Generalized whole-body Patlak parametric imaging for enhanced quantification in clinical PET

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Abstract

We recently developed a dynamic multi-bed PET data acquisition framework to translate the quantitative benefits of Patlak voxel-wise analysis to the domain of routine clinical whole-body (WB) imaging. The standard Patlak (sPatlak) linear graphical analysis assumes irreversible PET tracer uptake, ignoring the effect of FDG dephosphorylation, which has been suggested by a number of PET studies. In this work: (i) a non-linear generalized Patlak (gPatlak) model is utilized, including a net efflux rate constant $k_{loss}$, and (ii) a hybrid (s/g)Patlak (hPatlak) imaging technique is introduced to enhance contrast to noise ratios (CNRs) of uptake rate $K_i$ images. Representative set of kinetic parameter values and the XCAT phantom were employed to generate realistic 4D simulation PET data, and the proposed methods were additionally evaluated on 11 WB dynamic PET patient studies. Quantitative analysis on the simulated $K_i$ images over 2 groups of regions-of-interest (ROIs), with low (ROI A) or high (ROI B) true $k_{loss}$ relative to $K_i$, suggested superior accuracy...
for gPatlak. Bias of sPatlak was found to be 16–18% and 20–40% poorer than gPatlak for ROIs A and B, respectively. By contrast, gPatlak exhibited, on average, 10% higher noise than sPatlak. Meanwhile, the bias and noise levels for hPatlak always ranged between the other two methods. In general, hPatlak was seen to outperform all methods in terms of target-to-background ratio (TBR) and CNR for all ROIs. Validation on patient datasets demonstrated clinical feasibility for all Patlak methods, while TBR and CNR evaluations confirmed our simulation findings, and suggested presence of non-negligible $k_{\text{loss}}$ reversibility in clinical data. As such, we recommend gPatlak for highly quantitative imaging tasks, while, for tasks emphasizing lesion detectability (e.g. TBR, CNR) over quantification, or for high levels of noise, hPatlak is instead preferred. Finally, gPatlak and hPatlak CNR was systematically higher compared to routine SUV values.

Keywords: Patlak, whole-body, generalized, PET, quantification, detectability, parametric

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

1. Introduction


Nevertheless, dynamic PET acquisitions have been primarily constrained to single-bed axial field-of-views (FOVs), due to preference for continuous temporal sampling of the FOV (Torizuka et al 1995, 2000). Thus, dynamic PET has been mainly associated with oncology studies, involving specific tumor types, as well as cardiac or neurological PET studies, where single-bed acquisitions are adequate (Jagust et al 1991, Lortie et al 2007). As a result, dynamic PET has not yet been translated into clinical routine, where whole-body (WB) acquisitions are important. In particular, oncology would appreciate the enhanced quantification across WB FOVs, as the likelihood for metastases from the primary tumor location to other regions dictates multi-bed diagnostic evaluations (Wahl and Buchanan 2002).

On the other hand, single-frame (i.e. static) WB PET imaging, relying on the standardized uptake value (SUV) metric, has been established in routine clinical practice, mainly because of the simplicity of WB PET scan protocols, its sufficient test-retest repeatability and extensively validated clinical utility (Kubota et al 1985, Wahl and Buchanan 2002, Thie 2004). At the same time, SUV can be considered as a semi-quantitative metric, since it does not account for tracer concentration in blood (input function) and largely depends on the post-injection scan time and the current metabolic status of each patient (Keyes 1995, Huang 2000, Paquet et al 2004, Thie 2004, Durand and Besson 2015). As a result, SUV PET evaluations and treatment response assessments may suffer from poor accuracy (Hoekstra et al 2000, 2002, Adams et al 2010, Boellaard 2011, de Langen et al 2012). A number of studies have
attempted to partially overcome these limitations by employing either (i) delayed or dual-time point WB SUV PET imaging (Hustinx et al. 1999, Nakamoto et al. 2000, Kubota et al. 2001, Zhuang et al. 2001, Matthies et al. 2002, Nishiyama et al. 2006), (ii) various normalization factors for SUV, such as patient weight, lean body mass and body surface area (Zasadny and Wahl 1993, Kim et al. 1994) or (iii) simplified kinetic analysis (SKA) methods over regions-of-interest (ROIs) (Hunter et al. 1996, Sadato et al. 1998, Graham et al. 2000, Freedman et al. 2003, Sundaram et al. 2004). Nevertheless, all methods above heavily rely on very specific assumptions to retain simplicity for clinical protocols. Examples include assumption of the time integral of input function as being proportional to injected dose divided by lean body mass, or that the proportion of non-phosphorylated to phosphorylated FDG is minimal at time of imaging, which may not be valid, compromising the accuracy of these methods (Freedman et al. 2003, Sundaram et al. 2004).

Recently, we proposed a PET acquisition and imaging framework enabling clinically feasible WB dynamic PET imaging, thus combining the benefits of multi-bed FOVs with the ability to obtain images of Patlak kinetic macro-parameters (Karakatsanis et al. 2013a, 2013c). Quantitative analysis demonstrated enhanced tumor detectability over SUV in regions exhibiting high background signal, such as the liver. In this framework, the standard Patlak (sPatlak) linear graphical analysis had been selected as a robust modeling approach to directly estimate, from the reconstructed dynamic WB PET images, the tracer influx or uptake rate constant $K_i$ and blood distribution volume $V$ (Patlak et al. 1983).

The sPatlak graphical analysis method arrives at a linear model equation only when an irreversible 2-tissue compartment tracer kinetic model is assumed, a common model for fluoro-deoxyglucose (FDG) tracer in human organs and tumors (Phelps et al. 1979, Patlak et al. 1983, Kelloff et al. 2005). However, a number of studies have reported clinical kinetic parameter values suggesting a non-negligible degree of apparent FDG uptake reversibility, or dephosphorylation, for many normal organs such as the liver, brain and lung as well as for tumors (Anchors et al. 1977, Gallagher et al. 1978, Phelps et al. 1979, Huang et al. 1980, Messa et al. 1992, Okazumi et al. 1992, 2009, Nelson et al. 1996, Delbeke 1999, Zhuang et al. 2001, Dimitrakopoulou-Strauss et al. 2006, Grytz et al. 2006). As the sPatlak model inherently assumes irreversibility, it is forced to underestimate $K_i$ in regions where a non-negligible underlying reversibility truly exists, to explain the progressive loss of the signal portion originating from the erroneously assumed ‘irreversible’ compartment (Patlak et al. 1983, Patlak and Blasberg 1985). Consequently, when reversibility is neglected from model assumptions, the quantitative accuracy of $K_i$ images may be compromised in certain regions, with negative implications for highly quantitative imaging tasks, such as treatment response monitoring for prognostic or theranostic purposes.

On the other hand, a reversible 2-tissue compartment kinetic model can properly account for underlying tracer dephosphorylation. Thus, an extended version of the sPatlak model, accepting the possibility of relatively small uptake reversibility, could enhance its accuracy by attributing the observed progressive signal intensity loss to an additional kinetic parameter rate constant: the tracer efflux rate constant. In fact, the theoretically expected $K_i$ underestimation, when an irreversible compartment replaces a reversible one, has been also confirmed by a number of clinical dynamic PET studies, thus further suggesting the possibility for underlying FDG uptake reversibility in certain normal organs and tumors (Lammertsma et al. 1987, Messa et al. 1992, Choi et al. 1994, Hasselbalch et al. 2001, Graham et al. 2002, Wu et al. 2003, Hoh et al. 2011, Sayre et al. 2011).

Lin et al 2005, Prytz et al 2006), certain tumor types with non-negligible reversibility have been reported, such as in the case of hepatocellular carcinomas (HCC) tumors (Messa et al 1992, Torizuka et al 1995). As a result, $K_i$ estimates may be under- or even over-estimated and in various degrees at the target and background regions, depending on the presence (or not) of reversible kinetics in each region, thus affecting not only image quantification but also tumor-to-background contrast, potentially compromising tumor detectability as well. Moreover, as many normal tissues across the body reportedly exhibit some degree of reversibility, the likelihood of erroneous $K_i$ quantification within PET FOV becomes higher with multi-bed acquisitions. Consequently, the need to include reversibility in the kinetic model analysis becomes even more evident in WB PET parametric imaging applications.

Therefore, in this study, we propose a novel generalized Patlak (gPatlak) multi-bed framework to enhance quantitative WB PET imaging including in regions exhibiting non-negligible uptake reversibility. We focus on oncology applications when the imaging task involves tumor detection and staging or treatment response assessments, but our findings could also apply to other tasks, such as quantitative PET-based differentiation of malignant versus benign tumors and WB imaging of inflammation, infection, etc. (Hübner et al 1996, Dimitrakopoulou-Strauss et al 2002, Basu and Alavi 2007, Sanz and Fayad 2008, Choi et al 2013, Oo et al 2013). In addition, we currently evaluate our proposed method for $^{18}$F-FDG, the most common PET oncological radiotracer with well-modeled kinetics for a range of normal tissues and tumor regions across the human body (Phelps et al 1979, Hustinx et al 2002), though this approach could also apply to different radiotracers as well, such as $^{18}$F-FLT (Been et al 2004), $^{18}$F-FMISO (Thorwarth et al 2005), $^{18}$F-Fluoride (Grant et al 2008, Siddique et al 2011, 2012, 2014), $^{18}$F-Choline (Husarik et al 2008) and others (Groves et al 2007).

The extended Patlak method, originally proposed as theory and for region-based analysis by Patlak and Blasberg (1985), is equipped with an additional net efflux rate constant, $k_{\text{loss}}$, to properly account for tracer net uptake reversibility from the trapping or metabolic tissue compartment to the blood plasma. In fact, this model has been previously used in few PET studies involving FDG (Lodge et al 1999), $^{18}$F-Fluorodopa brain (Holden et al 1997, Doudet et al 1998, Sossi et al 2001) as well as $^{18}$F-Fluoride bone imaging (Siddique et al 2014) but only for ROI-based analysis and limited to a single bed.

In the present study, for the first time to our knowledge, an extended gPatlak method is implemented and assessed: (1) in the context of parametric imaging, i.e. involving kinetic parameters estimation at the voxel level, and (2) for WB dynamic acquisitions. The presented framework, also includes application of the basis function method (BFM) to effectively linearize the parameter estimation process in a computationally efficient algorithm (Gunn et al 1997). In addition, a hybrid parametric imaging method (hPatlak) is proposed which selectively applies either standard or generalized Patlak method at each voxel, according to a Patlak correlation-based binary classification scheme, to enhance tumor contrast-to-noise ratio (CNR) and detectability in $K_i$ images at the cost of quantification compared to gPatlak.

2. Materials and methods

2.1. Generalized Patlak graphical analysis

The linear Patlak model utilizes dynamic PET image data and the time course of blood plasma tracer concentration (input function) to estimate through linear regression the kinetic macro-parameters of tracer net influx rate constant $K_i$ and the total blood distribution volume $V$ at each voxel employing the following model equation (Patlak et al 1983):

\[ \frac{d}{dt} [18F] = K_i [18F]_i - k_{\text{loss}} [18F]_i, \]

\[ V = \int [18F]_i dt, \]

\[ K_i = \frac{V}{[18F]_i}, \]

where \([18F]_i\) is the input function (blood plasma concentration), \([18F]_i\) is the tracer concentration in the tissue, and \(k_{\text{loss}}\) is the net efflux rate constant.
where $C(t)$ is the measured time activity curve (TAC) at each voxel, $C_p(t)$ is the blood plasma TAC or input function estimated either from an image ROI or from blood sampling, $t_n$ with $n = 1 \ldots N$ denote the mid-time points for the $N$ dynamic PET frames/measurements and $t^*$ is the time after which relative kinetic equilibrium between the blood and the reversible compartment is attained. The standard Patlak equation describes the linear relationship between (i) the ratio of the measured tissue $C(t)$ to the plasma $C_p(t)$ activity concentration and (ii) the ratio of the running time integral of the plasma TAC to the plasma TAC, the latter also denoted as ‘normalized’ or ‘stretched’ time (Holden et al 1997).

Later, Patlak and Blasberg (1985) introduced an extended and more general graphical analysis model to account for potential reversible uptake rate. Thus, an additional kinetic parameter was introduced, here denoted as $k_{loss}$, to describe the net rate constant for metabolized tracer loss to the blood plasma (net efflux rate constant). By assuming $k_{loss} \ll K_i$ the following non-linear Patlak equation can be obtained for the kinetic analysis of $m$ dynamic frames:

$$C(t_n) = K_i \int_0^{t_n} e^{-k_{loss}t_n} \frac{C_p(\tau)}{C_p(t_n)} d\tau + V, \quad t_n > t^*, \quad n = 1 \ldots N$$

where $K_i = K_3/k_2 + k_3$ and $k_{loss} = k_2k_3/(k_2 + k_3)$ as defined by Patlak and Blasberg (1985).

As the newly introduced $k_{loss}$ parameter is included in an exponential term, the kinetic parameter estimation problem now becomes non-linear. As it will be demonstrated later, the accuracy of the two Patlak models depends on the ratio of $k_{loss}/K_i$. Sossi et al (2001) in particular also studied, in the case of region-based 18F-fluorodopa brain PET tracer kinetic analysis for Parkinson’s disease evaluations, the effect of this ratio, which they term as ‘effective dopamine turnover’ (EDT).

The standard Patlak model assumes a 2-tissue compartment model involving 3 parameter rate constants ($K_i, k_2$ and $k_3$) with the second compartment considered irreversible, i.e. $k_4 = 0$ (figure 1(a)). The measured tracer tissue concentration $C(t)$ is defined as the sum of the extravascular $C_e(t)$ and the metabolized $C_m(t)$ tracer tissue concentrations. By reformulating equation (1) that:

$$C(t_n) = K_i \int_0^{t_n} C_p(\tau) d\tau + V C_p(t_n) = K_i \otimes C_p(t_n) + V C_p(t_n), \quad t_n > t^*, \quad n = 1, \ldots, N$$

where $\otimes$ denotes the mathematical operation of single-dimensional (1D) convolution in the time domain.
On the other hand, the non-linear Patlak model assumes a two compartment kinetic model with a non-negative $k_4$ rate constant (figure 1, bottom left). Similarly, by restructuring equation (2) we have:

$$C(t_n) = K_i \int_0^{t_n} e^{-k_4d_{t_n}^-} C_P(t) d\tau + V C_P(t_n)$$

$$= (K_i e^{-k_4d_n}) \otimes C_P(t_n) + V C_P(t_n), \quad t_n > t^*, \quad n = 1, \ldots, N.$$

### 2.2. Whole-body non-linear parametric image estimation

In the case of the linear sPatlak model (equation (1) or (3)), the two parameters of interest, $K_i$ and $V$, can be estimated directly using the ordinary least squares (OLS) linear regression method. Let us consider the following sPatlak regression model:

$$\mathbf{Y}^j = \mathbf{X}_j \mathbf{\beta}^j + \mathbf{e}^j$$  (5a)

where:

$$\mathbf{Y}^j = \begin{bmatrix} C(t_1) & \cdots & C(t_N) \end{bmatrix}^T, \quad \mathbf{X}_j = \begin{bmatrix} \int_0^{t_1} C_P(t) d\tau & C_P(t_1) \\ \vdots & \vdots \\ \int_0^{t_N} C_P(t) d\tau & C_P(t_N) \end{bmatrix}, \quad \mathbf{\beta}^j = \begin{bmatrix} K_i^j & V^j \end{bmatrix}^T.$$

Note in equation (5a) that the input function measurements in standard Patlak model matrix $\mathbf{X}_j$ and the TACs column vector $\mathbf{Y}$ are linearly related with the unknown sPatlak kinetic macro-parameters $\mathbf{\beta}$ (slope $K_i$ and intercept $V$). This relationship can be expanded into the following set of sPatlak $N$ bilinear equations:

$$C(t_n) = K_i \int_0^{t_n} C_P(t) d\tau + V C_P(t_n) + \varepsilon_n, \quad t_n > t^*, \quad n = 1, \ldots, N.$$  (5b)

However, for the non-linear gPatlak model (equation (2) or (4)), we propose an efficient implementation of the basis function method (BFM) (Gunn et al 1997) as we have presented in a preliminary work (Karakatsanis et al 2013d). Initially, a pool of discrete candidate $k_{\text{loss}}$ values has to be determined. The range $[10^{-5}, 10^{-1}]$ of $M = 10^4$ candidate $k_{\text{loss}}$ values, in units of $s^{-1}$, is recommended, according to equation (7) and a wide collection of $k$-values, as reported in the literature (Okazumi et al 1992, 2009, Torizuka et al 1995, 2000, Dimitrakopoulou-Strauss et al 2006), a subset of which was later utilized to conduct simulations (table 1). Then a set of $M$ basis functions, each representing one of the $M$ candidate $k_{\text{loss}}$ values, is constructed to effectively linearize the non-linear parameters estimation problem:

$$\omega_m(t_n) = C_P(t_n) \otimes e^{-k_{\text{loss}}^m t_n}, \quad m = 1 \ldots M, \quad n = 1 \ldots N.$$  (6)

After replacing the exponential term in equation (4) with each of the $M$ basis functions (equation (6)), the following set of $M$ bilinear Patlak equations is constructed:

$$\mathbf{Y}^j = \mathbf{X}_m^j \mathbf{\beta}_m^j + \mathbf{e}_m^j, \quad m = 1 \ldots M.$$  (7a)

The definitions of the generalized Patlak model matrix $\mathbf{X}_m^j$ and the unknown kinetic macro-parameters vector $\mathbf{\beta}_m^j$ of Patlak slope $K_i^m$ and intercept $V^m$ depend, each time, on the currently selected $m$th basis function $\omega_m$ as follows:
Or, equivalently, we have $M$ different sets of equations, where each set is composed of $N$ bilinear Patlak formulas:

$$C(t_n) = K_i^{j,m} \omega_m(t_n) + V_i^{j,m} C_p(t_n) + \varepsilon_n, \quad t_n > t^*, \quad m = 1 \ldots M, \quad n = 1, \ldots, N.$$  \hspace{1cm} (7c)

Thus the original non-linear parameter estimation problem (equation (4)) has now been translated to a set of $n$ linear estimation problems (equation (7c)), as many as the initially selected number of basis functions or candidate $k_{loss}$ values. Therefore, the standard linear OLS regression can then be applied to each of the $n$ linearized Patlak equations in order to estimate the respective set of $K_i^{j,m}$ and $V_i^{j,m}$ parameters for the selected $k_{loss}^{j,m}$ value. Subsequently, the corresponding residual sum of squared error $RSS_{j,m}$ between our measurements $Y$ and our estimates $\hat{Y}_j = X \hat{\beta}_j$ is calculated:

$$RSS_{j,m} = (Y - X \hat{\beta}_j) \hat{\beta}_j^T, \quad \hat{\beta}_j = [K_i^{j,m} \ V_i^{j,m}]^T.$$  \hspace{1cm} (8)

The paired set of estimated parameters $\hat{\beta}_j^{i,m}$ and $k_{loss}^{j,m}$ for which the minimum $RSS_{j,m}$, for a fixed $j$th voxel over all $M$ RSS scores, was observed, is finally selected as the final BFM parametric estimate:

$$\hat{\beta}_{BFM} = \{\hat{\beta}_j^{i,m}, k_{loss}^{j,m}\}, \quad m_{opt} = \arg \min_m \{RSS_{j,m}\},$$

$$\hat{\beta}_j^{i,m}_{opt} = [K_i^{j,m}_{opt} \ V_i^{j,m}_{opt}]^T.$$  \hspace{1cm} (9)

By repeating the BFM estimation algorithm for each voxel, a set of $K_i$, $k_{loss}$, and $V$ parametric images can be produced in the end.

### 2.3. Hybrid generalized Patlak imaging

Multi-bed dynamic PET acquisition involves short frames (e.g. 45 s/bed in this study) non-continuously acquired over time at each bed position and with relatively large time gaps between the frames, thus tending to enhance noise levels compared to single-bed dynamic protocols. In addition, gPatlak method is non-linear involving three parameters as opposed to two for the linear sPatlak. As a result, noise may be considerable for gPatlak, though it is still expected to be lower than for full compartmental kinetic analysis (Carson et al 2005). For that
reason, although gPatlak might enhance $K_i$ estimates at the tumor ROIs, the respective (tumor-to-background) contrast to (background) noise ratio (CNR) metric, an important detectability index, may not be similarly enhanced, due to noise elevation at the background. Therefore, in this work we also propose a novel hybrid parametric imaging method, namely hybrid Patlak (hPatlak), involving the selective application of either sPatlak or gPatlak analysis at every voxel, aiming for higher $K_i$ CNR scores than those achieved by gPatlak or sPatlak alone, by exploiting the expected higher tumor contrast of the former and the low background noise of the latter within the same analysis framework. Consequently, hPatlak is not expected to be as quantitative as gPatlak, although it is more accurate than sPatlak. Our main motivation with hPatlak is to provide a complimentary method that would improve tumor detectability by targeting enhancement of tumor CNR scores.

The selection of the applied Patlak method at each voxel is based on the quantitative criterion of weighted Patlak correlation-coefficient WR, an index of the degree of linear correlation between the dynamic PET measurements and the sPatlak assumptions. By considering the sPatlak analysis, equation (1) can be rewritten, for a given dynamic frame $n$, as follows:

$$y_n = K_i x_n + V, \quad y_n = \frac{C(t_n)}{C_p(t_n)}, \quad x_n = \int_0^{t_n} \frac{C_p(\tau)d\tau}{C_p(t_n)}, \quad n = 1 \ldots N.$$ (10)

Then the weighted voxel-wise Patlak correlation coefficient WR can be calculated as follows [16]:

$$WR = \frac{\sum_n w_n \sum_n w_n x_n y_n - \sum_n w_n x_n \sum_n w_n y_n}{\left[\sum_n w_n \sum_n w_n x_n^2 - \left(\sum_n w_n x_n\right)^2\right]^{1/2} / \left[\sum_n w_n \sum_n w_n y_n^2 - \left(\sum_n w_n y_n\right)^2\right]^{1/2}},$$ (11)

The weights are defined as a function of the time duration $\Delta t_n$ and sinogram total counts $c_n$ in frame $n$:

$$w_n = \frac{(\Delta t_n)^2}{c_n}, \quad \Delta t_n \overset{\text{def}}{=} t_n^{\text{end}} - t_n^{\text{start}}, \quad n = 1 \ldots N.$$ 

After repeating the previous Patlak correlation calculations for every voxel TAC, a weighted Patlak correlation image (WR-image) can be generated from the acquired set of dynamic PET images.

The WR correlation metric essentially quantifies how well correlated each measured voxel TAC is with the sPatlak assumptions. In a hypothetical noise-free scenario, all measured voxel TACs would highly correlate with sPatlak model assumptions, regardless of the presence of uptake reversibility. Also, WR would approach unity in all voxel regions where underlying $k_{os}$ is nearly zero. However, in real dynamic PET scans, particularly when extended to the WB, noise can be considerably high, due to the short frames and the sparse temporal sampling at each bed. As the noise increases, WR is expected to drop in values. Thus, it is reasonable to expect that regions of lower uptake and, therefore, higher noise, such as most of the background normal tissue regions, will exhibit lower Patlak correlation coefficients, while regions of higher uptake and therefore better count statistics and lower noise, such as myocardium and most of suspected tumors, will be associated with relatively higher correlation coefficients. In fact, we have systematically observed that high Patlak correlation clusters are likely associated with voxel TACs of low noise, usually corresponding to tumors or high uptake regions, while low Patlak correlation cluster often
characterizes voxel TACs in regions of low uptake, such as in tumor background (Zasadny and Wahl 1996, Karakatsanis et al 2013a, 2013d). In addition, WR correlation may be also diminished for voxel TACs affected by bulk body motion across the different WB dynamic frames.

As a result, the proposed WR correlation-coefficient metric may act as an effective binary classification method between regions of low and high levels of noise or motion contamination. This feature can be utilized to selectively apply the less precise but more accurate non-linear BFM gPatlak parameter estimation method only to the highly correlated and statistically more reliable voxel TACs. By contrast, the more robust but potentially not as accurate sPatlak method can be selected for the remaining less correlated voxel TACs. An extra degree of freedom is introduced with the proposed hPatlak regression method thanks to the role of WR threshold, a free parameter quantitatively determining the level of Patlak correlation above which a voxel TAC can be characterized as of high correlation. Based on our clinical findings, we propose an initial range of possible WR threshold values between 0.75 and 0.98.

Initially, a user-defined correlation threshold is picked to classify the voxels of the WR-image into 2 clusters of relatively high (hWR cluster) and low (lWR cluster) Patlak correlation. Subsequently, gPatlak is assumed for the hWR voxel TACs, while sPatlak is used for the IWR voxel TACs. Non-linear BFM is employed for the estimation of the $K_i$, $k_{loss}$ and $V$ parameters in the hWR cluster, while OLS is applied for $K_i$ and $V$ parameter estimation in the IWR cluster. Thus, the $k_{loss}$ parameter is assumed to be zero for the IWR voxels. In the end, a set of hybrid $K_i$, $k_{loss}$ and $V$ parametric images is created. A flow chart illustrating the principal steps of the proposed hybrid parametric imaging method is presented in figure 2.

Obviously, hPatlak images will depend on the selection of the WR threshold. Therefore, for the clinical routine application of hPatlak through an image analysis software, we suggest performing this method for a predetermined number of WR thresholds, within our recommended range of [0.75 0.98]. Then, a sliding bar interface can be provided to enable online inspection of the corresponding hPatlak images while sliding over the predetermined WR threshold values. Thus, users may instantly visualize the effect of WR threshold on the hPatlak $K_i$ images over a range of correlation-coefficients and select the most appropriate threshold for the targeted imaging task. The extra computational cost of such type of analysis is negligible, as hPatlak images can be readily synthesized from the generated gPatlak and sPatlak images.

2.4. Simulation and clinical studies

2.4.1. Dynamic multi-bed acquisition. In both simulations and clinical studies, a previously validated dynamic multi-bed PET acquisition protocol was employed, after being optimized for clinically feasible acquisitions (Karakatsanis et al 2011) and according to the system specifications of current commercial clinical PET/CT scanners. The protocol consists of:

(i) an initial single-bed dynamic scan over the heart to acquire the initial phase (first 6-min post-injection) of the input function, followed by
(ii) a sequence of 6 WB passes, corresponding to a total time window of 10-45 min post-injection.

All bed positions were scanned in step-and-shoot mode for 45 s/bed to ensure enough counts per dynamic frame while allowing for a sufficient number of 6 passes in the clinically available time window (10-45 min post-injection) before the SUV static PET WB scan (figure 3).

In addition, two commercially available clinical PET/CT scanners were used for performance evaluation of the proposed method on clinical WB dynamic data. Initially, the GE Discovery RX scanner was utilized where the optimization of the acquisition protocol had been performed (Karakatsanis et al 2011), while later the more recent Siemens Biograph mCT scanner was employed to assess the performance of the proposed methods on a state-of-the-art
clinical PET/CT scanner with time-of-flight (TOF) and point-spread-function (PSF) resolution modeling capabilities (Jakoby et al 2011). A preliminary evaluation study of the benefits of TOF and PSF features in WB parametric PET imaging are presented here (Karakatsanis et al 2014b). The same acquisition protocol was applied for both scanners, to ensure a common ground when comparing the results.

2.4.2. Generation of simulated data. An extensive literature review was conducted to collect a characteristic set of FDG $k$-values (table 1) (Okazumi et al 1992, 2009, Torizuka et al 1995, 2000, Dimitrakopoulou-Strauss et al 2006). The kinetic data were used together with a 2-compartment 4-parameter kinetic model (figure 1(c)) and the Feng input function model (Feng et al 1993) to generate realistic noise-free TACs (figure 4(a)), that were later assigned to the XCAT phantom (figure 4(b)). Then, lung and liver spherical tumors of 15 mm and 10 mm in diameter were placed within the normal XCAT organs of lung and liver respectively. Table 1 includes a wide range of $k$-micro parameter values corresponding to a $k_{loss}$ range from zero or negligible up to very high values, i.e. comparable to $K_i$. We chose to evaluate such a wide range of FDG kinetics in order to validate the proposed gPatlak method under all potential clinical scenarios. We should also note that the very high $k_4$ and respective $k_{loss}$ values were considerably less frequent in the literature.

The resulting dynamic XCAT bed frames were used as input to perform analytic 4D simulations, using STIR open-source package, with realistic levels of Poisson noise determined by the number of counts per frame, as calculated based on the reported sensitivity of the mCT scanner, the 3D acquisition properties (e.g. max. ring difference and span factor), the injected activity, the FDG tracer decay and the time duration of each frame (Thielemans et al 2012). A total of $n = 15$ Poisson noise realizations were produced. Subsequently, the generated 4D simulated data were reconstructed with the ML-EM iterative reconstruction algorithm as implemented within the OS-MAP-OSL application of STIR reconstruction suite (Thielemans

![Flow chart illustrates the WR-based hPatlak imaging method. In the WR image, all voxels have been assigned either to the hWR (white) or IWR (black) cluster, according to their calculated WR coefficient value and a user-selected WR threshold (0.95 in this case). The depicted WR image classification may considerably change for different WR thresholds and patients but hWR cluster usually tends to include the high focal uptake regions.](image)
Final the dynamic reconstructed PET images from various iteration steps and all noise realizations were analyzed according to sPatlak, gPatlak and hPatlak methods to produce respective WB $K_i$ images. The generated images were then quantitatively analyzed in terms of noise versus bias, tumor-to-background (TBR) contrast and CNR performance at selected lung and liver tumor ROIs.

2.4.3. Clinical studies. In addition, the clinical performance of the proposed gPatlak and hPatlak WB $K_i$ imaging methods was evaluated for a set of $n = 11$ WB patient dynamic PET studies, of which the first six were obtained on the GE Discovery RX PET/CT scanner while the last five were acquired on the state-of-the-art Siemens Biograph mCT TOF PET/CT scanner, both installed at the Johns Hopkins PET center. In all clinical cases, the optimized WB dynamic acquisition protocol of figure 3 has been applied. The utilization of two widely
applicable modern clinical PET/CT scanners and the acquisition of oncology patient data allowed us to validate the proposed methods under a broad range of acquisition conditions often present in PET imaging centers nowadays.

3. Results

3.1. Tracer kinetic simulation studies

Figure 5(a) shows, on the left, the true $K_i$ image from a cardiac bed FOV, as constructed by directly assigning the true $K_i$ values, calculated from the $k$-micro-parameters of table 1 and equation (6), to the respective ROIs of normal organs (including liver, lung and myocardium) and tumor types A and B of 15 mm (A1, B1) and 10 mm (A2, B2) diameter respectively.

The central and right images of figure 5(a) represent the estimated sPatlak and gPatlak $K_i$ cardiac images, as derived by application of the respective Patlak model on 6 noise-free dynamic PET cardiac frames, acquired at exactly the time frames corresponding to our proposed WB dynamic PET scan protocol (figure 3). By visual comparison of sPatlak and gPatlak with respect to true $K_i$ image, significant underestimation (bias) in the normal liver and tumor ROIs B1 and B2 is evident for sPatlak, while gPatlak nearly eliminates bias. As the data are noise-free, underestimation of $K_i$ can be attributed to model-related factors and, in particular, the erroneous sPatlak assumption for zero $k_{loss}$ while, in fact it had been simulated as positive for those two particular ROIs. On the contrary, gPatlak method is able to estimate $K_i$ with a considerably smaller bias after accounting for the underlying presence of non-zero $k_{loss}$.

Moreover, we plot in figure 5(b) the Feng input function model (Feng et al 1993) and the simulated noise-free FDG TACs for B2 tumor. Due to a non-negligible simulated $k_{loss}$ value, with respect to $K_i$, B2 tumor TAC is reduced at later times.

Then, we present in figure 5(c) two groups of noise-free Patlak plots, as derived from simulated tumor B2 kinetics employing either sPatlak or gPatlak graphical analysis. The true $k$-values from table 1 are used as simulations input. For each method, the modeled (true) and ROI-based Patlak curves are plotted. The former is calculated from Patlak analysis on TACs...
directly modeled from the true $k$-values after convolving with the Feng input function model, while the latter is derived from ROI-based Patlak analysis on noise-free reconstructed images (ML-EM, 5 iterations), thus suffering from partial volume error (PVE) effect. All 4 Patlak curves are plotted in the same diagram, as gPatlak definition for stretched time variable in horizontal axis applies for sPatlak model too, assuming zero $k$ loss in that case. By comparing the true and ROI-based plots for each model, an underestimation of the curves slope ($K_i$) is observed for the latter, which is attributed to PVE, an effect inherent in the tomographic reconstruction process, particularly for smaller tumors (such as B2).

In addition, the modeled (true) data, when plotted in the Patlak diagram assuming zero $k_{loss}$, are not forming straight lines, as would have been expected by sPatlak, but instead exhibit a curvature (negative second derivative), resulting in OLS-fitted straight lines of reduced slope (first derivative), thus underestimating $K_i$. On the other hand, after accounting for true $k_{loss}$, the same data are aligned to form a nearly straight line. As a result, the OLS-fitted straight

**Figure 5.** (a) Simulated Patlak $K_i$ images of a cardiac XCAT bed, where 2 sets of spherical homogeneous tumor ROIs are identified: A1 (large), A2 (small) and B1 (large), B2 (small). Same underlying (true) kinetics were originally assigned between A1 and A2 ROIs (type A kinetics) and between B1 and B2 ROIs (type B kinetics) of the true PET frames. True $K_i$ image was derived from direct assignment of true $K_i$ values, while sPatlak and gPatlak noise-free $K_i$ images were generated with sPatlak- OLS and gPatlak-BFM analysis, respectively, on 6 noise-free PET frames. (b) Noise-free simulated input function and tumor ROI B1 or B2 TACs (same kinetics assigned to B1 and B2), as generated using the 2 compartment model (figure 1(c)), demonstrating decrease of activity at later times, due to underlying $k_{loss}$ reversibility. (c) Noise-free plots for sPatlak and gPatlak models after analyzing simulated tumor ROI B2 TAC, either directly modeled from $k$-values or extracted from B2 ROI on reconstructed dynamic PET images. The reduced slope of sPatlak and gPatlak plots for the B2 ROI extracted data, with respect to modeled B2 TAC case, is attributed to the partial volume error for the small B2 tumor.
line is then associated with a relatively increased slope or $K_i$. The same effect between the two models was also observed for the ROI-based analysis.

Since sPatlak plot assumes $k_{\text{loss}} = 0$ (equation (1)) while in fact simulation input involves positive $k_{\text{loss}}$ (B2 tumor true $k_{\text{loss}} = 0.0086$), sPatlak is consequently overestimating the stretched time (horizontal axis variable) for a given ratio of tissue to plasma signal (vertical axis variable). On the other hand, gPatlak recovers the expected linear relationship in the Patlak plot by correcting for the loss of metabolized tracer after multiplying the stretched time with the term $\exp(-k_{\text{loss}} t)$ (equation (2)). In figure 5(c), the negative curvature of Patlak plot for standard model, as well as its linearization when gPatlak assumptions are utilized, provide intuitive graphical illustrations for the actual causes of sPatlak $K_i$ underestimation and the correcting effect of gPatlak.

The % error (bias) quantitative analysis on the noise-free dynamic data for $K_i$ and $k_{\text{loss}}$ estimates is presented in figures 5 and 6, respectively. The plots suggest a considerable reduction of % bias for both parameters and for a large range of $k_{\text{loss}}/K_i$ ratios when gPatlak replaces sPatlak method. However, our results also confirm the limitations of gPatlak accuracy when true $k_{\text{loss}}$ becomes too high, i.e. comparable to $K_i$, as also expected from the theory (Patlak and Blasberg 1985). In particular, in figure 6(a), the % bias is equally zero for both models when underlying $k_{\text{loss}} = 0$, irrespective of $k_3$ or $K_i$, as expected from equations (1) and (3) too. However, as true $k_{\text{loss}}$ increases (assuming only $k_4$ increases, with the rest of the parameters constant) sPatlak $K_i$ % bias increases dramatically, while for gPatlak it does not exceed 5%, for small $k_{\text{loss}}$ values. In addition, a further decrease of $k_3$, such that $0 < k_{\text{loss}}/K_i < 2$, assuming $K_1$ and $k_2$ constant, causes an additional but relatively milder increase of $K_i$ % bias which however never exceeds 10% for gPatlak. It should be noted that, based on our collection of FDG tracer $k$-values from literature, the range of $k_{\text{loss}}$ and $K_i$ is always such that $0 < k_{\text{loss}}/K_i < 1.5$ with ratio values higher than 1 rarely observed in real data. In this study, we initialized our investigation with a set of $k$-values from literature and then carefully expanded our search space to more extreme cases such that $0 < k_{\text{loss}}/K_i < 2$. This allowed us to validate gPatlak $K_i$ bias in extreme cases, i.e. when $k_{\text{loss}}$ is comparable to $K_i$, in the absence of noise.

The previous $K_i$ % bias analysis for the same tumor region was repeated for a 30–90 min post-injection (p.i.) acquisition time window (figure 6(b)) confirming our conclusions above. However, the observed sPatlak $K_i$ % bias for the 30–90 min protocol is relatively larger than for 0–45 min window. On the other hand, gPatlak $K_i$ % bias is consistently low, irrespective of the acquisition time window, demonstrating the quantitative significance of gPatlak when (a) dynamic acquisitions last longer, as is inherently the case with WB dynamic protocols, or (b) they are delayed to include the time window of static SUV PET scans (60–80 min p.i.), as we recently proposed for combined SUV/Patlak imaging (Karakatsanis et al 2015).

A similar % bias analysis for noise-free simulated data was repeated for the $k_{\text{loss}}$ parameter as well. Figure 7(a) shows a very good correlation between the estimated noise-free $k_{\text{loss}}$ and the true $k_{\text{loss}}$ value, as the latter increases, for a range of true $k_{\text{loss}}$ values commonly found in the literature ($0 < k_{\text{loss}} < 0.04$). The % $k_{\text{loss}}$ bias was evaluated with respect to $k_{\text{loss}}/K_i$ ratio, assuming $K_1$, $k_2$ and $K_3$ constant for each error plot and only decreasing $k_3$ between different plots. As figure 7(b) illustrates, $k_{\text{loss}}$ % bias never exceeds 10% for $0 < k_{\text{loss}}/K_i < 1$. The same $k$-values search space as for $K_i$ bias analysis has been used here too.

### 3.2. Realistic 4D tomographic simulations

The resulting $K_i$ images from the sPatlak, gPatlak and hPatlak analysis of the reconstructed noisy simulated data are presented in figure 8(a) along with the quantitative noise versus bias analysis over 4 tumor ROIs: A1, A2, B1 and B2 in figures 8(b)–(e) respectively. For
the hPatlak method, 4 different WR thresholds were evaluated starting from 0.8 up to 0.95 with a step of 0.5. In this simulation study, we considered the cardiac bed sufficient as it includes in its FOV both the left-ventricle blood pool region, from which the input function is extracted, as well as all major tissue regions referred in table 1. Besides, all particularities of WB dynamic acquisitions were retained in our simulation study, as the data were acquired at exactly the times corresponding to our multi-bed dynamic PET acquisition protocol (figure 3).

By visual inspection of \( K_i \) images in figure 8, the simulated tumor regions B1 and B2 with non-negligible underlying \( k_{\text{loss}} \), are becoming less visible as we move from left (gPatlak) to right (sPatlak) through the intermediate (hPatlak) images. Meanwhile, visual detectability of tumors A1 and A2 is not significantly affected, since true \( k_{\text{loss}} \) is very small in their case. Moreover, the spatial image noise in the background regions is also gradually decreased along the same direction.
The above qualitative evaluations are also confirmed from the subsequent noise versus bias quantitative analysis. The % bias is gradually increasing with WR thresholds from gPatlak to sPatlak. The most apparent bias enhancement is observed in the case of highly $k_{\text{loss}}$-reversible B1 and B2 tumors with a total increase of 20–40% from sPatlak to gPatlak, while the corresponding bias enhancement was only 16–18% in the case of A1 and A2 less $k_{\text{loss}}$-reversible tumors. Furthermore, the stronger PVE in smaller A2 and B2 regions results in relatively larger $K_i$ underestimation and thus % $K_i$ bias enhancement relative to A1 and B1 larger tumor regions. Finally the % noise, as evaluated across the 15 realizations, decreased gradually for hPatlak for higher WR threshold levels, with the total reduction being 10% from gPatlak to sPatlak.

In addition, in terms of TBR (figure 9) and CNR (figure 10) detectability metrics, hPatlak with a WR threshold of 0.95 consistently achieved the best scores, along all MLEM iteration steps evaluated. However, between gPatlak and sPatlak methods, the former method produced higher scores for tumors B1 and B2 while the latter performed better for tumors A1 and A2.
3.3. Clinical studies

The quantitative performance of the proposed Patlak imaging methods has also been demonstrated on $n=11$ WB dynamic patient datasets. From these collection, a total of 6 characteristic high uptake (foci) target and respective background ROIs were selected for quantitative analysis, of which the first 4 were extracted from GE RX cases (figures 11–13) while the last two from state-of-the-art Siemens Biograph mCT scans (figure 14) in order to evaluate performance for a range of clinical study set-ups. Except for the mCT patient case, where 2 ROIs were identified (foci 1 and 2 in the thorax, figure 14), for the GE RX cases 1 characteristic ROI has been evaluated for each patient.

Figures 11–14 illustrate, for four patient cases, the reconstructed dynamic PET frames along with the SUV image, as well as the corresponding $K_i$ images of six Patlak methods ($g_{\text{Patlak}}, h_{\text{Patlak}}$ of 4 different WR thresholds and $s_{\text{Patlak}}$) and the WR image. Moreover, the $K_i$ ROI mean values between all Patlak methods as well as the TBR and CNR scores between the Patlak and SUV images are also presented.

Overall the clinical data analysis agreed with our simulation findings regarding the TBR and CNR performance of the proposed methods. Thus, $h_{\text{Patlak}}$ with a 0.95 WR threshold was associated with the best TBR and CNR performance among all other methods, except from GE RX patient case #5 (figure 13(c)) where $g_{\text{Patlak}}$ achieved the best scores, possibly because of potentially high $k_{\text{loss}}$ presence at the particular patient ROI. Furthermore, SUV consistently provided lower TBR and CNR scores, except from mCT patient case #1, where it outperformed $g_{\text{Patlak}}$ CNR score, due to $g_{\text{Patlak}}$ higher noise levels.

In addition, $g_{\text{Patlak}}$ always provided the highest $K_i$ mean value among the presented Patlak methods, suggesting reduced bias after accounting for underlying $k_{\text{loss}}$ reversibility. However, since the ground truth is not known in clinical cases, a relatively higher $K_i$ mean value may not be necessarily associated with less bias. For instance, $K_i$ may be overestimated too in some cases, due to underlying kinetic heterogeneity within each voxel, as discussed later. Overall, any potential $K_i$ overestimation effects are expected to be at least partially counteracted by PVE-induced $K_i$ underestimation.

Figure 9. Simulation results: target-to-background ratio (TBR) as a function of MLEM iterations between $s_{\text{Patlak}}, g_{\text{Patlak}}$ and $h_{\text{Patlak}}$ (various WR thresholds) $K_i$ images for tumor ROIs: (a) A1, (b) A2, (c) B1 and (d) B2.
Figure 10. Simulation results: contrast-to-noise ratio (CNR) as a function of MLEM iterations between sPatlak, gPatlak and hPatlak (various WR thresholds) $K_i$ images for tumor ROIs: (a) A1, (b) A2, (c) B1 and (d) B2.

Figure 11. Clinical results: RX patient case #3, scanned on the GE Discovery RX, designated focal uptake ROI in the lung (a) 1st row: 6 WB dynamic PET passes (45 s/bed) timely-ordered from left to right and a WB static SUV PET image (5 min/bed) beginning 60 min post FDG injection, all reconstructed after 2 full OSEM iterations with 21 subsets, 2nd row (left-to-right): WB $K_i$ images derived with gPatlak, hPatlak of increasing WR thresholds and sPatlak methods, as well as a Patlak correlation-coefficient image thresholded at WR = 0.95 (white color assigned only to voxels with values $>=0.95$). Quantitative evaluation on the designated ROI of: (b) $K_i$ ROI mean value and (c) TBR and CNR over all 6 Patlak methods and the SUV image.
4. Discussion

4.1. Patlak graphical analysis as the method of choice for WB parametric PET imaging

The proposed gPatlak method retains, unlike full kinetic modeling, much of sPatlak robustness to high levels of noise (Graham et al 2000, Hoekstra et al 2002, Krak et al 2003, Tomasi...
et al 2012). Furthermore, in terms of quantitative accuracy performance, despite the gPatlak assumption for a small efflux ($k_{\text{loss}}$) relative to influx ($K_i$) rate constant (Patlak and Blasberg 1985), our results demonstrated that the relative noise-free gPatlak $K_i$ bias is limited to less than 10% in all cases for a wide set of true $k_{\text{loss}}$ values, ranging from zero up to extremely rare and high values (figure 6). In addition, its WB dynamic PET application remains clinically feasible because, unlike Logan graphical analysis method (Logan et al 1990), it only requires the time integral of the input function from time of injection and not that of every voxel TAC across the entire WB FOV. By contrast, Logan analysis additionally requires TACs for all voxels across the entire WB FOV from injection time, which can depict very rapid dynamics at early times. Application of Logan analysis is thus significantly more challenging in WB dynamic PET studies, because of the need to perform considerably faster passes which may result in significantly higher noise levels for the given sensitivity of clinical PET scanners. For instance, 10 s or less per frame at the beginning of conventional single-bed dynamic scans must now be allocated to 6 or more beds in WB mode, thus substantially limiting the scan time per bed). Moreover, the observed underestimation of the total tissue distribution volume (DV) after applying simple linear regression with Logan technique needs to be evaluated against alternative graphical analysis methods (Zhou et al 2009).

In addition, Patlak was also preferred in this study as it directly estimates $K_i$, $k_{\text{loss}}$ and $V$ estimates, a set of macro-parameters highly relevant with the metabolic state of normal and

Figure 14. Clinical results: mCT patient case #1, scanned on the Siemens Biograph mCT, two designated focal uptake ROIs in the thorax (a) same as figure 11, (b) same as figure 11 but for two target ROIs: ROI 1 and (c) ROI 2.
tumor tissues and therefore widely applicable for our target oncology application of dynamic whole-body FDG imaging (Castell and Cook 2008). At the same time, we acknowledge the importance of other physiologically relevant macro-parameters, such as the total tissue distribution volume quantifying the capacity of a tracer binding to tissue and directly estimated by Logan method. Thus, we currently examine the future prospect of frameworks supporting additional WB graphical and multi-graphical analysis (Zhou et al 2009, 2010).

On the contrary, full kinetic modeling may offer a potentially more detailed, though less robust, description to the above set of macro-parameters through the non-linear estimation of individual kinetic micro-parameters ($k_1$, $k_2$, $k_3$ and $k_4$) with minimum assumptions for the underlying 2-tissue compartment model (Zaidi et al 2006). Thus, $K_i$ could also be indirectly provided by these estimates but with significantly less robustness (Castell and Cook 2008). Finally, WB full kinetic modeling would have required finer temporal sampling for all voxel TACs across all beds from time of injection resulting in very high noise levels with current clinical PET scanner technology. Thus, the feasibility and future prospects of the less robust compartment model-based WB parametric PET imaging need to be studied separately.

4.2. Likelihood of tracer uptake reversibility between target and background regions

It has been reported that FDG $k_{loss}$ effects are more likely observed in normal tissues (background), mainly in the liver and kidney, and less often in suspected tumor or high uptake (target) regions (Messa et al 1992, Hawkins et al 1992b, Okazumi et al 1992, Graham et al 2000, Huang et al 2000, Zhuang et al 2001, Lin et al 2005, Qiao et al 2007). This finding may, at first thought, render $s$Patlak more desirable over $g$Patlak, because a potential $K_i$ underestimation only in the background and not the target regions, as expected in such a scenario, would actually further enhance TBR contrast and even potentially favor target CNR and detectability (Messa et al 1992, Okazumi et al 1992, Lin et al 2005). Therefore depending on the kinetic properties of the targeted ROI and its background, $s$Patlak may be preferred over $g$Patlak, e.g. when targeting regions with $a$ priori negligible $k_{loss}$ expectations or when the imaging task promotes detectability over quantification.

On the other hand, such potential TBR contrast enhancement may not be quantitative for tumor assessment in oncology, as it is triggered by the incidental underestimation of $K_i$ only in background normal tissues and not the respective target regions. In addition, the probability of $k_{loss}$ effect not being expressed in tumors versus in background can vary among different regions or different tumor types of the same region (Lin et al 2005). In fact, it has been shown that the probability for non-negligible $k_{loss}$ in targeted tumor regions cannot be excluded, as in the case of hepatocellular carcinoma (HCC) tumor types (Okazumi et al 1992, Lin et al 2005).

4.3. Tumor FDG dephosphorylation and kinetics heterogeneity

As discussed in sections 1 and 4.2, FDG dephosphorylation has been suggested by numerous PET studies mainly in normal healthy tissues, such as the liver, and less often, in tumor regions, such as the case of HCC liver tumors. By contrast, a limited number of dynamic brain PET studies have reported or referred to simulation results that point to considerable overestimation (up to 20%) of regional $K_i$ from kinetically heterogeneous regions, e.g. mixing of white and grey matter values in the same ROI, due to limited PET resolution and PVE (Schmidt et al 1991, 1992, Lucignani et al 1993, Vriens et al 2011).

That bias was observed when a 2-tissue compartment 4-parameter (4 K) kinetic model was applied, assuming a non-zero FDG dephosphorylation rate constant ($k_4$). However, the
reported bias was reduced when a 2-tissue 3-parameter (3 K) kinetic model was utilized instead, i.e. assuming zero $k_4$. Schmidt et al (1991, 1992) attributed this effect to the tendency of the 4 K model to compensate for the reduced true FDG phosphorylation ($k_3$) rate constant, caused by the mixture of heterogeneous kinetics in the same region, with $k_4$ overestimation, thus resulting in subsequent overestimation of $k_3$, $K_i$ and $k_{\text{loss}}$ parameters too. In the case of the 3 K model, this would not have been possible, as $k_4$ is forced to be zero. Thus, they concluded that the application of certain compartmental kinetic models, designed for physiologically homogeneous regions, on dynamic PET measurements extracted from heterogeneous regions may lead to erroneously overestimated $K_i$ and $k_{\text{loss}}$ regional estimates. Moreover, they conjectured that region-based kinetic analysis of dynamic brain FDG PET measurements cannot provide solid evidence of presence of true underlying FDG dephosphorylation, as non-zero $k_4$ estimates in specific regions may simply be the result of heterogeneity rather than actual dephosphorylation.

Although in this study we have only simulated physiologically homogeneous regions, there still remains the possibility for limited kinetic heterogeneity at the boundaries of the evaluated regions, especially in small tumors, due to PVE effects. In addition, the clinical data may also include suspected tumor regions with some heterogeneity. However, in all cases, our voxel-wise parametric estimation is expected to drastically limit this effect. When the input dynamic PET measurements are heterogeneous, the parameter estimation process may introduce bias in an attempt to explain heterogeneous input data, which are not expected by the model. An example of this effect could be the overestimation of $k_4$, as an attempt of the 4 K model to explain a heterogeneity-induced decrease of $k_3$ (Schmidt et al 1992). In this study, we employed voxel-wise parametric estimation to minimize inter-voxel kinetic cross-contaminations, and constrain any bias propagation between $K_i$ and $k_{\text{loss}}$. Nevertheless, there still remains a yet small but non-negligible probability for intra-voxel tissue kinetics heterogeneity, i.e. for each voxel TAC to be a weighted average, or mixture, of different kinetics in highly heterogeneous regions or at regional boundaries. However, our simulation results suggest that $K_i$ bias was consistently reduced in all regions, regardless of true underlying $k_{\text{loss}}$ effect, when gPatlak was applied. Thus, it is suggested that the positive effect in quantitative accuracy (bias) when accounting for non-zero $k_{\text{loss}}$ outperforms any potential negative effect of PVE-induced intra-voxel kinetic heterogeneities.

In addition, the findings of previous studies by Schmidt et al (1991, 1992) regarding heterogeneity-induced artificially non-zero $k_{\text{loss}}$ estimates, though valid and quite probable, do not necessarily exclude the probability for true underlying $k_{\text{loss}}$ effects as well, as many other studies have suggested (Messia et al 1992, Hawkins et al 1992b, Okazumi et al 1992, Graham et al 2000, Huang et al 2000, Zhuang et al 2001, Lin et al 2005). Moreover, we did not observe $K_i$ bias enhancement for any of the evaluated regions when $k_{\text{loss}}$ was assumed non-zero. In clinical results, $K_i$ estimates were systematically higher with gPatlak, an observation consistent with both theories. However, since the ground truth is not known in clinical data, it is not possible to conjecture if gPatlak relatively higher $K_i$ estimates suggest (i) bias enhancement, i.e. $K_i$ overestimation due to heterogeneity effects, or (ii) bias reduction, due to properly accounting for non-zero $k_{\text{loss}}$, or actually (iii) a combination of both effects.

Finally, as the previous studies have also reported, the utilization of the Patlak framework to robustly estimate $K_i$ and $k_{\text{loss}}$ macro-parameters, as opposed to application of fully compartmental kinetic analysis (3 K or 4 K models) for the individual estimation of $k_3$ and $k_4$ micro-parameters, may have also further reduced any potential negative tissue kinetics heterogeneity effects, as Patlak methods are considered less sensitive to kinetically heterogeneous data (Mori et al 1990, Schmidt et al 1992, Lucignani et al 1993).
4.4. Task-based recommendations for different WB Patlak methods

Having demonstrated the pros and cons of each method, in this section we provide our recommendations regarding the choice of the most appropriate Patlak method for the imaging task and underlying type of kinetics (e.g. different tracers and targets) expected in a clinical study (figure 15).

When the imaging task involves quantitative assessments and comparisons between different scans, such as in longitudinal studies or treatment response monitoring and follow-up tasks, the gPatlak method is recommended for enhanced quantification, unless there exist sufficient indications that the targeted regions exhibit negligible $k_{loss}$, in which case sPatlak is sufficient for robust parametric imaging. On the other hand, for imaging task prioritizing detectability hPatlak method is recommended, when no underlying kinetic information is known a priori, as it can potentially trigger higher TBR and CNR scores, provided the appropriate WR correlation threshold being selected. However, for target regions with expected negligible $k_{loss}$, we suggest the more robust sPatlak analysis for detectability tasks as well.

4.5. Generalized Patlak as a complementary framework to SUV and standard Patlak

Despite its quantitative limitations, WB static SUV imaging remains the most established PET imaging technique in the clinic. Thanks to its simplicity and routine clinical implementation, SUV imaging has allowed for the standardization of diagnostic and treatment response criteria in the clinic (Wahl et al 2009, Boellaard et al 2010). On the other hand, WB Patlak imaging methods, although potentially more accurate than SUV, are associated with higher complexity and noise levels. Yet, they are nowadays steadily gaining more attention, as emerging commercial PET technologies, such as continuous bed motion, time-of-flight and resolution modeling, help to overcome these challenges, paving the way towards their clinical adoption (Karakatsanis et al 2014b). Moreover, following sPatlak, the proposed gPatlak framework
can be easily applied as an additional kinetic analysis method, utilizing the same set of reconstructed images at a small computational cost.

Our primary aim here is the design of a clinically feasible multi-bed parametric PET imaging framework to enhance quantitative information content with respect to single-pass SUV imaging alone. At the same time, we recognize the important clinical value of the SUV metric as well, particularly in relation to the currently established SUV-based treatment response criteria. In this context, SUV and parametric PET imaging frameworks could efficiently complement each other. Currently, we are investigating clinically adoptable novel PET scan protocols that simultaneously enable WB SUV and Patlak imaging from a single acquisition performed over the conventional 60 min post-injection SUV time window (Karakatsanis et al 2015). This study aims to introduce additional WB Patlak imaging frameworks to enhance quantification or detectability with respect to more conventional Patlak schemes. In future work, a comparative clinical study between WB Patlak and SUV imaging method would be important so as to also assess the clinical potential of combined SUV/Patlak WB imaging.

4.6. Hybrid WB Patlak regression: pearls and pitfalls

The performance of hPatlak in enhancing suspected tumor ROI CNR and, thus, detectability, depends on the user-defined WR threshold level. A very large threshold, i.e. a value very close to unity, may substantially reduce background noise, but it may also exclude some tumor voxels from being accurately estimated with the gPatlak method, especially those situated at tumor boundaries, susceptible to PVE or at kinetically heterogeneous tumor sections. As a result, a high WR threshold is expected to reduce noise at the cost of quantification and contrast, with respect to pure gPatlak, while a low WR threshold may enhance quantification and contrast at the cost of additional noise, compared to sPatlak.

As hPatlak is targeting the enhancement of tumor detectability, a potential criterion for the choice of an appropriate WR threshold could have been the tumor CNR score either at a particular target tumor ROI or weighted averaged over a set of target ROIs, with the weights defined as the relative size, in number of voxels, of each ROI. On the other hand, CNR can be substantially different among patients or even between target ROIs of the same patient and, as such, we cannot recommend a data-independent globally optimal WR threshold. Alternatively, a data-driven algorithm could automatically select for every patient a WR threshold and respective \( K_i \) clinical image based on the highest evaluated CNR score for the target ROI or set of ROIs. In fact, other nuclear imaging studies have in the past followed similar CNR-based data-driven optimization schemes when designing reconstruction algorithms (Qi and Leahy 1999), imaging systems and scan protocols (Asma and Manjeshwar 2010, da Rocha Vaz Pato et al 2012).

However, since CNR scores may depend on the tumor and background ROI delineation techniques, CNR-based optimization should be exercised with care. Therefore, in this study we suggest not to necessarily optimize WR threshold based on CNR and, instead, to provide the users in the future with the flexibility to alter this parameter (analogously to sliding the color bar) for an enhanced perspective onto the suspected tumor of interest.

4.7. Future prospects

The present work has scope for significantly enhanced performance. Kinetic parameter estimation commonly involves two main steps: (i) image reconstruction of individual dynamic frames, followed by (ii) application of kinetic modeling to the resulting dynamic images.
This common process poses limitations due to the poor characterization of the complex noise distribution in the reconstructed images. On the contrary, direct 4D reconstruction schemes enable kinetic modeling within a comprehensive reconstruction framework, allowing accurate noise characterization directly in the projection-space (Tsoumpas et al 2008, Rahmim et al 2009, 2012, Tang et al 2010, Wang and Qi 2010, 2012, 2013). As such, 4D parametric reconstruction methods could be particularly important for gPatlak, where noise is relatively higher than sPatlak. By integrating the gPatlak model within 4D ML-EM reconstruction we expect Patlak images of both superior precision (low noise) and less noise-induced bias.

Previously, we confirmed the benefit of direct 4D reconstruction in limiting noise propagation in WB sPatlak imaging (Karakatsanis et al 2013b). However the convergence of the iterative algorithm can be very slow, due to the correlation between \( K_i \) and \( V \) estimates (Wang et al 2010). In addition, the non-linearity of gPatlak 4D reconstruction, which we are presently exploring, can further impact the convergence rates (Wang and Qi 2012, 2013). Therefore, we are investigating the utilization of optimization transfer methods to enable accelerated gPatlak 4D reconstruction (Karakatsanis et al 2014a).

5. Conclusion

In this work, we implemented and quantitatively assessed a family of WB parametric imaging methods, utilizing both simulated and clinical PET studies, as acquired with a clinically feasible multi-bed dynamic PET scan protocol. Specifically, we extended our standard WB Patlak (sPatlak) graphical analysis method to sufficiently account for potential underlying tracer uptake reversibility. By properly incorporating the net efflux rate constant parameter of \( k_{\text{loss}} \) in a generalized Patlak (gPatlak) imaging framework, it became possible to generate parametric WB tracer influx rate constant \( K_i \) images of enhanced quantitative accuracy, compared to SUV, including in regions with non-negligible \( k_{\text{loss}} \), where sPatlak introduced bias. At the same time, our results also indicated reduced gPatlak robustness to high noise levels and, thus relatively lower tumor CNR scores than sPatlak, except if \( k_{\text{loss}} \) effect is strong enough to provide sufficiently high contrast to counteract any CNR losses due to background noise amplification.

Furthermore, in order to efficiently enhance tumor CNR and detectability and, at the same time, to retain sufficient quantitative accuracy, we proposed a hybrid Patlak (hPatlak) method to selectively apply gPatlak analysis only to voxel TACs exhibiting high Patlak correlation coefficients and sPatlak method elsewhere. According to both simulations and clinical results, hPatlak was always associated with the highest TBR and CNR scores, while its accuracy and precision performance was placed between that of gPatlak and sPatlak methods, thus demonstrating primary clinical usefulness mainly for detectability tasks. Finally, for the clinical study, the measured CNR in SUV images was consistently lower than that of sPatlak and gPatlak in most regions and that of hPatlak in all regions, demonstrating enhanced detectability performance for Patlak imaging over conventional SUV PET.

Although gPatlak and hPatlak schemes are presented here for WB dynamic PET clinical acquisitions, they are also applicable to more common dynamic PET protocols, such as single-bed dynamic cardiac or oncologic PET studies, where temporal sampling is continuous and noise levels are lower. Moreover, although the current study has focused on FDG scans, the proposed methods may also be applied to other PET tracers which are used in WB imaging and which exhibit considerable net efflux rate constants, such as \( ^{18}\text{F}-\text{FLT} \) and \( ^{18}\text{F} \)-fluoride bone parametric imaging (Kim et al 2008, Siddique et al 2014).
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