frac{n\|\hat{\mathbf{p}}\|_1}{n\|\hat{\mathbf{p}}\|_2 - \|\hat{\mathbf{p}}\|_1} V(\hat{\mathbf{s}}). \tag{27}
\]

2. The sign of the intercept \( \hat{\mathbf{b}} \) is determined as follows:
   - \( \hat{\mathbf{b}} > 0 \) if \( \hat{\mathbf{s}}/\hat{\mathbf{p}} \) is a non-constant decreasing vector,
   - \( \hat{\mathbf{b}} < 0 \) if \( \hat{\mathbf{s}}/\hat{\mathbf{p}} \) is a non-constant increasing vector,
\[ \hat{b} = 0 \text{ if } \bar{s}/\bar{p} \text{ is a constant vector.} \]

In addition,

\[ \hat{b} > \sum_{i=1}^{n} \bar{s}_i/n \text{ if } \bar{s} \text{ is a non-constant decreasing vector,} \]

\[ \hat{b} < \sum_{i=1}^{n} \bar{s}_i/n \text{ if } \bar{s} \text{ is a non-constant increasing vector,} \]

\[ \hat{b} = \sum_{i=1}^{n} \bar{s}_i/n \text{ if } \bar{s} \text{ is a constant vector;} \]

3. **Given** \( x = x^* \), the LS solution of \( \bar{p}x - be \approx \bar{r} \) for \( b \) is \( b = \sum_{i=1}^{n} \bar{s}_i/n; \)

4. **Given** \( b = \sum_{i=1}^{n} \bar{s}_i/n \), the LS solution of \( \bar{p}x - be \approx \bar{r} \) for \( x \) and the true solution \( x^* \) are related as stated in the first conclusion of this theorem.

**Proof.** Most results are a direct Corollary of Lemma 3 by setting \( q = e \). We only prove the new results (1) and (2).

1. We just need to prove the bounds for \( |\hat{x} - x^*| \). Setting \( q = e \) in (25) we have

\[
\hat{x} = x^* + \frac{\|\bar{p}\|_1 \sum \bar{s}_i - n\bar{p}^T\bar{s}}{n\|\bar{p}\|_2^2 - \|\bar{p}\|_1^2}.
\]  

Because

\[
\|\bar{p}\|_1 \sum \bar{s}_i - n\bar{p}^T\bar{s} \leq n \cdot \max_i(\bar{s}_i)\|\bar{p}\|_1 - n \cdot \min_i(\bar{s}_i)\|\bar{p}\|_1 = n\|\bar{p}\|_1(\max_i(\bar{s}_i) - \min_i(\bar{s}_i)),
\]

\[
\|\bar{p}\|_1 \sum \bar{s}_i - n\bar{p}^T\bar{s} \geq n \cdot \min_i(\bar{s}_i)\|\bar{p}\|_1 - n \cdot \max_i(\bar{s}_i)\|\bar{p}\|_1 = n\|\bar{p}\|_1(\min_i(\bar{s}_i) - \max_i(\bar{s}_i)),
\]

and \( n\|\bar{p}\|_2^2 - \|\bar{p}\|_1^2 > 0 \) we obtain

\[
|\hat{x} - x^*| = \frac{\|\bar{p}\|_1 \sum \bar{s}_i - n\bar{p}^T\bar{s}}{n\|\bar{p}\|_2^2 - \|\bar{p}\|_1^2} \leq \frac{n\|\bar{p}\|_1(\max_i(\bar{s}_i) - \min_i(\bar{s}_i))}{n\|\bar{p}\|_2^2 - \|\bar{p}\|_1^2} = \frac{n\|\bar{p}\|_1}{n\|\bar{p}\|_2^2 - \|\bar{p}\|_1^2} V(\bar{s}).
\]

2. Setting \( q = e \) in (26) we have

\[
\hat{b} = \frac{\|\bar{p}\|_2^2\|\bar{s}\|_1 - \|\bar{p}\|_1\bar{p}^T\bar{s}}{n\|\bar{p}\|_2^2 - \|\bar{p}\|_1^2}.
\]
The results on the sign follow from Lemma 3. For the remaining three inequalities, we only prove the case for which \( \bar{s} \) is decreasing. Proofs of the other two are similar. Setting \( q = e \) in (26) we have

\[
\hat{b} = \frac{||P||_2^2||s||_1 - ||P||_1P^Ts}{n||P||_2^2 - ||P||_1^2}
\]

\[
> \frac{||P||_2^2||s||_1 - ||P||_1^2}{n||P||_2^2 - ||P||_1^2}
\]

\[
= \frac{||s||_1}{n} = \frac{\sum_{i=1}^{n} \bar{s}_i}{n}.
\]

9. Appendix B: component-wise perturbation analysis for LS solution of (18)

In Remark 2, we claimed that “the estimate of DV is much more robust to noise in the formulation than are the estimates of \( A \) and \( B \) because \( \int_0^t C_p(\tau)d\tau \) is much larger than both \( C_T(t) \) and \( C_S(t) \) for \( t > t^* \)”. Here we present a theoretical explanation, which is helpful for algorithm design in quantification.

Instead of considering a general linear equation, which is out of the range of this paper, we assume a system of equations \( Ax = y \) with only two independent variables \( x = [x_1, x_2]^T \). The two columns of the system matrix \( A \) are denoted by \( a_1 \) and \( a_2 \), i.e. \( A = [a_1, a_2] \).

**Theorem 1.** Suppose the linear system \( Ax \approx y + \epsilon \), for \( A = [a_1, a_2] \), has the exact solution \( x = [x_1^*, x_2^*] \), the uncorrelated noise vector \( \epsilon \) obeys a multi-variable Gaussian distribution with zero means and common variance \( \sigma^2 \) and that \( ||a_1|| >> ||a_2|| \). Then least squares solution \( \hat{x} = [\hat{x}_1, \hat{x}_2]^T \) has the following statistical properties

1. \( E(\hat{x}_1) = x_1^* \) and \( E(\hat{x}_2) = x_2^* \), and
2. \( \text{Var}(\hat{x}_1) << \text{Var}(\hat{x}_2) \).

**Proof.** We assume matrix \( A \) has the following singular value decomposition

\[
A = [a_1, a_2] = USV^T = U \begin{pmatrix} s_1 & 0 \\ 0 & s_2 \\ \vdots & \vdots \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \cos \theta & \sin \theta \\ -\sin \theta & \cos \theta \end{pmatrix},
\]

in which \( s_1 \geq s_2 \). Then

\[
\hat{x} = VS^T(U^T(y + \epsilon) = x^* + VS^T(U^T \epsilon)
\]

where

\[
S^T = \begin{pmatrix} 1/s_1 & 0 & \cdots & 0 \\ 0 & 1/s_2 & \cdots & 0 \end{pmatrix}.
\]

Because \( U \) is an unitary matrix and \( ||a_1|| >> ||a_2|| \) we immediately derive the following inequality from equation (29):

\[
s_1^2 \cos^2 \theta + s_2^2 \sin^2 \theta >> s_1^2 \sin^2 \theta + s_2^2 \cos^2 \theta.
\]
This inequality is equivalent to \((s_1^2 - s_2^2) \cos^2 \theta + s_2^2 > \left(s_1^2 - s_2^2\right) \sin^2 \theta + s_2^2\), which implies \(\cos^2 \theta >> \sin^2 \theta\), i.e. \(\cos^2 \theta \approx 1\) and \(\sin^2 \theta \approx 0\), and \(s_1^2 >> s_2^2\). If we denote the two rows of matrix \(VS^\dagger\) by \(q_1\) and \(q_2\) then

\[
\|q_1\|^2 = \frac{\sin^2 \theta/s_1^2 + \cos^2 \theta/s_2^2}{1/s_1^2 + \cos^2 \theta(1/s_2^2 - 1/s_1^2)},
\]
\[
\|q_2\|^2 = \frac{\cos^2 \theta/s_1^2 + \sin^2 \theta/s_2^2}{1/s_1^2 + \sin^2 \theta(1/s_2^2 - 1/s_1^2)}.
\]

Because \(\cos^2 \theta >> \sin^2 \theta\) and \(1/s_2^2 >> 1/s_1^2\) we conclude \(\|q_2\|^2 >> \|q_1\|^2\). If we let \(p_1\) and \(p_2\) be the two rows of matrix \(VS^\dagger U^T\) then \(\|p_1\| = \|q_1\|\) and \(\|p_2\| = \|q_2\|\) because \(U\) is unitary. Thus \(\|p_2\|^2 >> \|p_1\|^2\).

Let

\[d = \hat{x} - x^* = VS^\dagger U^T \epsilon.\]

It is clear \(E(d_1) = 0\) and \(E(d_2) = 0\) because the means of \(\epsilon\) are zero, and \(\operatorname{Var}(d_1) = \sum_i p_{1i}^2 \sigma^2 = \|p_1\|^2 \sigma^2\) and \(\operatorname{Var}(d_2) = \sum_i p_{2i}^2 \sigma^2 = \|p_2\|^2 \sigma^2\) resp.. Therefore \(\operatorname{Var}(\hat{d}_1) << \operatorname{Var}(\hat{d}_2)\). Because \(d = \hat{x} - x^*\) we conclude \(E(\hat{x}) = x^*\) and \(\operatorname{Var}(\hat{x}_1) << \operatorname{Var}(\hat{x}_2)\).

This result is illustrated by the following simple example:

\[
\begin{pmatrix}
4 & 1 \\
8 & 1 \\
10 & 1
\end{pmatrix}
\begin{pmatrix}
x_1 \\
x_2
\end{pmatrix}
= 
\begin{pmatrix}
5 \\
9 \\
11
\end{pmatrix} + 
\begin{pmatrix}
\epsilon_1 \\
\epsilon_2 \\
\epsilon_3
\end{pmatrix}
\]

The first column is much larger than the second column. If we add 1% noise to the right hand side, i.e. \(\epsilon_1 \sim N(0, 0.05), \epsilon_2 \sim N(0, 0.09)\) and \(\epsilon_3 \sim N(0, 0.115)\), and perform simulation with 1000 realizations the distribution of the resulted \(x_1\) and \(x_2\) are illustrated in Figure 9. These results are consistent with the conclusions in Theorem 1.
10. Appendix C: derivation for equation (12)

Integrating (5) and (6) from 0 to \( t \) we obtain

\[
C_{F+NS}(t) = K_1 \int_0^t C_F(\tau)d\tau - (k_2 + k_3) \int_0^t C_{F+NS}(\tau)d\tau + k_4 \int_0^t C_S(\tau)d\tau, \tag{30}
\]

\[
C_S(t) = k_3 \int_0^t C_{F+NS}(\tau)d\tau - k_4 \int_0^t C_S(\tau)d\tau, \tag{31}
\]

\[
= k_3 \int_0^t C_{F+NS}(\tau)d\tau - k_4 \int_0^t (C_T(\tau) - C_{F+NS}(\tau))d\tau,
\]

\[
= -k_4 \int_0^t C_T(\tau)d\tau + (k_3 + k_4) \int_0^t C_{F+NS}(\tau)d\tau. \tag{32}
\]

Taking the sum of equations (30) and (31) yields:

\[
C_T(t) = K_1 \int_0^t C_F(\tau)d\tau - k_2 \int_0^t C_{F+NS}(\tau)d\tau, \tag{33}
\]

and canceling \( \int_0^t C_{F+NS}(\tau)d\tau \) from (32) using (33) gives:

\[
C_S(t) = -k_4 \int_0^t C_T(\tau)d\tau + \frac{k_3 + k_4}{k_2} \left( K_1 \int_0^t C_F(\tau)d\tau - C_T(t) \right).
\]

This can be transformed to (12) immediately by using \( DV = \frac{k_3}{k_2}(1 + \frac{k_3}{k_4}) \).

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