

# Model Error Correction for Linear Methods in PET Neuroreceptor Measurements

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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 for neuroreceptor studies, 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

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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  $\beta$  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.

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## 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, Patlak et al. (1983); Patlak and Blasberg (1985), and extended for measuring tracer distribution (accumulation) in reversible systems by Logan, Logan et al. (1990). 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.

The well-known bias, particularly for reversible kinetics, in parameters estimated by GA is commonly attributed to noise in the data, Slifstein and Laruelle (2000); Ichise et al. (2002); Logan (2003), 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), Ichise et al. (2002), and a second multi-linear approach (MA2) which is based on extension of Blomqvist's method, Blomqvist (1984), to reversible systems, Ichise et al. (2002), (ii) preprocessing using the method of generalized linear least squares (GLLS), Feng and Huang (1996), yielding a hybrid GLLS-GA method, Logan et al. (2001), (iii) use of the method of perpendicular least squares, Varga and Szabo (2002), also known as total least squares (TLS), Golub and Loan (1980), (iv) likelihood estimation, Ogden (2003), (v) Tikhonov regularization Buchert et al. (2003), (vi) principal component analysis, Joshi et al. (2008), and (vii) reformulating the method of Logan so as to reduce the noise in the denominator, Zhou et al. (2008). 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]), Mathis et al. (2003), 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, Logan et al. (1990):

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

Here  $C_T(t)$  is the measured *tissue time activity curve* (TTAC),  $C_p(t)$  is the *input function*, and DV represents the *distribution volume*. This model, which we denote by MA0 to distinguish it from MA1 and MA2 introduced in Ichise et al. (2002), 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,

$$\text{Logan - GA : } \frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} \approx DV \frac{\int_0^t C_P(\tau)d\tau}{C_T(t)} - b, \quad (2)$$

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 (1) is the so-called MA1,

$$\text{MA1 : } C_T(t) \approx \frac{DV}{b} \int_0^t C_P(\tau)d\tau - \frac{1}{b} \int_0^t C_T(\tau)d\tau, \quad (3)$$

for which the DV can again be obtained using LS Ichise et al. (2002). Recently another formulation, obtained by division in (1) by  $C_p(t)$  instead of  $C_T(t)$ , has been developed by Zhou *et al*, Zhou et al. (2008). But, as noted by Varga *et al* in Varga and Szabo (2002) 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  $[^{18}\text{F}]\text{FCWAY}$  and  $[^{11}\text{C}]\text{MDL 100,907}$ , Ichise et al. (2002), that MA1 (3) performs better than other linear methods, including Logan-GA (2), TLS and MA2 Blomqvist (1984); Ichise et al. (2002), none of these techniques explicitly deals with the inherent error due to the assumption of model MA0 (1). 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 radioligand-neuroreceptor kinetics of a given brain region or a voxel can be illustrated as follows, Frost

et al. (1989); Slifstein and Laruelle (2001):

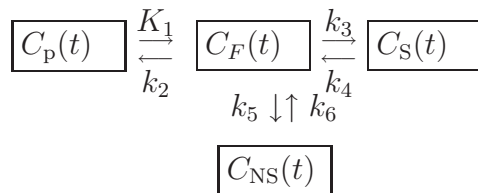


Figure 1: Three-tissue compartmental model of radioligand-neuroreceptor dynamics.

Here  $C_p(t)$  (kBq/ml) is the input function, i.e. the unmetabolized radio-tracer 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),  $i = 2, \dots, 6$ , are rate constants. The DV is related to the rate constants as follows Gunn et al. (2001),

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

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, Slifstein and Laruelle (2001). Specifically, without the inclusion of additional prior knowledge, the rate constants may be unidentifiable, Godfrey (1983). 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  $C_1(t) = C_F + C_{NS}$ . This is equivalent to taking  $k_5 = k_6 = 0$ , and hence  $C_{NS}(t) = 0$ . On the other hand, for nonspecific binding regions 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 nonspecific binding regions. 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  $C_{\text{NS}}(t)$  and  $C_{\text{F}}(t)$ , Price et al. (2005). 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 specific and non-specific binding regions, resp. Ignoring the notational differences between the two models, for specific and non-specific binding regions, 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,

$$\frac{dC_1(t)}{dt} = K_1C_p(t) - (k_2 + k_3)C_1(t) + k_4C_S(t) \quad (5)$$

$$\frac{dC_S(t)}{dt} = k_3C_1(t) - k_4C_S(t). \quad (6)$$

To obtain the equations appropriate for nonspecific binding regions,  $C_S(t)$  is replaced by  $C_{\text{NS}}(t)$  and  $k_3$  and  $k_4$  are interpreted as the association and dissociation parameters of nonspecific binding regions. To simplify the explanation  $C_S(t)$ ,  $k_3$  and  $k_4$  are used throughout for both specific and nonspecific binding regions, with the assumption that  $C_S(t)$ ,  $k_3$  and  $k_4$  should automatically be replaced by  $C_{\text{NS}}(t)$ ,  $k_5$  and  $k_6$  respectively, when relevant.

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

$$C_1(t) = (a_1e^{-\alpha_1 t} + b_1e^{-\alpha_2 t}) \otimes C_p(t) \quad (7)$$

$$C_S(t) = a_2(e^{-\alpha_1 t} - e^{-\alpha_2 t}) \otimes C_p(t) \quad (8)$$

where  $\otimes$  represents the convolution operation,

$$\begin{aligned}\alpha_{1,2} &= (k_2 + k_3 + k_4 \mp \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4})/2, \quad \text{and} \\ a_1 &= \frac{K_1(k_4 - \alpha_1)}{\alpha_2 - \alpha_1}, \quad b_1 = \frac{K_1(\alpha_2 - k_4)}{\alpha_2 - \alpha_1}, \quad \text{and} \quad a_2 = \frac{K_1k_3}{\alpha_2 - \alpha_1}.\end{aligned}\quad (9)$$

The overall concentration of radioactivity is

$$C_T(t) = C_1(t) + C_S(t) = ((a_1 + a_2)e^{-\alpha_1 t} + (b_1 - a_2)e^{-\alpha_2 t}) \otimes C_p(t). \quad (10)$$

Integrating (5)-(6) and rearranging yields

$$\int_0^t C_T(\tau) d\tau = DV \int_0^t C_p(\tau) d\tau - \frac{k_3 + k_4}{k_2 k_4} C_1(t) - \frac{k_2 + k_3 + k_4}{k_2 k_4} C_S(t) \quad (11)$$

$$= DV \int_0^t C_p(\tau) d\tau - \frac{k_3 + k_4}{k_2 k_4} C_T(t) - \frac{1}{k_4} C_S(t). \quad (12)$$

This is model (1) 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 (1) is thus dependent on the validity of the assumption that  $C_S(t)$  and  $C_1(t)$  are approximately linearly proportional to  $C_T(t)$  over a time window within  $[0, T]$ . For the estimation of the tracer uptake rate in irreversible systems, Patlak assumed that both  $C_1(t)$  and  $C_S(t)$  are almost proportional to  $C_p(t)$  after some time  $t'$ , Patlak et al. (1983). On the other hand, Logan observed that  $C_1(t)$  and  $C_S(t)$  are roughly proportional to  $C_T(t)$ , after some time point  $t^* < t'$  when estimating the  $DV$  of reversible systems, Logan et al. (1990). If the assumption of linear proportionality breaks down for the given window,  $[t', T]$  for Patlak and  $[t^*, T]$  for Logan-GA, 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  $\alpha_2 \gg \alpha_1 > 0$  and  $C_p(t)$  is very small for large time we can safely assume that the ratio of  $e^{-\alpha_2 t} \otimes C_p(t)$  to  $e^{-\alpha_1 t} \otimes C_p(t)$  is roughly 0 for  $t > t^*$ . Then  $C_S(t)$  is approximately proportional to  $e^{-\alpha_1 t} \otimes C_p(t)$  for  $t > t^*$ . In our tests with PIB, the neglected component  $a_2 e^{-\alpha_2 t} \otimes C_p(t)$  is less than 8%  $C_S(t)$  for  $t \geq 35$ . On the other hand, this is not the case for  $C_1(t)$  because  $a_1$  and  $b_1$  need not be of the same scale. For example, if  $k_4 \ll k_2 + k_3$ , which is the case for FDG and PIB, we know  $b_1 \gg a_1 > 0$ . Specifically,  $b_1 e^{-\alpha_2 t} \otimes C_p(t)$  may not be small in relation to  $a_1 e^{-\alpha_1 t} \otimes C_p(t)$ . Thus, it is not appropriate, as is assumed for the Logan-GA (2) and other linear methods derived from MA0, to approximate

$$\bar{s}(t) = \frac{k_3 + k_4}{k_2 k_4} \cdot \frac{C_1(t)}{C_T(t)} + \frac{k_2 + k_3 + k_4}{k_2 k_4} \cdot \frac{C_S(t)}{C_T(t)}, \quad (13)$$

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  $e^{-\alpha_2 t} \otimes C_p(t)$  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,  $0.05 \leq (a_1 + a_2)/(b_1 - a_2) \leq 0.65$ , and 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  $C_T(t) = C_1(t) + C_S(t)$ , and positivity of both  $C_1(t)/C_T(t)$  and  $C_S(t)/C_T(t)$ , that  $\bar{s}(t)$  is bounded above and below,

$$\frac{k_3 + k_4}{k_2 k_4} < \bar{s}(t) < \frac{k_2 + k_3 + k_4}{k_2 k_4} = \frac{k_3 + k_4}{k_2 k_4} + \frac{1}{k_4}, \quad (14)$$

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 non-specific binding region ROI **6** is determined by  $1/k_6$ .

Noting now that (6) implies

$$C_S = k_3 e^{-k_4 t} \otimes C_1(t),$$

it is apparent that the ratio  $C_S(t)$  to  $C_1(t)$  is not constant in finite time when  $k_4$  is very small. On the other hand, when  $k_4$  is large,  $e^{-k_4 t}$  behaves like an impulse function which guarantees that  $C_S(t)$  is proportional to  $C_1(t)$  after a very short time interval. 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 (11) by a constant intercept  $b$  introduces an error in the least squares solution for the DV which can be specifically quantified.

**Theorem 1.** *Suppose Logan-GA, or respectively MA0, are used for data acquired for  $n$  frames with  $t^* = t_p$ . Then, with  $\bar{\mathbf{s}}(t)$  as defined in (13), for each method the same conclusions are reached:*

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

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

$$V(\mathbf{x}(t)) = \left| \max_{t \in [t_p, t_n]} \mathbf{x}(t) - \min_{t \in [t_p, t_n]} \mathbf{x}(t) \right|. \quad (15)$$

Then the bias in  $DV_L$  calculated by Logan-GA is bounded by

$$|DV_L - DV_T| \leq \frac{(n-p+1) \sum_{i=p}^n \bar{\mathbf{p}}_i}{\sum_{i \neq j, p \leq i, j \leq n} (\bar{\mathbf{p}}_i - \bar{\mathbf{p}}_j)^2} V(\bar{\mathbf{s}}(t)), \quad (16)$$

where  $\bar{\mathbf{p}}_i = \int_0^{t_i} C_p(\tau) d\tau / C_T(t_i)$ .

This theorem is an immediate result of Lemma 1 and Corollary 1 in the *Appendix* for the vectors obtained from the sampling of the functions

$$\mathbf{s}(t) = \frac{k_3 + k_4}{k_2 k_4} C_1(t) + \frac{k_2 + k_3 + k_4}{k_2 k_4} C_S(t), \text{ and}$$

$$\mathbf{r}(t) = \int_0^t C_T(\tau) d\tau, \quad \mathbf{p}(t) = \int_0^t C_p(\tau) d\tau, \quad \mathbf{q}(t) = C_T(t),$$

at discrete time points  $t = t_p, \dots, t_n$ . The relevant vectors are defined by  $\bar{\mathbf{r}} = \mathbf{r}/\mathbf{q}$ ,  $\bar{\mathbf{p}} = \mathbf{p}/\mathbf{q}$ ,  $\bar{\mathbf{s}} = \mathbf{s}/\mathbf{q}$ , where the division corresponds to component-wise division. It is easy to check that all these vectors are positive vectors,  $\mathbf{p}$ ,  $\bar{\mathbf{p}}$ ,  $\mathbf{r}$  and  $\bar{\mathbf{r}}$  are non-constant increasing vectors and  $\mathbf{q}$  is decreasing. Thus all conditions for Lemma 1 and Corollary 1 are satisfied. Note that in the denominator of (16) the simplification  $(n - p + 1) \sum_{i=p}^n (\bar{\mathbf{p}}_i)^2 - (\sum_{i=p}^n \bar{\mathbf{p}}_i)^2 = \sum_{i \neq j, p \leq i, j \leq n} (\bar{\mathbf{p}}_i - \bar{\mathbf{p}}_j)^2$  is used. In the latter discussion we may use the variation (increasing or decreasing) of  $C_S(t)/C_T(t)$  instead of that of  $\bar{\mathbf{s}}(t)$  because

$$\bar{\mathbf{s}}(t) = \frac{k_3 + k_4}{k_2 k_4} + \frac{1}{k_4} C_S(t)/C_T(t).$$

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, 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  $V(\bar{\mathbf{s}})$  is flat. Unfortunately,  $V(\bar{\mathbf{s}})$  may become flat only for a late time interval. Thus our interest, in Section 3, 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 1.

### 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,  $\alpha_2 \gg \alpha_1$ , 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

$$\int_0^t C_T(\tau) d\tau \approx DV \int_0^t C_p(\tau) d\tau - AC_T(t) - B e^{-\alpha_1 t} \otimes C_p(t), \quad (17)$$

where  $A = (k_3 + k_4)/k_2 k_4$  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 Gunn et al. (1997), 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  $i = 1, \dots, n$  and  $t^* = t_p$ , 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

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

with data at  $t_i$ ,  $i = p, \dots, n$ , 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, Gunn et al. (1997). Second by point (2) of Corollary 1 in the *Appendix*,  $b$  should be positive and near the average value of  $\bar{s}(t)$ , where, by (14),  $\frac{k_3+k_4}{k_2k_4} < \bar{s}(t) < \frac{k_2+k_3+k_4}{k_2k_4}$ . On the other hand,  $\frac{k_2+k_3+k_4}{k_2k_4} \approx \frac{1}{\alpha_1}$  if  $4k_2k_4$  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  $(k_3 + k_4)/(k_2k_4)$  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 implemented to calculate the DV for any number of TTACs simultaneously, or for generating a parametric image of the DV. This can significantly improve the algorithmic efficiency.

## 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-neuroreceptor 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 1, are adopted from published clinical data, Price et al. (2005); Yaqub et al. (2008). 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 Price et al. (2005) while the last four are from Yaqub et al. (2008). Rate constants for ROIs **5** to **11** are directly adopted from the published literature, while those for ROIs **1** to **4** are created using partial information from Price et al. (2005) along with reasonable complementary information. Specifically, ROI **1** and **2** are complemented by setting the ratio  $k_2/k_3$  to 10 and 2 resp.; these are average ratios for the PCG of NC and AD subjects as presented in Price et al. (2005). ROIs **3** and **4** are complemented by setting  $K_1$  to 0.25 and 0.22 resp.; which

are again average values of cortical regions for NC and AD as presented in Price et al. (2005). 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 Price et al. (2005); Yaqub et al. (2008). For ROIs **6**, **7**, **10** and **11** no specific binding activity is assumed, i.e.  $k_3 = k_4 = 0$ ,  $DV = K_1/k_2(1 + k_5/k_6)$ ; 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).

ROI/Group	Area	$K_1$	$k_2$	$k_3$	$k_4$	$k_5$	$k_6$	DV	$\frac{a_1+a_2}{b_1-a_2}$
<b>1/NC</b>	<b>Cort</b>	0.250	0.152	0.015	0.0106	0	0	3.9722	0.11
<b>2/AD</b>	<b>Cort</b>	0.220	0.113	0.056	0.023	0	0	6.6872	0.65
<b>3/NC</b>	<b>PCG</b>	0.250	0.150	0.015	0.0106	0	0	4.0252	0.11
<b>4/AD</b>	<b>PCG</b>	0.220	0.100	0.050	0.017	0	0	8.6706	0.63
<b>5/AD</b>	<b>PCG</b>	0.262	0.121	0.044	0.015	0	0	8.5168	0.44
<b>6/AD</b>	<b>Cere</b>	0.273	0.144	0	0	0.007	0.005	4.5500	0.05
<b>7/AD</b>	<b>Cere</b>	0.333	0.172	0	0	0.029	0.042	3.2728	0.26
<b>8/NC</b>	<b>Cort</b>	0.250	0.140	0.020	0.018	0	0	3.7480	0.18
<b>9/AD</b>	<b>Cort</b>	0.220	0.110	0.050	0.025	0	0	5.9841	0.63
<b>10/NC</b>	<b>Cere</b>	0.270	0.140	0	0	0.020	0.026	3.4353	0.20
<b>11/AD</b>	<b>Cere</b>	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 Price et al. (2005). 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:

$$u(t) = \begin{cases} 0 & t \in [0, 0.3] \\ 407.4933(t - 0.3) & t \in [0.3, 0.6] \\ -436.6t + 384.208 & t \in [0.6, 0.76] \\ 46.6747(t + 0.24)^{-2.2560} + 5.7173(t + 0.24)^{-0.5644} & t \geq 0.76. \end{cases} \quad (18)$$

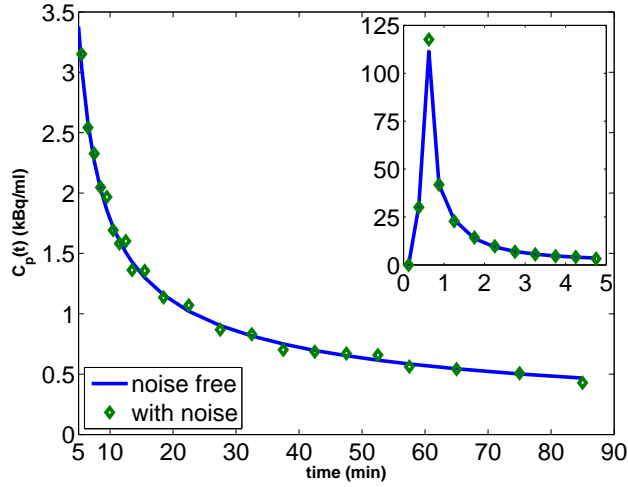


Figure 2: The true input function as given by (18), and the simulated measurements with noise. The simulated measurements are generated by (20) with  $CV_S = 0.05$ ,  $e = 50\%$ ,  $\mu = 0.5\text{ml}$  and  $\Delta w_i = 100$  seconds.

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 Price et al. (2005),

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, Mueller et al. (2005).

#### 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  $t^* = 35$ , and  $T = 240$  minutes with  $t^* = 100$ , 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  $\bar{s}$  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  $\bar{s}$  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  $[100, 240]$  than over the earlier window. Equivalently, as given by (16), a small variation in  $\bar{s}$  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 integrals required for Logan-GA and MA1 use numerical quadrature with data sampled every second, rather than a single time point per time frame, 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.

Table 2: The DV calculated using Logan-GA and MA1 for the noise-free case. DV is calculated for scan durations  $T = 90$  minutes with  $t^* = 35$ , and  $T = 240$  minutes with  $t^* = 100$ . For the numerical quadrature the data are sampled each **second**. The percentage bias is listed in parentheses.

ROI	True	35-90 min		100-240 min	
ID	DV	Logan-GA	MA1	Logan-GA	MA1
<b>1</b>	3.9722	3.549(−10.65%)	3.542(−10.84%)	3.981(0.22%)	3.977(0.12%)
<b>2</b>	6.6872	6.585(−1.53%)	6.577(−1.65%)	6.709(0.33%)	6.709(0.33%)
<b>3</b>	4.0252	3.593(−10.73%)	3.586(−10.92%)	4.034(0.22%)	4.030(0.11%)
<b>4</b>	8.6706	8.342(−3.79%)	8.331(−3.92%)	8.687(0.19%)	8.685(0.16%)
<b>5</b>	8.5168	8.129(−4.55%)	8.117(−4.69%)	8.536(0.23%)	8.533(0.19%)
<b>6</b>	4.5500	3.204(−29.58%)	3.208(−29.50%)	4.281(−5.91%)	4.273(−6.10%)
<b>7</b>	3.2728	3.300(0.82%)	3.298(0.76%)	3.286(0.41%)	3.288(0.45%)
<b>8</b>	3.7480	3.635(−3.01%)	3.625(−3.28%)	3.780(0.84%)	3.779(0.84%)
<b>9</b>	5.9841	5.910(−1.23%)	5.902(−1.37%)	6.007(0.38%)	6.007(0.39%)
<b>10</b>	3.4353	3.416(−0.57%)	3.408(−0.78%)	3.462(0.77%)	3.463(0.80%)
<b>11</b>	3.5810	3.552(−0.81%)	3.544(−1.04%)	3.608(0.75%)	3.609(0.79%)

### 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 numerical quadrature, sampling in seconds, is 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<sup>®</sup> functions `fmincon` and `lsqnonlin`, resp. In order to provide the most fair comparison the results presented are 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  $t^* = 35$ . In each case the percentage bias is listed in parentheses.

ROI	Logan-GA	MA1	KA	Algorithm 1
<b>1</b>	3.395(-14.54%)	3.392(-14.61%)	3.928(-1.12%)	4.014(1.05%)
<b>2</b>	6.511(-2.64%)	6.506(-2.71%)	6.552(-2.02%)	6.777(1.34%)
<b>3</b>	3.436(-14.65%)	3.433(-14.71%)	3.982(-1.08%)	4.066(1.00%)
<b>4</b>	8.163(-5.86%)	8.157(-5.92%)	8.535(-1.56%)	8.743(0.83%)
<b>5</b>	7.931(-6.88%)	7.925(-6.95%)	8.383(-1.57%)	8.530(0.16%)
<b>6</b>	3.004(-33.97%)	3.007(-33.92%)	4.675(2.74%)	3.972(-12.71%)
<b>7</b>	3.293(0.63%)	3.292(0.58%)	3.188(-2.59%)	3.277(0.12%)
<b>8</b>	3.555(-5.15%)	3.549(-5.30%)	3.679(-1.84%)	3.784(0.95%)
<b>9</b>	5.847(-2.28%)	5.842(-2.37%)	5.859(-2.10%)	6.008(0.40%)
<b>10</b>	3.376(-1.73%)	3.371(-1.87%)	3.361(-2.17%)	3.451(0.47%)
<b>11</b>	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 Logan et al. (2001); Varga and Szabo (2002); Ichise et al. (2002). 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  $^{11}\text{C}$ ) and a

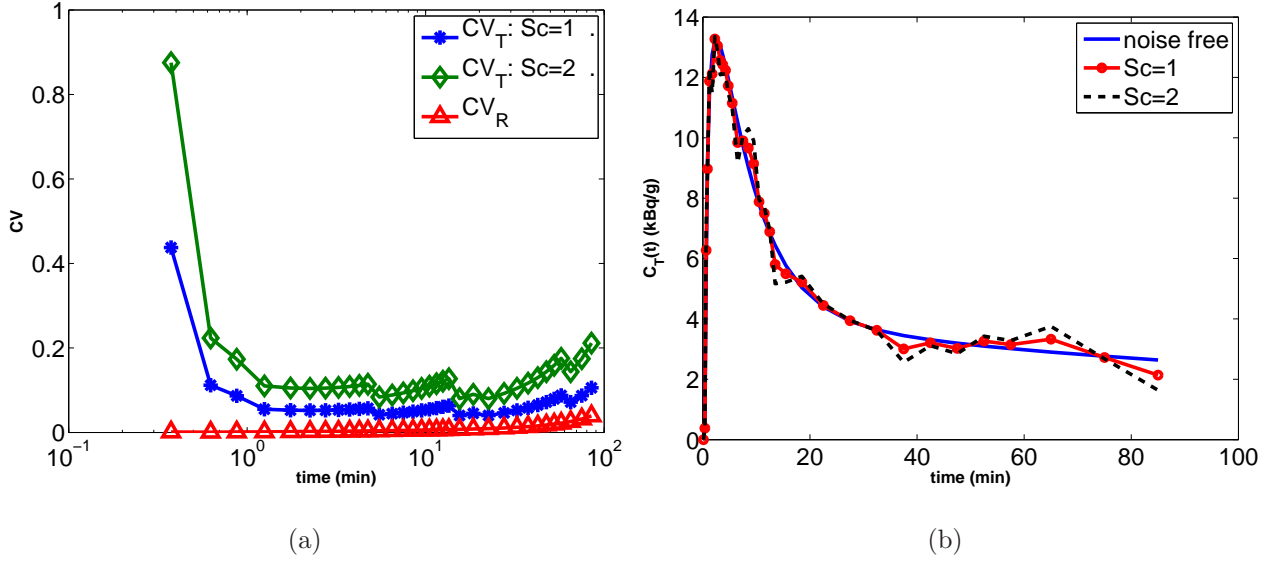


Figure 3: (a) The coefficients of variation  $CV_T$  for the noisy TTAC associated with ROI **3**, obtained with  $Sc = 1$  and  $Sc = 2$ , resp. and  $CV_R$ , for the input function calculated for  $e = 50\%$ ,  $\mu = 0.5\text{ml}$  and  $\Delta w_i = 100$  seconds. (b) The noise-free and noisy TTACs for ROI **3** obtained with  $Sc = 1$  and  $Sc = 2$ , resp.

scale factor  $Sc$

$$\sigma(C_T(t_i)) = Sc \sqrt{\frac{C_T(t_i) e^{\lambda t_i}}{\Delta t_i}}. \quad (19)$$

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 (18), 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 3. 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

$$C_p(t_i) = u(t_i)(1 + (CV_R + CV_S)\eta_i), \quad (20)$$

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 1. 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 uses only the measured scan points  $C_p(t_i)$  and  $C_T(t_i)$ .

We present histograms for the percentage relative error of the bias  $100(DV_{\text{est}} - DV_T)/DV_T$  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 1 is close to a Gaussian random distribution; the mean is near zero and the distribution is approximately symmetric. Moreover, Algorithm 1 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 5.4. From the results for the higher noise  $Sc = 2$

we conclude that Algorithm 1 using the shorter 70 minutes scan duration outperforms the other algorithms, even in comparison to their results for the longer scan duration.

Obviously Algorithm 1 is more expensive computationally than Logan-GA and MA1. In the simulations, the average CPU time, in seconds, per TTAC was  $8.3e - 4$ ,  $5.7e - 4$ , 12.2 and  $3.6e - 3$ , for Logan-GA, MA1, KA and Algorithm 1, 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. 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.  $k_6$ ). 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

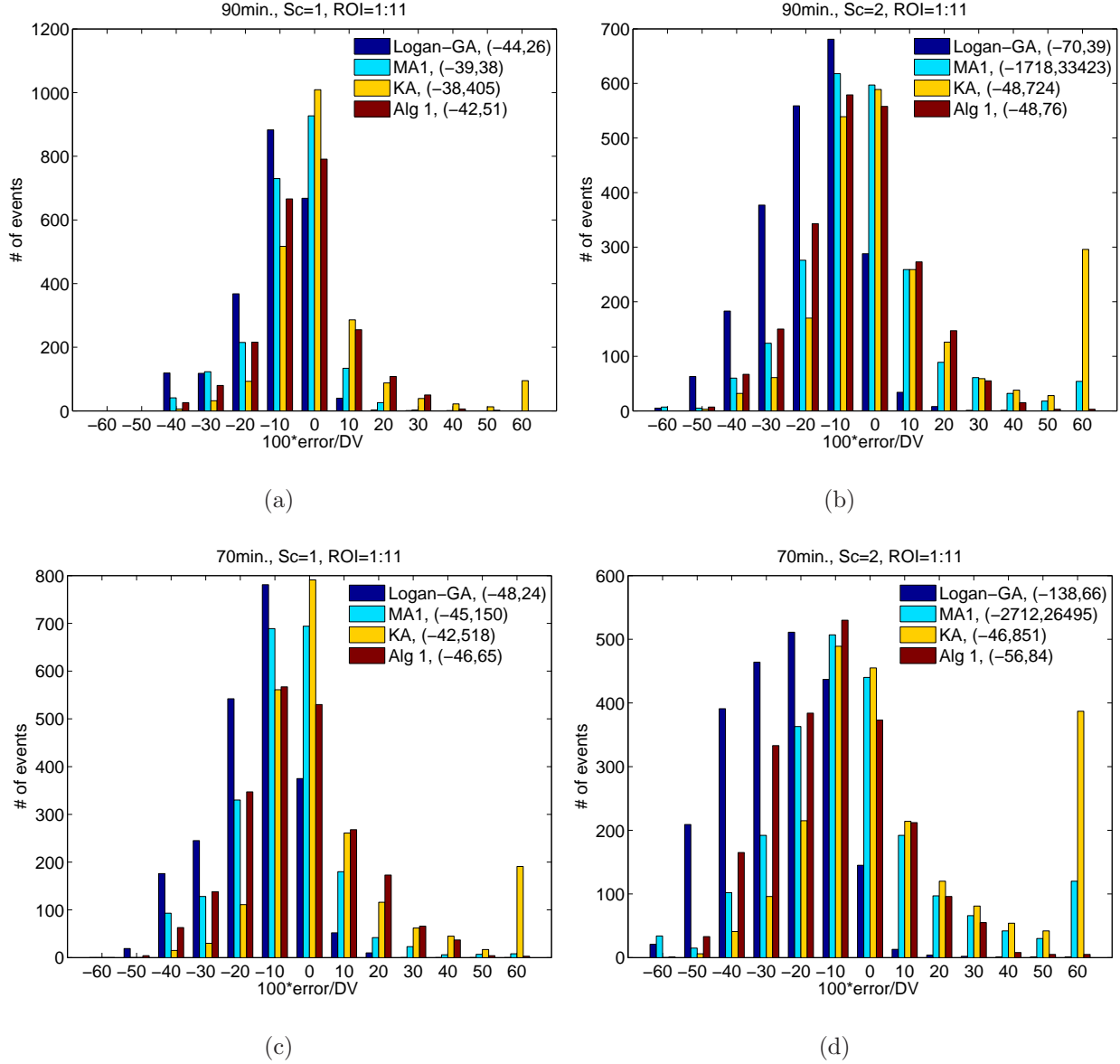


Figure 4: Histograms for normalized error (in percentage),  $100(DV_{\text{est}} - DV_T)/DV_T$ , of the results for all eleven ROIs and four methods. The error ranges are presented in the legends.

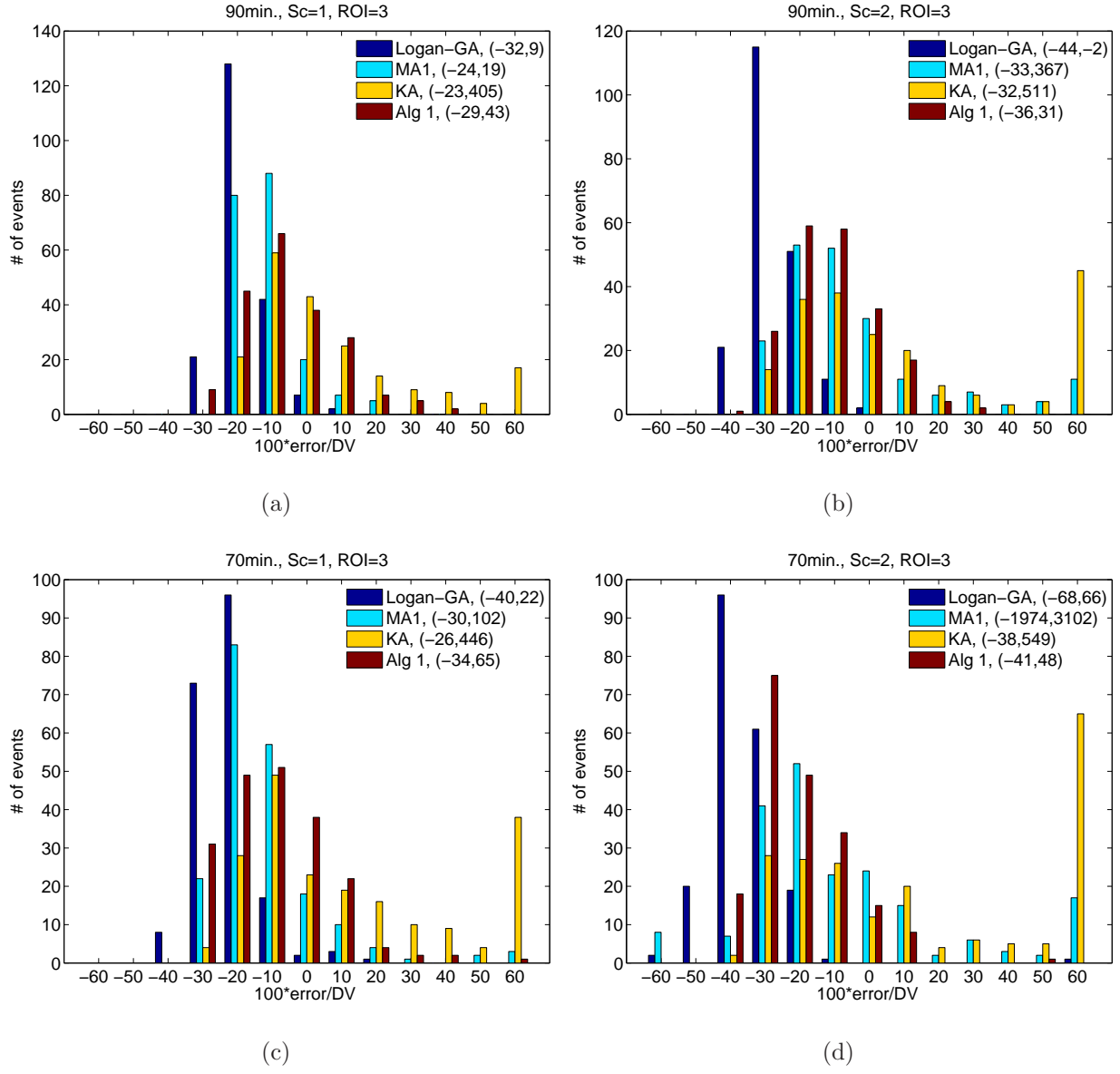


Figure 5: Histograms for normalized error (in percentage),  $100(DV_{\text{est}} - DV_T)/DV_T$ , of the results for ROI **3** and four methods. The error ranges are presented in the legends.

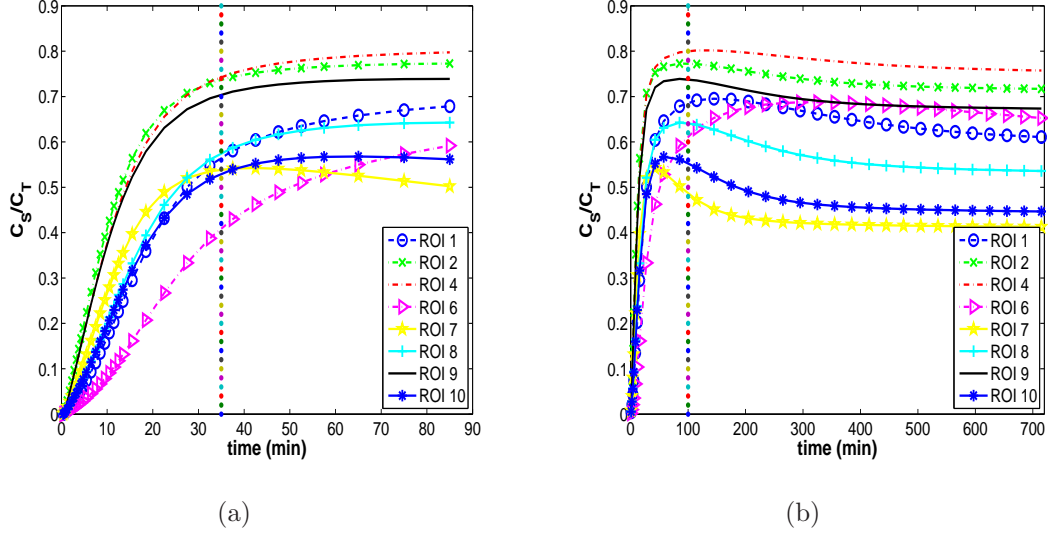


Figure 6:  $C_S(t)/C_T(t)$  against time for all test ROIs except ROIs **3**, **5** and **11** for the first 90 minutes (a) and 720 minutes (b). Dotted vertical lines are plotted at time  $t^* = 35$  (a) and  $t^* = 100$  (b). The curves for ROIs **3**, **5** and **11** are similar to those for ROIs **1**, **4** and **10** resp..

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

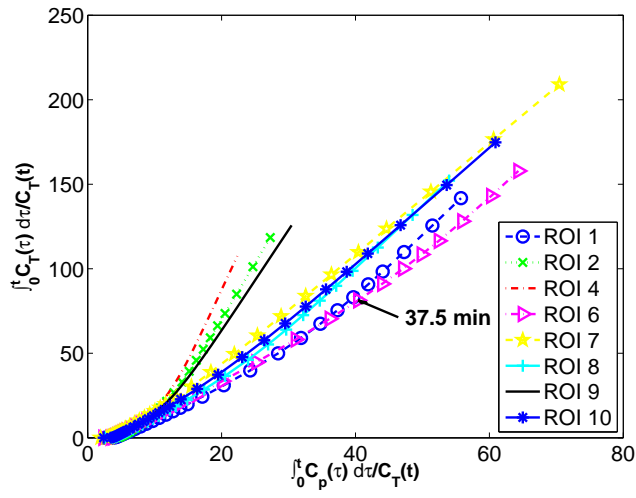


Figure 7:  $\int_0^t C_T(\tau) d\tau / C_T(t)$  (y-axis) against  $\int_0^t C_p(\tau) d\tau / C_T(t)$  (x-axis) for all test ROIs except ROIs **3**, **5** and **11** for the first 90 minutes. The last eight points correspond to the time interval 35 to 90 minutes. The curves for ROIs **3**, **5** and **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**.

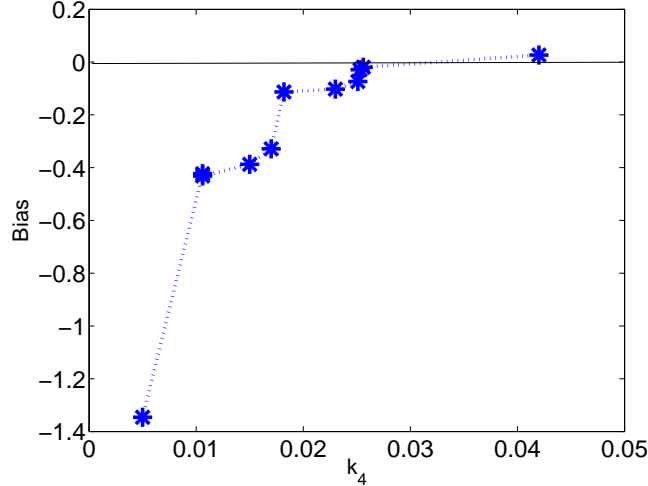


Figure 8: The bias in the Logan-GA estimation of the DV against the value of  $k_4$  for the eleven ROIs, assuming noise-free data, a scan duration of 90 minutes and  $t^* = 35$ . The specific data pairs ( $k_4$ , bias) are, for ROIs **1** to **11**, respectively, (0.0106, -0.4231), (0.0230, -0.1024), (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).

noise in the data.

### 5.2. The effects of quadrature error

Both Logan-GA and MA1, (2) and (3) resp., require the use of numerical quadrature for the calculation of integrals  $\int_0^t C_T(\tau)d\tau$  and  $\int_0^t C_p(\tau)d\tau$ . The accuracy of the numerical quadrature depends on the sampling of the function values at the scanning time points, which in turn impacts the accuracy of the parameter estimates.

We recalculate the DV for the experiments reported in Section 4.2, but now using numerical quadrature for data sampled one time point per time

frame, instead of sampling at every second. The bias for each ROI of the estimated DV by Logan-GA and MA1 using 90 minutes scan data with  $t^* = 35$  minutes is  $-12.09\%$ ,  $-3.30\%$ ,  $-12.16\%$ ,  $-5.23\%$ ,  $-5.97\%$ ,  $-30.67\%$ ,  $-1.39\%$ ,  $-4.85\%$ ,  $-3.10\%$ ,  $-2.61\%$  and  $-2.84\%$  when calculated using Logan-GA, and  $-12.28\%$ ,  $-3.42\%$ ,  $-12.36\%$ ,  $-5.35\%$ ,  $-6.11\%$ ,  $-30.60\%$ ,  $-1.47\%$ ,  $-5.12\%$ ,  $-3.23\%$ ,  $-2.83\%$  and  $-3.08\%$  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 bias is reduced. 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.

While there is progress in data measurement in the PET community, due to improvements in both hardware and software, the use of shorter time frames has been proposed and practised. Additional studies are needed to investigate the trade-off between the quadrature accuracy ( $\int_0^t C_T(\tau)d\tau$  and  $\int_0^t C_p(\tau)d\tau$ ) and the variability in PET data ( $C_T(t_i)$ ) due to lower count statistics.

### 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 Ichise et al. (2002). Careful study of these results shows that the negative DVs arise when  $-1/b$  has the wrong sign. For most neuroreceptor 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 and KA methods using longer scan data (90 minutes). The proposed approach can be easily extended for DVR estimation. This is a focus of our future work.

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## 8. Appendix

Here we present the major theoretical result from which Theorem 1 is obtained. The complete mathematical analysis which leads to this re-

sult is currently posted at <http://math.asu.edu/~hongbin/GAmodelerror.php>. We use the notation that  $\mathbf{a} = (a_1, a_2, \dots, a_n)^T$  and  $\mathbf{b} = (b_1, b_2, \dots, b_n)^T$ , are vectors with entries  $a_i$  and  $b_i$ , resp. The notation  $\mathbf{a}/\mathbf{b}$  denotes component wise division, namely entries  $a_i/b_i$ ,  $\|\mathbf{a}\|_1$  is  $\sum_{i=1}^n |a_i|$  and  $\|\mathbf{a}\|_2 = \sqrt{a_1^2 + a_2^2 + \dots + a_n^2}$  is the Euclidean norm. We call  $\mathbf{a}$  decreasing (**increasing**) if  $a_1 \geq a_2 \geq \dots \geq a_n$  ( $\mathbf{a}_1 \leq \mathbf{a}_2 \leq \dots \leq \mathbf{a}_n$ ), and non-constant decreasing (**non-constant increasing**) if it is decreasing (**increasing**) and at least one of the  $\geq$  ( $\leq$ ) signs is strict,  $>$  ( $<$ ). If all of the  $\geq$  ( $\leq$ ) signs are strict, we call  $\mathbf{a}$  strict decreasing (**strict increasing**). A vector  $\mathbf{a}$  is constant if  $a_i = a$  for some constant  $a$  and for all  $i$ .

**Lemma 1.** *Suppose  $\mathbf{p}, \mathbf{q}$  and  $\mathbf{s}$  are positive vectors,  $\mathbf{p}$  is a strict increasing vector and  $\mathbf{q}$  is a decreasing vector.  $x^*$  satisfies  $\mathbf{p}x^* - \mathbf{s} = \mathbf{r}$ , and that  $[\hat{x}, \hat{b}]$  solves the least squares problem*

$$\min \|\mathbf{p}x - b\mathbf{q} - \mathbf{r}\|^2; \quad (21)$$

then

1.  $\hat{x}$  is bigger, **less**, or **equal** to  $x^*$  if  $\mathbf{s}/\mathbf{q}$  is a non-constant decreasing, **non-constant increasing**, or **constant vector**, resp.;
2. intercept  $\hat{b}$  is bigger, **less**, or **equal** to 0 if  $\mathbf{s}/\mathbf{p}$  is a non-constant decreasing, **non-constant increasing**, or **constant vector**, resp.;
3. given  $x = x^*$ , the LS solution of  $b\mathbf{q} \approx \mathbf{p}x^* - \mathbf{r}$  for  $b$  is  $b = \mathbf{q}^T \mathbf{s} / \|\mathbf{q}\|_2^2$ ;
4. given  $b = \mathbf{q}^T \mathbf{s} / \|\mathbf{q}\|_2^2$ , the LS solution  $\hat{x}$  of  $\mathbf{p}x \approx \mathbf{r} + b\mathbf{q}$  is related to  $x^*$  in the same way as stated in the first conclusion of this list.

To obtain Theorem 1 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  $\bar{\mathbf{p}} = \mathbf{p}/\mathbf{q}$ ,  $\bar{\mathbf{s}} = \mathbf{s}/\mathbf{q}$  and

$\bar{\mathbf{r}} = \mathbf{r}/\mathbf{q}$ . Correspondingly, we find the LS solution of  $\bar{\mathbf{p}}x - \mathbf{e}b \approx \bar{\mathbf{r}}$  for  $\mathbf{e} = (1, 1, \dots, 1)^T$ , and where  $\bar{\mathbf{p}}$  and  $\bar{\mathbf{r}}$  are non-constant increasing vectors.

**Corollary 1.** *Suppose  $\bar{\mathbf{p}}$  and  $\bar{\mathbf{s}}$  are positive vectors,  $\bar{\mathbf{p}}$  is strict increasing.  $x^*$  satisfies  $\bar{\mathbf{p}}x^* - \bar{\mathbf{s}} = \bar{\mathbf{r}}$ , and that  $[\hat{x}, \hat{b}]$  solves the least squares problem*

$$\min \|\bar{\mathbf{p}}x - \mathbf{e}b - \bar{\mathbf{r}}\|_2^2; \quad (22)$$

then

1.  $\hat{x}$  is bigger, **less**, or **equal** to  $x^*$  if  $\bar{\mathbf{s}}$  is a non-constant decreasing, **non-constant increasing**, or **constant vector**, resp. Moreover, the following inequality is true without any monotonicity assumptions:

$$|\hat{x} - x^*| \leq \frac{n\|\bar{\mathbf{p}}\|_1}{n\|\bar{\mathbf{p}}\|_2^2 - \|\bar{\mathbf{p}}\|_1^2} V(\bar{\mathbf{s}}). \quad (23)$$

2. intercept  $\hat{b}$  is bigger, **less**, or **equal** to 0 if  $\bar{\mathbf{s}}/\bar{\mathbf{p}}$  is a non-constant decreasing, **non-constant increasing**, or **constant vector**, resp. In addition,  $\hat{b}$  is bigger, **less**, or **equal** to  $\sum_{i=1}^n \bar{s}_i/n$  if  $\bar{\mathbf{s}}$  is a non-constant decreasing vector, **non-constant increasing**, or **constant vector**, resp.;
3. given  $x = x^*$ , the LS solution of  $\bar{\mathbf{p}}x - \mathbf{e}b \approx \bar{\mathbf{r}}$  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  $\bar{\mathbf{p}}x - \mathbf{e}b \approx \bar{\mathbf{r}}$  is related to  $x^*$  in the same way as stated in the first conclusion of this list.

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