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Noninvasive bi-graphical analysis for the quantification of slowly reversible radioligand binding

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Abstract

In this paper, we presented a novel reference-region-based (noninvasive) bi-graphical analysis for the quantification of a reversible radiotracer binding that may be too slow to reach relative equilibrium (RE) state during positron emission tomography (PET) scans. The proposed method indirectly implements the noninvasive Logan plot, through arithmetic combination of

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the parameters of two other noninvasive methods and the apparent tissue-to-plasma efflux rate constant for the reference region (k'_2). We investigated its validity and statistical properties, by performing a simulation study with various noise levels and k'_2 values, and also evaluated its feasibility for [^{18}F] FP-CIT PET in human brain. The results revealed that the proposed approach provides distribution volume ratio estimation comparable to the Logan plot at low noise levels while improving underestimation caused by non-RE state differently depending on k'_2 . Furthermore, the proposed method was able to avoid noise-induced bias of the Logan plot, and the variability of its results was less dependent on k'_2 than the Logan plot. Therefore, this approach, without issues related to arterial blood sampling given a pre-estimate of k'_2 (e.g. population-based), could be useful in parametric image generation for slow kinetic tracers staying in a non-RE state within a PET scan.

Keywords: [^{18}F]FP-CIT, distribution volume ratio, graphical analysis, parametric image, positron emission tomography

 Online supplementary data available from stacks.iop.org/PMB/61/6770/mmedia

(Some figures may appear in colour only in the online journal)

1. Introduction

In quantitative dynamic positron emission tomography (PET) studies, graphical analysis (GA) methods are widely used (Logan 2003, Zhou *et al* 2010, Seo *et al* 2014b); the best-known ones are the Gjedde–Patlak (GP) plot for the quantification of irreversible tracer uptake (Gjedde 1981, Patlak *et al* 1983, Patlak and Blasberg 1985) and the Logan plot for reversible tracer binding (Logan *et al* 1990, 1996). These GA methods are computationally simple and model-independent. Thus, the parametric images of kinetic parameters with a relatively low noise level can be readily generated using these approaches, allowing the easy visual interpretation of tracer behavior. These advantages of the GA methods come mainly from linearizing the standard compartmental model equations into simple linear regression models.

However, each of the GA approaches relies on its particular conditions, violation of which can lead to an inaccurate estimation of parameters of interest (Logan 2003, Zhou *et al* 2010, Seo *et al* 2014b). In particular, in every GA, only the later parts of data points should be used to satisfy the linearity of the underlying model equation. Besides the linearization condition, the Logan plot requires that the tissue time-activity curve (TAC), which is involved in an independent variable of the model, should be noiseless for unbiased least squares estimation of total distribution volume (V_T) or tissue-to-reference ratio of V_T (DVR: distribution volume ratio) (Innis *et al* 2007). However, this assumption is impractical in a voxel-by-voxel estimation of these parameters, leading to the generation of noisy and biased parametric images because of the high-level noise at the individual voxel level (Carson 1993, Abi-Dargham *et al* 2000, Slifstein and Laruelle 2000). Conversely, the relative equilibrium-based graphical method (RE plot), suggested by Zhou *et al* (2009) to address the bias issue in Logan plot, demands that the tracer distribution in tissue attains an equilibrium relative to the input function, the so-called RE state; however, tracers with slow kinetics cannot easily reach the RE state during PET scan, causing biases in the results of the RE plot (Zhou *et al* 2010).

Recently, a bi-graphical analysis method named ‘RE-GP plots’, which relies on the plasma input function, has been suggested for the quantification of a reversible tracer binding that may not reach the RE state during PET scans because of its slow kinetics (Zhou *et al* 2010). In the plasma-input-based (invasive) RE-GP method, the slope of the invasive Logan plot, V_T , is obtained indirectly through arithmetic combination of the parameters of the invasive RE and GP plots. Estimation of the RE and GP parameters requires no assumption of noiseless tissue TAC in contrast with the Logan plot. Furthermore, the use of the GP parameters compensates for the bias in RE parameters, which is caused by the violation of the RE condition. Thus, the original RE-GP yields much less bias than the Logan and RE plots.

However, the original RE-GP requires an arterial blood sampling that should be avoided if possible because of its invasiveness and technical demands, and that would cause more problems in a long-duration PET scan for slow kinetic tracers, such as a dopamine transporter (DAT) imaging radioligand, N-(3-[^{18}F]fluoropropyl)-2-carboxymethoxy-3-(4-iodophenyl) nortropane ([^{18}F]FP-CIT) (Chaly *et al* 1996). Therefore, we undertook to devise a reference-region-based (noninvasive) extension of the invasive RE-GP. In this method, the slope of the noninvasive Logan plot, DVR, is computed indirectly from the parameters of the noninvasive RE and GP plots and the effective efflux rate constant from the reference region to plasma (k'_2).

This paper is organized as follows. We first describe how we derived the noninvasive RE-GP method. Then, we detail the validation of the proposed method using simulation data and its application to human brain PET studies of [^{18}F]FP-CIT, a slowly binding radioligand. The evaluation results of the statistical properties and its feasibility for [^{18}F]FP-CIT are presented in the next section. The discussion and conclusion follow in the remaining sections.

2. Materials and methods

2.1. Theory

2.1.1. Invasive Logan plot. The invasive Logan plot (Logan *et al* 1990) for reversible tracers is based on the following linear equation,

$$\frac{\int_0^t C_T(s)ds}{C_T(t)} = V_{T,\text{Logan}} \frac{\int_0^t C_P(s)ds}{C_T(t)} + \beta_{\text{Logan}} \quad \text{for } t > t^*, \quad (1)$$

where $C_P(t)$ and $C_T(t)$ are the tracer concentrations (kBq ml^{-1}) at the post-injection time $t(\text{min})$ in arterial plasma and in the region-of-interest (ROI) or voxel spanning the target tissue, respectively, $V_{T,\text{Logan}}$ is the corresponding total distribution volume (ml cm^{-3}), and $t^*(\text{min})$ is the time when the intercept β_{Logan} becomes effectively constant. The linearity or the constant intercept can be attained if the tissue kinetic approximately follows a one-tissue compartment model (ITCM) for $t > t^*$. The slope and the intercept can be estimated by applying simple linear regression analysis for (1).

2.1.2. Noninvasive Logan plot. For a reference region devoid of specific binding sites, (1) can be re-arranged as follows:

$$\int_0^t C_P(s)ds = \frac{1}{V'_{T,\text{Logan}}} \left(\int_0^t C_R(s)ds + \frac{1}{k'_2} C_R(t) \right) \quad \text{for } t > t^*, \quad (2)$$

where $C_R(t)$ is the time course of tracer concentration (kBq ml^{-1}) in the reference region and k'_2 is the apparent tissue-to-plasma efflux rate constant (l min^{-1}) in that region (Logan *et al* 1996, Logan 2003) when the reference data can be approximately described with a 1TCM after t^* (Zhou *et al* 2010) (hereafter, we will refer to this linearity condition as 1TCM approximation for $t > t^*$). Throughout the paper, the superscript prime will mean that the parameter is associated with the reference region. By substituting (2) for the plasma integral in (1), the linear equation for the noninvasive Logan plot (Logan *et al* 1996) can be derived:

$$\frac{\int_0^t C_T(s)ds}{C_T(t)} = \text{DVR}_{\text{Logan}} \left(\frac{\int_0^t C_R(s)ds + C_R(t)/k'_2}{C_T(t)} \right) + \beta_{\text{Logan}}, \quad (3)$$

where $\text{DVR}_{\text{Logan}} = V_{T,\text{Logan}}/V'_{T,\text{Logan}}$. Using a pre-estimated population average of k'_2 ($\bar{k}'_2$) instead of individually estimated k'_2 , we can obtain the $\text{DVR}_{\text{Logan}}$ and β_{Logan} parameters through simple linear regression. In addition, the term $C_R(t)/(k'_2 C_T(t))$ can be merged with β_{Logan} as a constant term when it has relatively small magnitude or becomes constant (Logan *et al* 1996), which indicates the RE state.

2.1.3. Invasive RE-GP plots. The invasive RE-GP method (Zhou *et al* 2010) is based on the following equation,

$$\frac{\int_0^t C_T(s)ds}{C_T(t)} = V_{T,\text{REGP}} \frac{\int_0^t C_P(s)ds}{C_T(t)} + \beta_{\text{REGP}} \text{ for } t > t^*, \quad (4)$$

$$V_{T,\text{REGP}} = V_{T,\text{RE}} - \frac{\beta_{\text{RE}}}{\beta_{\text{GP}}} K_{\text{in},\text{GP}}, \quad (5)$$

$$\beta_{\text{REGP}} = \frac{\beta_{\text{RE}}}{\beta_{\text{GP}}}, \quad (6)$$

where $V_{T,\text{RE}}$ and β_{RE} , and $K_{\text{in},\text{GP}}$ and β_{GP} are the estimates of the slopes and intercepts of the invasive RE and the invasive GP plots, respectively (see appendix A for their operational equations). Though (4) has an equivalent form with (1), the parameters in the invasive RE-GP method are estimated not by linear regression as in the Logan plot but by the arithmetic operations in (5) and (6). The parameters obtained from the RE plot describe the components achieving the RE state during the PET scan, while those from the GP plot compensate for the non-relative equilibrium (NRE) components inducing a bias in the RE parameters. Since the direct application of (5) and (6) to voxel TACs can lead to large spatial variations in the resulting images because of the division operations and the high-variance property of the GP plot, Zhou *et al* (2010) applied spatial smoothing filter to the GP parameters in advance.

2.1.4. Noninvasive RE-GP plots. By substituting the plasma integral in (4) with (2) similarly as in the noninvasive Logan plot, we newly derived the following relationships:

$$\frac{\int_0^t C_T(s)ds}{C_T(t)} = \text{DVR}_{\text{REGP}} \left(\frac{\int_0^t C_R(s)ds + C_R(t)/k'_2}{C_T(t)} \right) + \beta_{\text{REGP}}, \quad (7)$$

$$\text{DVR}_{\text{REGP}} = \text{DVR}_{\text{RE}} - \frac{\beta_{\text{RE}}}{\beta_{\text{GP}}} K_{\text{in,GP}}^{\dagger}, \quad (8)$$

where DVR_{RE} and $K_{\text{in,GP}}^{\dagger}$ are the estimates of the slopes of the noninvasive RE plot (Zhou *et al* 2009) and the noninvasive GP plot (Patlak and Blasberg 1985), respectively (see appendix A for their operational equations). Hereafter, the superscript $\dagger$ will indicate the parameters obtained from the noninvasive methods. Furthermore, the $\beta_{\text{RE}}/\beta_{\text{GP}}$ can also be obtained using the intercept estimates ($\beta_{\text{RE}}^{\dagger}$ and $\beta_{\text{GP}}^{\dagger}$) from the two methods as follows,

$$\frac{\beta_{\text{RE}}}{\beta_{\text{GP}}} = \beta_{\text{REGP}} = \frac{\beta_{\text{RE}}^{\dagger} - \text{DVR}_{\text{RE}}/k_2'}{\beta_{\text{GP}}^{\dagger} - K_{\text{in,GP}}^{\dagger}/k_2'}. \quad (9)$$

Thus, given a pre-estimate of k_2' (such as $\bar{k}_2'$ mentioned in section 2.1.2), we are able to compute both the parameters corresponding to those of the noninvasive Logan plot by using the results from the noninvasive RE and the noninvasive GP plots.

2.2. Computer simulations

We performed a simulation study to validate the method and evaluate its statistical properties. We generated 90 min noiseless tissue (striatum) and reference (cerebellum) TACs using a metabolite-corrected plasma input function and reversible two-tissue compartmental model (2TCM) parameters for [^{18}F]FP-CIT: $K_1 = 0.37(\text{ml cm}^{-3} \text{ min}^{-1})$, $k_2 = 0.04(1 \text{ min}^{-1})$, $k_3 = 0.09(1 \text{ min}^{-1})$, $k_4 = 0.0196(1 \text{ min}^{-1})$ and blood volume fraction $V_b = 0.05$ for the striatum (the corresponding total distribution volume $V_T = (K_1/k_2)(1 + k_3/k_4) = 51.77(\text{ml cm}^{-3})$; and $K_1 = 0.48$, $k_2 = 0.05$, $k_3 = 0.02$, $k_4 = 0.0267$ and $V_b = 0.05$ for the cerebellum ($V_T' = 16.84$) (Yaqub *et al* 2007). Then, we simulated noisy TACs by adding Gaussian noise with zero mean and Poisson-like variance, as modeled in previous studies (Ichise *et al* 2003, Logan 2003, Kim *et al* 2008, Seo *et al* 2015) to the non-decay-corrected TAC of the tissue at each of 5 different noise levels α ($=0.1, 0.2, 0.4, 0.6$, and 0.8); the noise levels of real ROI and voxel data correspond to $\alpha \leq 0.1$ and $0.4 < \alpha \leq 0.8$, respectively. For each α , we analyzed a total of 1000 realizations of noisy TAC using the noninvasive RE, GP, and Logan plots using $t^* = 60$ min. Then, we computed the parameters of the proposed RE-GP method by applying (8) and (9) to those of the RE and GP methods; moreover, we used the mean of the GP parameters instead of applying a spatial smoothing filter to reduce their high variances (see section 2.1.3).

At the first stage of evaluations, because the proposed and Logan methods require a pre-estimate of k_2' , we tested different k_2' estimation approaches for the two methods: (1) With the assumption that a reliable population-based k_2' ($\bar{k}_2'$) is available, k_2' ($=\bar{k}_2' = 0.0200$) computed from the simulation parameters by the 1TCM approximation for $t > t^*$ was used (see section 2.1.2 or Logan *et al* (1996) and Logan (2003)). (2) For the tracers with no available information on the $\bar{k}_2'$, k_2' ($= 0.0303$) estimated by the SRTM from the noiseless TAC was used. (3) The infinite value corresponding to ignoring the k_2' term was used. We computed DVR by applying the two methods with these k_2' values to noiseless data ($\alpha = 0$), and compared with the results of the RE plot and also the simplified reference tissue model (SRTM) (Lammertsma and Hume 1996); we included the SRTM because of its reliability in the quantification of [^{18}F]FP-CIT binding as shown in Yaqub *et al* (2007).

At the next stage, we examined the effect of variation in k_2' estimate on the noninvasive RE-GP and the noninvasive Logan plot. Using $k_2' = 0.017, 0.023, 0.027$, and 0.033 in

addition to the above k'_2 values, we computed DVR for each noise level. Then, for each set of the 1000 resulting DVR estimates, we measured bias and coefficient of variation (CV) as in Kim *et al* (2008) after removing outliers; the ground truth ($\text{DVR} = V_T/V'_T = 3.0743$) was computed using the simulation parameters, and outliers were defined by physiologically extreme values that are smaller than 1 or larger than 15 as in Yaqub *et al* (2007). We compared these results with those of the SRTM and, because of large variability at high noise level of the SRTM even after removing outliers, its reduced model with fixing k'_2 as a pre-estimated one (SRTM2) (Wu and Carson 2002). As alternatives of the SRTM and the SRTM2 for parametric image generation, we also considered the multilinear reference tissue model (MRTM) and its reduced version (MRTM2) (Ichise *et al* 2003) because their applications with $t^* = 0$ are the linearized implementations of the SRTM and the SRTM2, respectively (Zhou *et al* 2003, Normandin *et al* 2012, Seo *et al* 2015), and thus computationally simpler.

2.3. Human [^{18}F]FP-CIT PET data

To assess the applicability to real data, we used dynamic [^{18}F]FP-CIT human brain PET data from nineteen Parkinson's disease (PD) patients (mean age, 56.6 ± 7.1 years; age range, 42–69 years) and nine age-matched healthy volunteers (mean age, 56.0 ± 7.0 years; age range, 45–65 years), which were selected from our previous study (Lee *et al* 2014). A detailed description of the characteristics of the participants and image acquisition can be found in the previous study. In brief, after an intravenous bolus injection of 185 MBq (5.0 mCi) [^{18}F]FP-CIT, each participant underwent a 90 min dynamic scan (Siemens Biograph 40 Truepoint PET/CT, Knoxville, TN, USA). The PET data were acquired in 3D list mode and then rebinned into 50 time frames (8×15 , 16×30 , 10×60 , 10×240 , and 6×300 s). Dynamic PET images were subsequently reconstructed by filtered back projection with routine corrections for physical effects; each reconstructed image had a dimension of $256 \times 256 \times 148$ and a voxel size of $1.3364 \times 1.3364 \times 1.5 \text{ mm}^3$.

2.3.1. Regional quantification. For putamen, caudate nucleus, globus pallidus, amygdala, and cerebellum, regional average TACs were extracted from the dynamic images by applying MR-based ROI masks (see Lee *et al* (2014) for details of processing). Average ROI size of left and right sides for all subjects was $4782.91 \pm 550.89 \text{ mm}^3$ for putamen; $3352.87 \pm 365.21 \text{ mm}^3$ for caudate nucleus; $1778.05 \pm 315.07 \text{ mm}^3$ for globus pallidus; $1231.41 \pm 291.55 \text{ mm}^3$ for amygdala; and $82449.16 \pm 24778.32 \text{ mm}^3$ for cerebellum. We analyzed each ROI TAC using the proposed method, the noninvasive Logan plot, and the SRTM with the cerebellum for the reference region. Then, we assessed agreements of the ROI DVR estimates between each GA method and the SRTM. We explored the effect of neglecting k'_2 terms on the two GA methods as well. For further comparison at voxel level (see section 2.3.2), we also analyzed the data using MRTM2 instead of the SRTM2 requiring a large computational load at the voxel level. We used $t^* = 60$ for graphical methods while $t^* = 0$ for MRTM2, and the k'_2 values obtained by the SRTM for all the methods fixing k'_2 parameter.

2.3.2. Voxel-wise quantification. DVR parametric images were generated by applying the proposed method, the noninvasive Logan plot, and the MRTM2 to voxel TACs on the reconstructed dynamic images. As in Zhou *et al* (2010) (see also section 2.1.3), to reduce the variability of GP parameters, we applied a 2D spatial smoothing on each transverse slice of the

$K_{\text{in,GP}}^{\dagger}$ image with equal weighting for 10×10 pixels and on the $(\beta_{\text{GP}}^{\dagger} - K_{\text{in,GP}}^{\dagger}/k_2')$ image with a larger window of 30×30 pixels. Finally, the ROI-mean values of DVR images, obtained by applying the ROI masks to parametric images, were compared with the corresponding results of regional quantification (section 2.3.1) to investigate the effects of high-level noise on each method.

3. Results

3.1. Regional TACs and graphical plots

Figure 1 shows representative simulated TACs and *in vivo* population-averaged ROI TACs of [^{18}F]FP-CIT, and the corresponding tissue-to-reference ratios. For all the ROIs except for the cerebellum, the curves showed early rapid increase and subsequent slow clearance as in previous studies (Kazumata *et al* 1998, Yaqub *et al* 2007); as a result, the tissue-to-reference ratios increased with time, indicating that the corresponding kinetics were not in the RE state until 90 min after injection.

For both the simulated and real ROI data, the RE plot, the GP plot, and the Logan plot (for all the considered k_2' values) attained approximately linearity after $t^* = 60$ min post-injection (corresponding to the last 6 time points) as illustrated in figure 2. The GP plot showed positive slopes owing to the NRE kinetics. In the meantime, the RE plot demonstrated the lowest slopes while the Logan plot yielded larger and k_2' -dependent slopes, implying the NRE-induced bias in the DVR_{RE} and, furthermore, the NRE-induced and k_2' -dependent bias in the $\text{DVR}_{\text{Logan}}$.

3.2. Simulation results

For noiseless data ($\alpha = 0$), the noninvasive RE-GP and Logan plots produced similar DVR estimates independent of k_2' while their accuracies were dependent on the k_2' values as shown in figure 3. With the accurate population-based $k_2' (= 0.0200)$, the two methods produced almost unbiased results. However, the use of $k_2' (= 0.0303)$ estimated by the SRTM led to biased results, which were similar to that of the SRTM (about -20%). When ignoring the k_2' term, we observed the largest biases in both the RE-GP and Logan methods, the amounts (40%) of which were nevertheless smaller than about 48% of the noninvasive RE plot.

As noise levels increased, large errors occurred in the results of the noninvasive RE-GP method without averaging the GP parameters, which exacerbated the CV largely and also the bias to some extent as shown in figure 4(a). With the use of averaged GP parameters, however, the CVs of DVR_{REGP} were largely reduced and the bias became almost independent of noise levels for each k_2' value (figure 4(b)).

Although the discrepancy between the noninvasive RE-GP and Logan plots was negligible at the ROI-like noise level ($\alpha = 0.1$), the discrepancy increased with increasing noise level owing to noise-induced bias in the Logan plot (figure 4(c)). Furthermore, the discrepancy increased as the k_2' values decreased (from infinity to 0.0200) because the noise-induced bias in the Logan plot was more severe for smaller k_2' and the NRE-induced bias in the RE-GP was more corrected.

When the k_2' estimated by the SRTM was used, the results of the RE-GP and the SRTM2 showed similar levels of bias consistently at all noise levels without introducing outliers (figures 4(b) and (d); see also table S1 (stacks.iop.org/PMB/61/6770/mmedia) for the number of outliers in each method.). However, the bias of the SRTM2 was more sensitive to

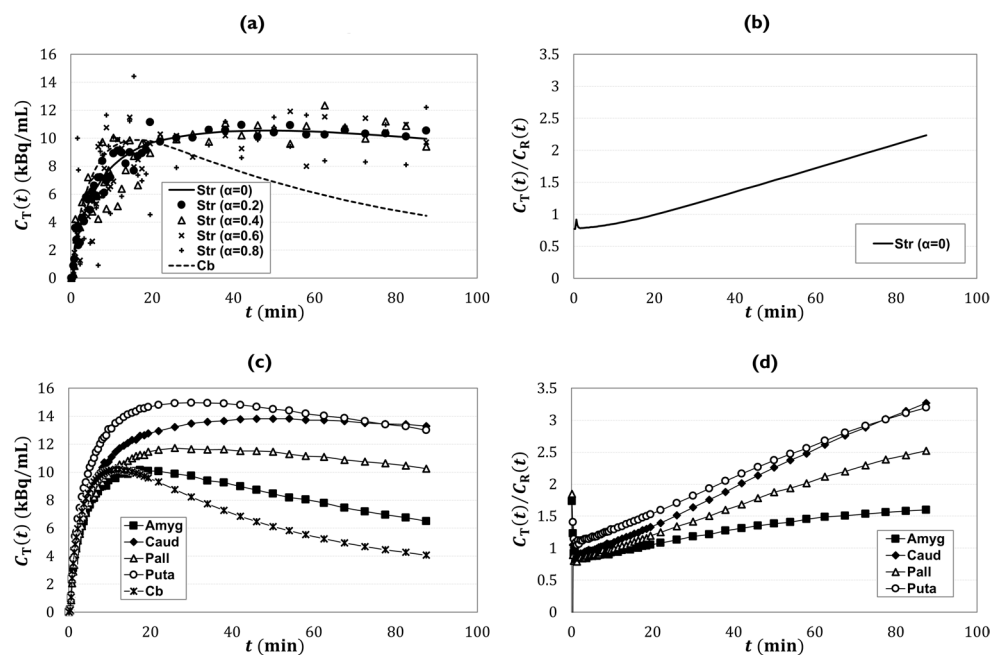


Figure 1. Kinetics of [^{18}F]FP-CIT. (a) Simulated time-activity curves (TACs) over a range of noise levels (α) for tissue (striatum, Str) and a noiseless one for reference (cerebellum, Cb). (b) The ratio of noiseless tissue TAC to reference TAC. (c) Region-of-interest TACs in amygdala (Amyg), caudate (Caud), globus pallidus (Pall), and putamen (Put) averaged over 28 participants from [^{18}F]FP-CIT PET in the human brain. (d) The corresponding ratio of tissue-to-reference activities from the human data.

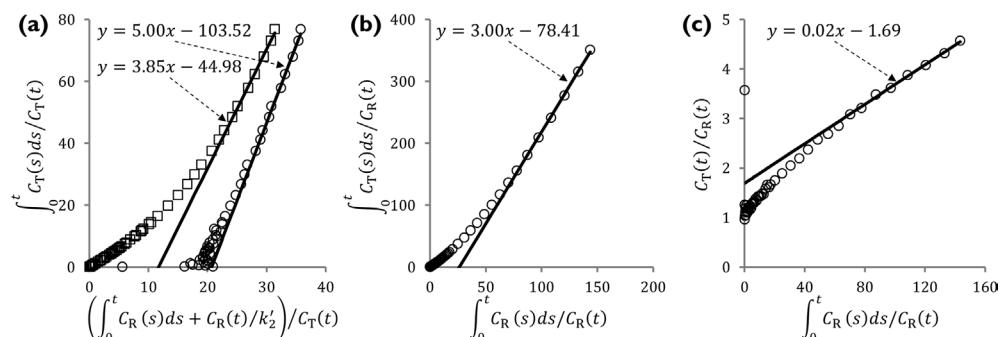


Figure 2. Typical graphical plots for the measured regional TACs from the [^{18}F]FP-CIT PET studies: (a) Logan plot with k_2' (circle) and Logan plot without k_2' (square), (b) relative equilibrium (RE) plot, and (c) Gjedde-Patlak (GP) plot.

variation in k_2' than the RE-GP. Meanwhile, the bias of the SRTM declined along with higher noise levels at the expense of considerable increases of CVs even after excluding extreme outliers, showing growing deviations from those of the RE-GP and the SRTM2 with the k_2' by SRTM.

As shown in figure 4(d), the SRTM demonstrated the highest CV values among the methods. The CVs of the SRTM2 was reduced considerably compared to the SRTM but they were

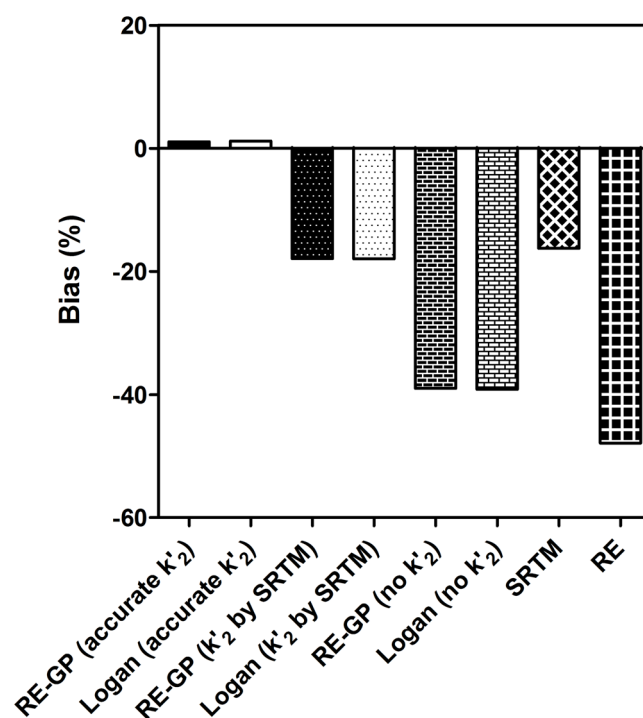


Figure 3. Comparison of bias in DVR estimates among various methods for simulated noiseless [^{18}F]FP-CIT TACs. For the noninvasive RE-GP and Logan methods, we used $k'_2 = 0.0200$ (1 min^{-1}) (accurate population-based one), 0.0303 (by the SRTM), and infinity (no k'_2 term).

still larger than those of the RE-GP based on the same k'_2 value. Meanwhile, the CVs of the RE-GP results were lowest, most stable over a range of noise levels, and independent of k'_2 (figure 4(b)) whereas those from the Logan plot were intermediate, slightly increased with higher noise levels, and decreased with larger k'_2 (figure 4(c)).

3.3. Application to human data

3.3.1. Regional parameter estimates. In common with the simulation, because of the NRE effects, ROI DVR estimates from the RE, the Logan, and the RE-GP methods when neglecting k'_2 were severely lower compared with those from the SRTM as illustrated in figure 5; nonetheless, they showed high correlations with the SRTM ($r \geq 0.90$). Conversely, when using the k'_2 obtained by the SRTM, the results from the Logan and RE-GP methods demonstrated good agreements with the SRTM results (figures 5(d) and (e)). MRTM2 yielded less correlated results with the SRTM (figure 5(f)). Regardless of whether k'_2 was used, the RE-GP method provided similar DVR values to the Logan plot, as shown in figures 6(a) and (b).

3.3.2. Parametric images. In voxel-wise quantification, the RE-GP with k'_2 (by the SRTM) produced parametric images with good quality (figure 7(a)) and ROI-mean values similar to the corresponding results of ROI analysis (figure 8(a)). However, ignoring k'_2 decreased the image intensity while maintaining the image quality (figures 7(d) and 8(d)). Meanwhile, the DVR

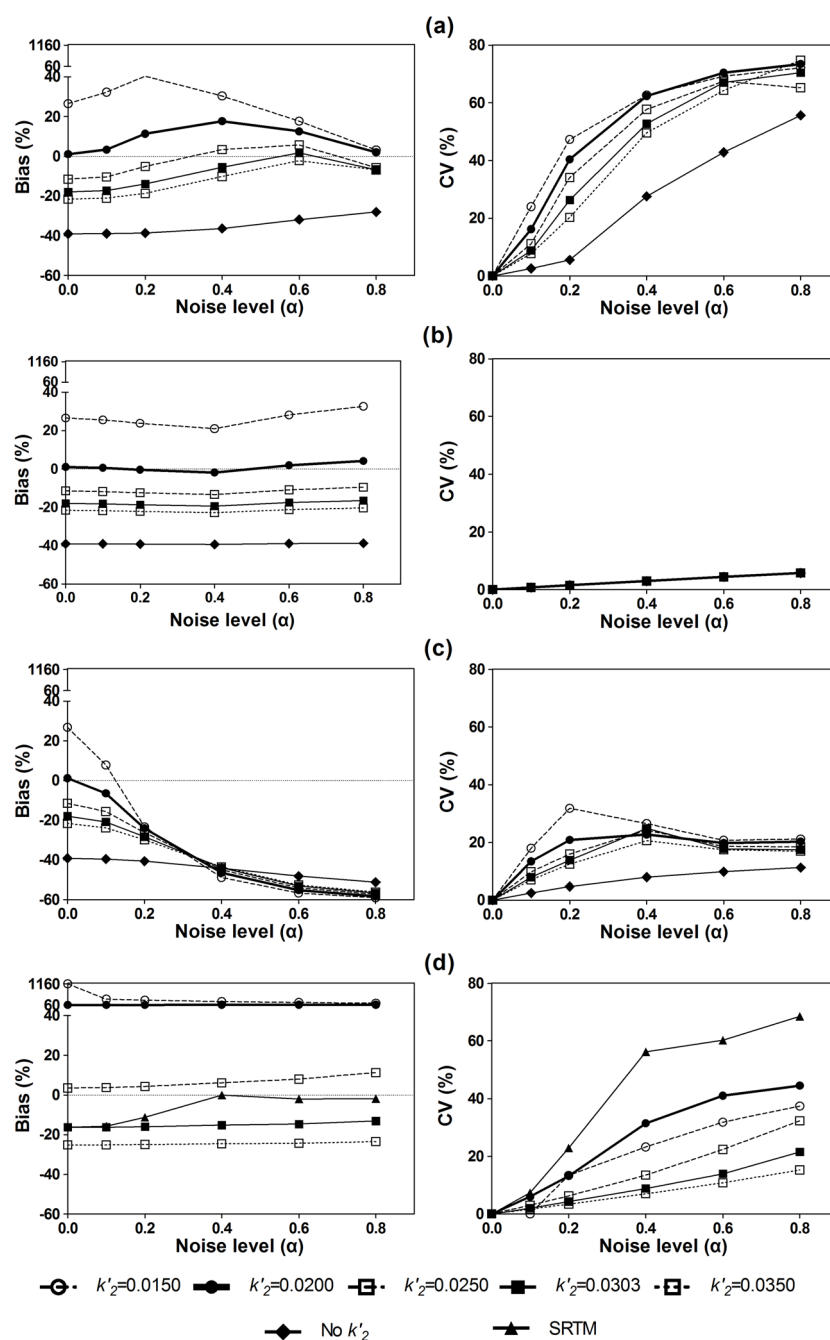


Figure 4. Bias (left) and coefficient of variation (CV, right) of DVR estimated with various methods for simulated $[^{18}\text{F}]\text{FP-CIT}$ TACs with different noise levels (α) and k'_2 values: (a) the noninvasive RE-GP without averaging GP parameters, (b) the noninvasive RE-GP, (c) the noninvasive Logan, and (d) the SRTM2. The bias and CV were computed after removing outliers (see supplementary table S1 for percentage of outliers in each method). The results of the MRTM2 (or the MRTM) were effectively identical to those of the SRTM2 (or the SRTM) and therefore omitted.

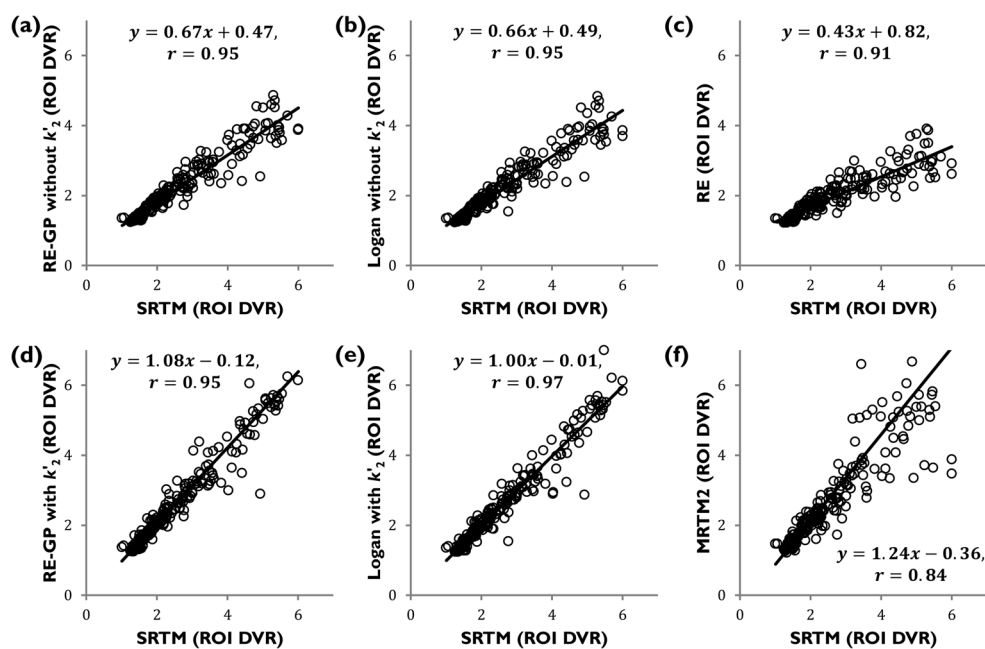


Figure 5. Linear relationship between regional DVR estimates from the simple reference tissue model (SRTM) and those from various noninvasive methods: (a) RE-GP without k'_2 ; (b) Logan without k'_2 ; (c) RE; (d) RE-GP with k'_2 ; (e) Logan with k'_2 ; and (f) multilinear reference tissue model with two parameters (MRTM2). For k'_2 , we used the values pre-estimated by the SRTM.

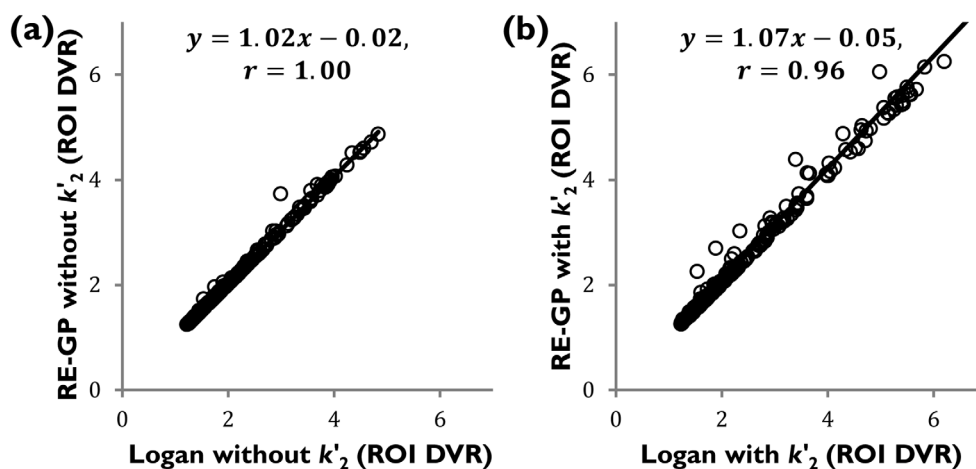


Figure 6. Agreement of regional DVR between the proposed and the noninvasive Logan methods when (a) neglecting k'_2 and (b) using it.

images from the Logan plot showed lower image intensity and poorer quality than those from the RE-GP as illustrated in figures 7(b) and (e). The Logan plot with k'_2 suffered from noticeable noise-induced bias (figure 8(b)) unlike the RE-GP with k'_2 . Conversely, despite the NRE induced bias, the ROI-mean values of DVR images from the Logan plot when neglecting k'_2 were less sensitive to high-level noise in each voxel than those obtained using k'_2 , showing a good consistency

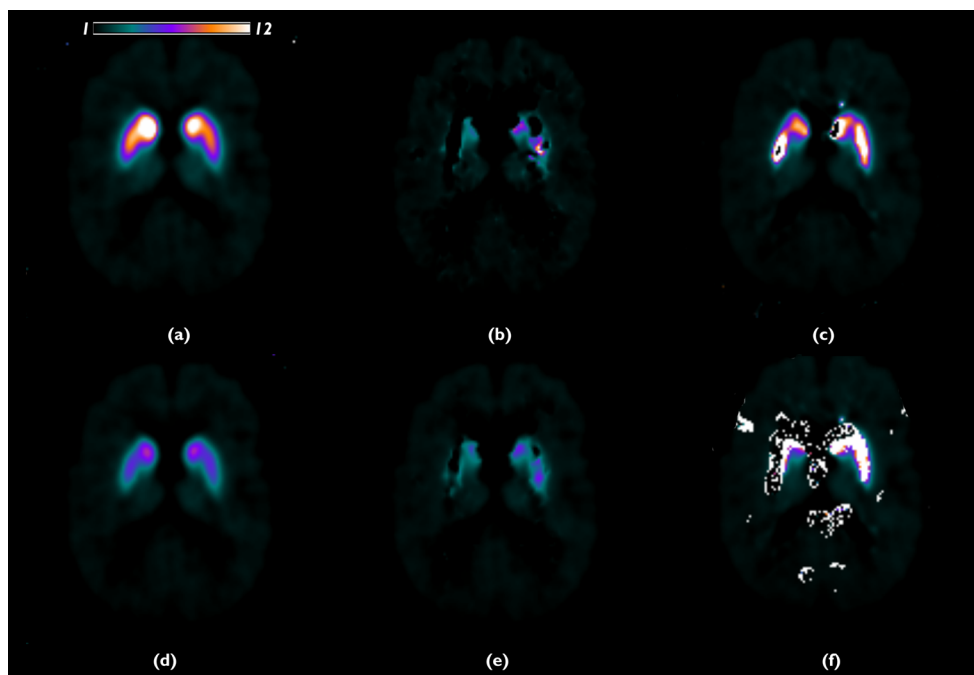


Figure 7. Transverse planes of representative parametric images of DVR generated by (a) RE-GP with k'_2 ; (b) Logan with k'_2 ; (c) MRTM2; (d) RE-GP without k'_2 ; (e) Logan without k'_2 ; and (f) SRTM2. For k'_2 , we used the values pre-estimated by the SRTM. For the image from the SRTM2 in (f), one slice image was generated only for visual comparison because of computational burden, and initial parameter values for nonlinear fitting were obtained by fitting the SRTM (without fixing k'_2) to spatially smoothed dynamic images in advance. We omitted the SRTM image because of its worse quality compared to the SRTM2 image.

with the corresponding ROI results (figure 8(e)). However, the image quality of the Logan plot without k'_2 was still inferior to that of the RE-GP without k'_2 , showing a discrepancy between their ROI-mean values ($y = 0.87x + 0.15$ ($r = 0.97$); see also supplementary figure S1). The MRTM2 DVR image showed an acceptable quality in many cases, which was comparable to that of the RE-GP. In some cases, however, it suffered from ‘holes’ near the boundary between high- and low-binding regions (figure 7(c)), which led to 1.79% outliers in terms of ROI-mean values. Thus, as shown in figure 8(c), the ROI mean values from MRTM2 images presented the lowest correlation with the corresponding ROI analysis even after removing the outliers.

4. Discussion

In this study, we presented a new bi-graphical method based on reference region data and the noninvasive RE and GP plots. We investigated its validity and statistical properties with a simulation study and then evaluated its feasibility for the quantification of [^{18}F]FP-CIT PET in the human brain. The results indicated that the arithmetic combination of the RE and GP parameters yields DVR estimates in agreement with the noninvasive Logan plot for low-noise simulated and clinical ROI data by correcting the NRE-induced bias, and that k'_2 determines their accuracies or the amount of bias correction. The use of reliable population-based k'_2

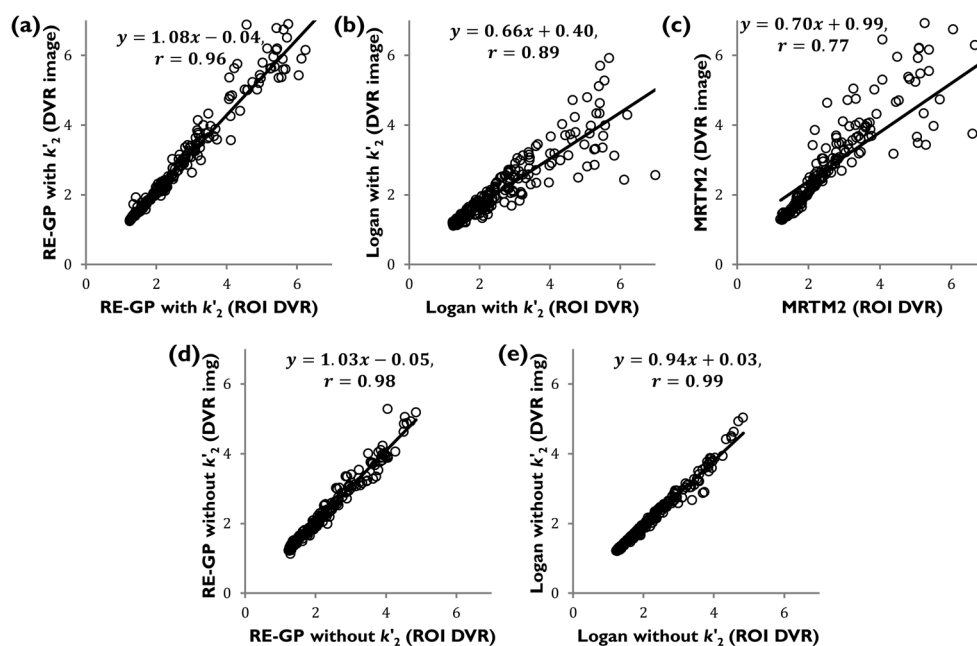


Figure 8. Linear relationship between ROI-mean values of DVR parametric images and the corresponding estimates in ROI analysis for various methods: (a) RE-GP with k'_2 ; (b) Logan with k'_2 ; (c) MRTM2 (1.79% outliers were removed); (d) RE-GP without k'_2 ; and (e) Logan without k'_2 .

(satisfying the 1TCM approximation for $t > t^*$) turned out to be the optimal choice, which led to almost unbiased results. The use of k'_2 from the SRTM led to biased results, but they showed good agreement with those from the SRTM, implying that estimating k'_2 from the SRTM would be a practical approach for the tracers without the availability of reliable population-based k'_2 . Furthermore, unlike the Logan plot whose accuracy and variability depended on both the noise levels and the k'_2 values, the proposed RE-GP approach showed the accuracy almost independent of the noise levels, and the variability independent of k'_2 and relatively stable over the noise levels. These favorable statistical properties made the proposed method outperform the Logan plot in the parametric image generation using *in vivo* data.

4.1. Characteristics of [^{18}F]FP-CIT PET data

The [^{18}F]FP-CIT is a very promising radioligand for DAT imaging because of high affinity and selectivity for the DAT and relatively faster kinetics than other DAT-imaging tracers (Lundkvist *et al* 1997, Kazumata *et al* 1998, Yaqub *et al* 2007, Eo *et al* 2014). Nevertheless, its slow kinetics in striatum required a dynamic PET scan of more than 90 min duration for the reliable quantification of its specific binding to the DAT through a kinetic analysis (Yaqub *et al* 2007) and yielded NRE components in 90 min data as illustrated in figures 1(b) and (d). Moreover, its rapid metabolism might hamper the accurate measurement of plasma input function for such long scan duration (Kazumata *et al* 1998), thereby demanding the use of reference-region-based approaches for the quantification. These characteristics of [^{18}F]FP-CIT present the rationale for a noninvasive method capable of enduring the slow kinetics, such as the proposed RE-GP method.

4.2. Kinetic methods for [^{18}F]FP-CIT PET

The [^{18}F]FP-CIT PET has been used via a ratio analysis for studying various kinds of Parkinsonism (Ma *et al* 2002, Wang *et al* 2007, Park *et al* 2014, Seo *et al* 2014a, Lee *et al* 2015) or migraine (Park *et al* 2015). However, kinetic methods to quantify the specific bindings have been evaluated in a very limited number of studies, mostly by ROI analysis. In Kazumata *et al* (1998), the regional brain uptake of [^{18}F]FP-CIT was evaluated using both the invasive and noninvasive Logan methods (using the population average of k'_2 , in occipital lobe, estimated by the invasive Logan plot). Although a good agreement was found between the two methods, they were not compared with any compartmental model, but were compared only with a ratio method. In Yaqub *et al* (2007), the SRTM provided a negatively biased but noise-robust estimation of binding potential for 90 min striatal ROI data. Conversely, the plasma-input compartment models suffered from large numbers of outliers because of the unclear preference between reversible and irreversible model structures (or very small k_4). In this work, we have compared the proposed method with the noninvasive Logan plot and the SRTM (or the SRTM2) by both ROI- and voxel-level analyses; the results suggest that the proposed method outperforms them in the parametric imaging of [^{18}F]FP-CIT binding.

4.3. k'_2 -dependent correction for NRE effects

The aforementioned unclear model preference is likely based on the NRE components because their slow kinetics could be considered as approximately irreversible within a limited scan duration (Zhou *et al* 2010). Based on this premise, the invasive RE-GP method employs the invasive GP plot to capture the V_T information from the apparently irreversible components that could be hardly quantified using the invasive RE plot only. Similarly, the noninvasive RE-GP method takes advantage of the noninvasive RE and GP methods to describe the RE components and the NRE components of DVR, respectively. As described in section 3.1 and figure 2, the NRE components might affect not only the results from the noninvasive RE plot but also those from the noninvasive Logan and RE-GP approaches without k'_2 . Thus, unlike the invasive RE-GP, the proposed RE-GP method requires k'_2 as well as the GP plot to correct for the NRE effects.

Since the correction of NRE-induced bias relies on k'_2 , its accurate pre-estimation is important for practical applications of the proposed method. However, so far, there is no existing approach to obtain unbiased k'_2 estimates (satisfying the 1TCM approximation for $t > t^*$) without plasma input function. In this situation, estimating k'_2 from the SRTM would be a promising surrogate when no arterial input is given, despite leading to biased results. However, its application should be careful because the resulting bias can be different between different groups. Alternatively, a population average of k'_2 , obtained from preliminary studies using the invasive Logan plot, may provide more accurate estimation though not evaluated in this study. Based on our results that the noninvasive RE-GP and Logan methods showed equivalent k'_2 -dependent correction of NRE effects, we expect that the noninvasive RE-GP would be applicable for tracers, such as [^{11}C]d-threo-methylphenidate ([^{11}C]dMP) (Logan *et al* 1996), for which the noninvasive Logan has been validated with the population average of k'_2 .

4.4. Linearity condition

Besides the k'_2 -dependent correction of NRE effects, the noninvasive RE-GP method and the noninvasive Logan plot share the linearity condition. The validity of V_T estimates from the invasive RE-GP method relies on the linearity condition of the invasive Logan plot, which requires the tracer kinetics in tissue to follow 1TCM after t^* and can usually be achieved earlier

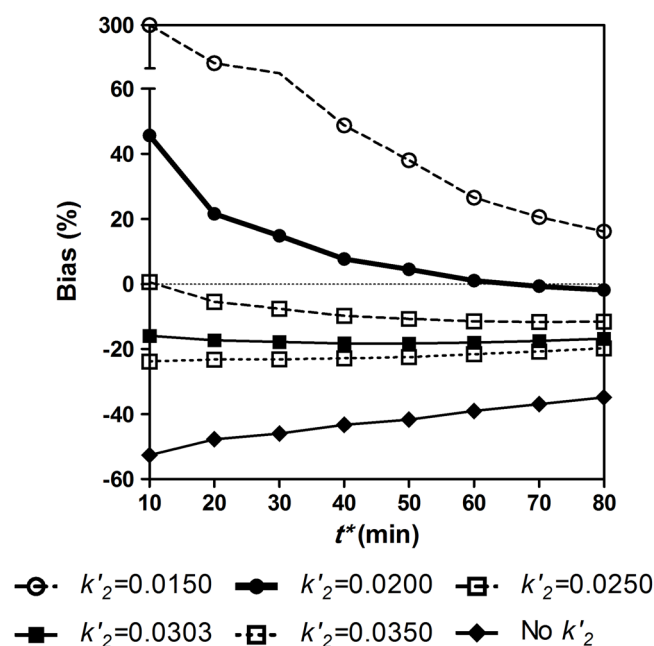


Figure 9. Effect of variation in t^* on DVR estimation. The bias was computed using noiseless TAC and the noninvasive RE-GP method. The noninvasive Logan produced very similar result (omitted).

than the RE condition (Zhou *et al* 2010, Wong *et al* 2012, Seo *et al* 2014b). Theoretically, the noninvasive Logan and RE-GP methods should follow that linearity condition as well since it is invariant during the derivations of the two methods. Therefore, even if the apparently irreversible components achieve asymptotic linearity in the noninvasive GP plot, a violation to the Logan linearity condition may lead to biased DVR estimates. In practice, error in the pre-estimated k'_2 may change the linearity condition as illustrated in figure 2(a). In our study, the Logan linearity condition was approximately achieved after $t^* = 60$ min. Therefore, the use of earlier t^* yielded a larger amount of bias, which was reduced with increasing t^* , as shown in figure 9; furthermore, the sensitivity to t^* was more severe for k'_2 values of larger error. Overall effect of variation in t^* was very similar between the RE-GP and Logan methods.

4.5. Advantages over the noninvasive Logan plot

The indirect implementation gives the RE-GP method more favorable statistical properties than the Logan plot, which are determined by the properties of the RE and GP methods. These are particularly useful for parametric image generation, which is challenging because of the high-level noise in image voxels (Lee *et al* 2005, Cselényi *et al* 2006, Kim *et al* 2008, Seo *et al* 2014b).

First, the parameters of the RE and GP methods can be estimated without noise-induced bias since the two methods share almost noiseless independent variable ((A.2) and (A.4)) in contrast to the Logan plot. These properties make the accuracies of the RE-GP results robust to the noise levels, as supported by our results. Conversely, because of noise-induced bias, k'_2 -dependent accuracies of the Logan plot increasingly deteriorated as the noise level rose. Furthermore, the noise-induced biases were more severe for smaller k'_2 ; this is because smaller k'_2 yields larger (or less underestimated) DVR as demonstrated in our results for noiseless data,

and the extent of the bias depends on the magnitude of the parameters as well as on the noise level (Slifstein and Laruelle 2000).

On the contrary, noise in data seems to affect dominantly the variability of the results from the RE-GP rather than the accuracy as shown in figure 4(a). The results of the GP plot usually have higher variability than those of the RE plot because the numerator ($C_T(t)$) in its dependent variables has higher noise levels than that ($\int_0^t C_T(s)ds$) of the RE plot. Moreover, the results from the GP plot are incorporated in the denominator for the computation of the RE-GP parameters. Consequently, propagation of errors in GP parameters can lead to increased variance and even loss of accuracy in the results of RE-GP. Nevertheless, our results indicate that the use of smoothing or mean filters for the GP parameters can improve the variability property without severe loss of accuracy. It is noteworthy that the smoothing effect may be different between groups of subjects because of dissimilarity in spatial heterogeneity of GP parameters; the heterogeneity within regions of interest may be larger in patient group than in healthy group whereas the heterogeneity across high-binding regions of interest and peripheral low-binding regions would be larger in healthy group.

Meanwhile, the independent variable of the RE and GP methods consists of only reference region data, and is thus applied commonly to all voxels or ROIs. This common independent variable facilitates reconstructing parametric images using the RE or GP plot directly from raw projection data (Wang and Qi 2013, Wentao *et al* 2014, 2015). Conversely, a nonlinear involvement of $C_T(t)$ in the independent variable of the Logan plot makes direct reconstruction using the Logan plot more difficult (Wang and Qi 2013).

4.6. Comparison with the SRTM

In the *in vivo* quantifications, we compared the ROI results from both the RE-GP and Logan methods to those from the SRTM because of SRTM's reliability as shown in Yaqub *et al* (2007). The results demonstrated good agreements when k'_2 pre-estimated by the SRTM was used; additionally, even when the k'_2 term was ignored, they showed good correlations despite the NRE-induced bias.

We observed a similar trend of good agreement in the low-noise simulation. In keeping with the previous study (Yaqub *et al* 2007), however, the results from the SRTM and the SRTM2 with $k'_2 = 0.0303$ (by SRTM) showed negative biases for the noiseless data, compared with the simulated value of DVR ($=V_T/V'_T = 3.0743$). Conversely, given the accurate estimate of $k'_2 (= 0.0200)$, both the Logan and RE-GP methods led to almost unbiased results. Considering the model independence of the GA approaches, these results imply that the biases in the SRTM and the SRTM2 were based on the conflict between their 1TCM assumptions for tissue and reference regions and the data simulated using 2TCMs.

In the simulation, the bias of RE-GP was less sensitive to error in k'_2 than that of the SRTM or the SRTM2 (figure 4) although they were similar when $k'_2 = 0.0303$ (obtained by SRTM at $\alpha = 0$) was used; in addition, when k'_2 was estimated by the SRTM at $\alpha = 0.1$, the error (± 0.0025) in k'_2 caused acceptable variation of bias ($< 4\%$). Moreover, the RE-GP showed smaller CVs than the SRTM and the SRTM2. These trends may be reflected as the poorer performance of the MRTM2 in the real application (figures 7 and 8).

4.7. Simulation setting

Our simulation results may seem to be different from the results of Yaqub *et al* (2007) because of different simulation setting between the two studies. However, their results are very similar after accounting for the following differences.

First, the range of noise levels considered is inconsistent. In Yaqub *et al* (2007), simulations were performed only at low noise levels seen in ROI analysis: 2.5 and 5% in terms of average CV over the last 60% of the frames (i.e. for the curve >5 min) (also refer to Yaqub *et al* (2006) for the definition of noise level). However, in our study, we included a broader range of noise levels ($0.1 \leq \alpha \leq 0.8$), and the levels considered in Yaqub *et al* (2007) correspond to $\alpha < 0.2$ level (about $<7\%$ CV).

Second, the definition of bias and the ground truth for its computation are not same. In Yaqub *et al* (2007), the accuracy was determined as the ratio of the estimated binding potential (BP) value over simulated BP value. The simulated BP value was computed as $BP_{2T-4k}^{\text{striatum}} - BP_{2T-4k}^{\text{Cerebellum}} = k_3^{\text{str}}/k_4^{\text{str}} - k_3^{\text{cb}}/k_4^{\text{cb}} = 0.09/0.0196 - 0.02/0.0267 \approx 3.85$ under the assumption that there are components of not only specific binding but also slow nonspecific binding; $BP_{2T-4k} = k_3/k_4$ is the BP estimated from 2TCM with 4 parameters. In addition, the average accuracy of BP values estimated by the SRTM was 0.4 ± 0.1 in their simulation, which corresponds to $DVR = BP + 1 = 0.4 \times 3.85 + 1 = 2.54$. However, in our simulation, we used $DVR = V_T/V'_T = 3.0743$ as the ground truth, and observed about $\leq 20\%$ bias in the SRTM results at $\alpha \leq 0.2$ level, which corresponds to $DVR = 2.46$.

5. Conclusion

The noninvasive RE-GP approach provides DVR estimation comparable to the noninvasive Logan GA for low-noise simulated and clinical ROI data. In common with its invasive counterpart, the proposed RE-GP can reduce a noise-induced bias of the Logan method at high noise levels. Contrary to the invasive approach, which can almost reduce the NRE-induced bias, this approach yields partial to full reduction of the NRE-induced bias, depending on k'_2 value. Therefore, given a pre-estimate of k'_2 (i.e. population-based), this approach might be useful in parametric image generation for slow kinetic tracers that require a long-lasting PET scan.

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Disclosure/conflict of interest

Seongho Seo reports no disclosures.

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Appendix A

The invasive Gjedde–Patlak (GP) plot (Gjedde 1981, Patlak *et al* 1983) for irreversible tracers has the following operational equation,

$$\frac{C_T(t)}{C_P(t)} = K_{in,GP} \frac{\int_0^t C_P(s)ds}{C_P(t)} + \beta_{GP} \text{ for } t > t^*, \quad (\text{A.1})$$

where $K_{in,GP}$ is the influx rate constant and β_{GP} is the intercept term which should become constant after t^* , the time when reversible compartments achieve a steady state. Given a reference region having only reversible binding, we can substitute (2) into (A.1) as explained in section 2.1.2. Then, multiplying both sides of (A.1) by $C_P(t)/C_R(t)$, we derive the following equation for the noninvasive GP plot (Patlak and Blasberg 1985, Logan 2003),

$$\frac{C_T(t)}{C_R(t)} = K_{in,GP}^\dagger \frac{\int_0^t C_R(s)ds}{C_R(t)} + \beta_{GP}^\dagger, \quad (\text{A.2})$$

where $K_{in,GP}^\dagger = K_{in,GP}/V'_{T,Logan}$ and $\beta_{GP}^\dagger = K_{in,GP}^\dagger/k'_2 + \beta_{GP}C_P(t)/C_R(t)$. Thus, the linearity holds if $\beta_{GP}C_P(t)/C_R(t)$ and k'_2 become effectively constant for $t > t^*$ (Logan 2003). Notice that the Logan linearity condition for the reference region yielded the constant k'_2 in (2); furthermore, the constancies of $C_R(t)/C_P(t)$ as well as k'_2 can be achieved if the RE state is attained in the reference region.

The invasive RE plot (Zhou *et al* 2009) has a similar equation to the invasive GP plot except for the numerator of the independent variable ($\int_0^t C_T(s)ds$):

$$\frac{\int_0^t C_T(s)ds}{C_P(t)} = V_{T,RE} \frac{\int_0^t C_P(s)ds}{C_P(t)} + \beta_{RE} \text{ for } t > t^*. \quad (\text{A.3})$$

Thus, the derivation, similar to that of (A.2), leads to

$$\frac{\int_0^t C_T(s)ds}{C_R(t)} = DVR_{RE} \frac{\int_0^t C_R(s)ds}{C_R(t)} + \beta_{RE}^\dagger, \quad (\text{A.4})$$

where $DVR_{RE} = V_{T,RE}/V'_{T,Logan}$ and $\beta_{RE}^\dagger = DVR_{RE}/k'_2 + \beta_{RE}C_P(t)/C_R(t)$.

On the other hand, the original noninvasive RE plot suggested by Zhou *et al* (2009) is given by

$$\frac{\int_0^t C_T(s)ds}{C_R(t)} = \frac{V_{T,RE}}{V'_{T,RE}} \frac{\int_0^t C_R(s)ds}{C_R(t)} + \frac{C_P(t)}{C_R(t)} \left(\beta_{RE} - \frac{V_{T,RE}}{V'_{T,RE}} \beta_{RE}' \right). \quad (\text{A.5})$$

Here, (A.5) was derived by using a different approximation for the plasma integral:

$$\int_0^t C_P(s)ds = \frac{1}{V'_{T,RE}} \left(\int_0^t C_R(s)ds - \beta_{RE}' C_P(t) \right), \quad (\text{A.6})$$

which can be rearranged from the invasive RE plot for the reference region. It is noteworthy that $\beta_{RE}' C_P(t)/C_R(t) = -1/k'_2$ and therefore (A.4) and (A.5) are identical because (2) and (A.6) are equivalent when assuming the RE state of the reference region (hence, constant $C_P(t)/C_R(t)$).

Appendix B

Please see table B1 for a summary of variables in model equations.

Table B1. Summary of variables in model equations.

Variable	Description
$C_P(t)$	Concentration of radioligand in arterial plasma ($\text{kBq} \cdot \text{ml}^{-1}$)
$C_R(t)$	Total concentration of radioligand in reference region ($\text{kBq} \cdot \text{ml}^{-1}$)
$C_T(t)$	Total concentration of radioligand in tissue ($\text{kBq} \cdot \text{ml}^{-1}$)
DVR	Distribution volume ratio or tissue-to-reference ratio of V_T (unitless)
$\text{DVR}_{\text{Method}}$	DVR estimated as the slope parameter in a noninvasive GA method: Logan plot, RE plot, or RE-GP method (unitless)
k'_2	Apparent rate constant for efflux of radioligand from reference tissue ^a to plasma when the kinetics in reference tissue can be approximately described with a one-tissue compartment model (min^{-1})
K_{in}	Net influx rate of radioligand from plasma into irreversible compartment in tissue ($\text{ml} \cdot \text{cm}^{-3} \cdot \text{min}^{-1}$)
$K_{\text{in,GP}}$	K_{in} estimated as the slope parameter in the invasive GP plot ($\text{ml} \cdot \text{cm}^{-3} \cdot \text{min}^{-1}$)
$K_{\text{in,GP}}^\dagger$	K_{in}/V'_T estimated as the slope parameter for in the noninvasive GP plot ^b (min^{-1})
V_T (or V'_T)	Total distribution volume in tissue (or in reference tissue) ($\text{ml} \cdot \text{cm}^{-3}$) ^a
$V_{T,\text{Method}}$	V_T (for target tissue) estimated as the slope parameter in an invasive GA method: Logan, RE, or RE-GP method ($\text{ml} \cdot \text{cm}^{-3}$)
$V'_{T,\text{Method}}$	V'_T (for reference tissue) ^a estimated as the slope parameter in an invasive GA method: Logan, or RE method ($\text{ml} \cdot \text{cm}^{-3}$)
β_{Method}	The intercept parameter for target tissue in an invasive GA method: Logan, RE, RE-GP, or GP method (unitless)
$\beta_{\text{Method}}^\dagger$	The intercept parameter in the noninvasive GA method: RE or GP plot ^b (unitless)
β'_{RE}	The intercept parameter for reference tissue ^a in an invasive RE plot (unitless)

^a Superscript *i* denotes for the parameters in reference tissue.

^b Superscript $\dagger$ indicates the parameters in a noninvasive RE or GP plot.

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