Validation study of a 3 Compartment Model for 18F-FDG PET Studies on Oncology Patients

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Abstract

A pharmacokinetic study was performed with a 3-compartment model to investigate the relationship among 4 statistical parameters and criteria: sum-squared residues (SSR), chi-square (χ^2), Akaike information criterion (AIC) and model selection criteria (MSC). A pharmacokinetic model describes a biologic process depending on tracer distribution and the above 4 criteria are used to assess whether the tracer distribution over a biologic process suits the proposed model. Model validation is accounted by assessing the goodness-of –fit between experimental and model data. Pharmacokinetic data of a total of 121 tumor-lesions from 51 cancer patients were studied. Dynamic data were acquired with the ECAT EXACT HR+ PET system (Siemens). An image-derived input function was used to generate input curves for the 3-compartment model. For every lesion, PK parameters (k1 to k4, vascular fraction) were estimated with PMOD (provided through cooperation with PMOD Technologies Ltd.). This program also calculated SSR, χ^2, AIC, and MSC for each PK modeling study. The cost function χ^2 showed very good agreement ($p<0.001$) between the measured and estimated model data for 108 studies (89%). The scatter plots for χ^2 and AIC against lesion volume were distributed within a narrow range (less scattered) than that obtained for MSC and lesion volume. Very high positive-correlation between χ^2 and AIC and negative correlation between AIC and MSC were observed at significance level $p<0.001$. The curve fitting equations for AIC and MSC were generated for the same model but with different parameters (4 parameter and 3 parameter model). Both the fitting equations were logarithmic (natural) functions (fitted at 95% confidence level). AIC showed decreasing and MSC showed increasing trend when they were plotted against tumor volume. Input volume showed significant correlation with MSC. χ^2 statistics showed very good agreement ($p<0.001$) between model and experimental data (89% cases). In comparison to MSC, AIC showed better correlation with corresponding lesion volume. The number of lesions those existed within the confidence boundary (95% level) for both AIC and MSC criteria were found more when 3 model parameters (instead of 4 parameters) were considered for the 3 compartment model. Larger lesions yielded gradual consistent χ^2 and AIC, i.e. the data converged to fitting line.

Key words: F-18 FDG PET, Tracer Kinetics, 3 Compartment model

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Introduction

The distribution of radiotracers within a biological system, commonly termed as tracer kinetics, can be modeled as a combination of compartments. In nuclear medicine, compartment model-studies based on PET data are very efficient and powerful ways for quantitative physiologic analyses. A biologic system can be modeled mathematically by the compartment model that calculates certain parameter-values, which correlate to the blood-tissue functions, receptor density etc. The values of these parameters are governed by the rates of exchange of material between the compartments. Different compartmental models have been developed and studied so far in order to describe different physiologic systems and phenomenon (1). Models used in PET include those for blood flow, oxygen metabolism, glucose metabolism, estimation of receptor concentration etc. Compartmental modeling and tracer kinetic analysis require two sets of data to yield estimates of physiologic parameters (2). These include i) the arterial plasma concentration curve or input function, and ii) tissue concentration.

Once the compartment-parameters are estimated, it essentially requires quantifying the overall performance of the kinetic model in order to analyze how well the model configuration describes the kinetic behavior of the radiotracer and how accurately the model parameters are calculated. One aspect of parameter estimation is the assessment of the goodness-of-fit that measures how well the model describes the model data. Commonly used optimization criterions for PET studies are least-square estimation, $\chi 2$-statistics, Akaike information criterion (AIC), maximum likelihood estimator, calculation of correlation coefficients, model selection criterion (MSC), etc.

The 3-compartment model that is used in this study is described schematically in figure 1. Compartment C_{plasma} represents the tracer concentration in the arterial plasma, C1 represents free and non-specifically bound tracer in a volume of tissue (e.g. tumor lesion), C2 represents specifically bound or metabolized tracer within the tissue volume. Tracer is extracted with rate constant *k1* from the arterial plasma (input curve C_{plasma}) to compartment C1 and diffuses back to plasma with the rate constant *k2*. Another fraction *k3* moves further from C1 to compartment C2. Unless tracer is trapped in the C2 compartment, a fraction *k4* transfers back to C1.

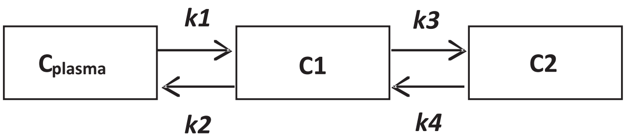

Fig. 1. Block-diagram of 3-compartment model used in the present study

The analysis of 18F-flurodeoxylucose (FDG) data is useful for determining the glucose transport rate in a region of tissue or tumor. The proposed 3-compartment model (considered as 2-tissue compartment model) has been used in many FDG studies to calculate the compartment-parameters and blood component v_b as well for PET studies (3,4,5,6).

For the present study, such a 3-compartment model has been extensively used on FDG PET data to investigate the relationship among different goodness-of-fit parameters (SSR,$\chi 2$) and model-characterizing parameters (AIC, MSC) and their dependence on the tumor and input volumes.

Theory

In general, a dynamic PET measurement exhibits the average activity in the image pixels at a series of times *t* that starts right after injection. The activity concentration measured by PET (C_{PET})(for a certain tissue volume can be written as (7):

$$C_{PET}(t) = (1 - v_b)C_{Tissue}(t) + v_b C_{Spillover}(t) \qquad (1)$$

Where $C_{Tissue}(t)$ the instantaneous concentration of tracer in the tissue is extracted from the blood, $C_{Spillover}(t)$ is the concentration of tracer in the circulating blood, v_b is the fractional volume of the capillaries $(1-v_b)$ and is the fractional tissue volume.

Goodness-of-fit and Model Characterizing Parameters

If a pharmacokinetic model correctly describes a physiologic process, then the model-parameters which are obtained by fitting the model data with the experimental data, in fact, would represent the measurements of the expected physiologic parameters. Once a model is specified with its parameters, and data have been collected, then it's necessary to evaluate its goodness-of- fit, that is, how well the model data fit with the experimental data. The most common way to assess the goodness-of-fit for a model is to minimize the difference between model and experimental data (i.e. minimization of residual). PMOD program calculates the squared residuals and the differences between experimental and model data are described by the $\chi 2$ criterion. Two model-characterizing parameters, namely Akaike information criterion (AIC) and model selection criterion (MSC) are also implemented to evaluate the validity of a model, i.e. how suitable the model is to describe a physiologic process. Due to the relevance of these statistical parameters in the present study, a general description of parameter estimation with different cost functions and different model characterizing parameters are presented here.

In general, there are two methods of parameter estimation. One is the least-square estimation (LSE), i.e., minimization of residual and another is the maximum likelihood estimation (MLE). LSE provides a descriptive measure of the measured data and relates to many familiar statistical concepts such as linear regression, sum of squares error, root mean square deviation etc. This estimation normally requires no distribution assumptions and not useful enough for parameter estimation (8).

On the other hand, MLE is a standard approach to parameter estimation, especially in the cases of non-linear regression analysis (8). The principle of MLE states that the desired probability distribution is the one that makes the experimental data “more likely” (2). Many of the inference methods in statistics are developed based on MLE, such as chi-square test, Akaike information criterion (AIC), model selection criterion (MSC) etc.

Least-squares estimation can also provide the maximum likelihood estimation under some assumptions: the errors in the measured data are normally distributed and have uniform error variance during the parameter estimation (2). The general expression of the sum-squared residues (SSR) used in PMOD manual is:

$$\mathrm{SSR} = \sum \left[y(t_i) - \hat{y}(t_i) \right]^2, \qquad (2)$$

Where $y(t_i)$ is the measured values, $\hat{y}(t_i)$ is the estimated values from the model curve.

χ2 is the most widely used statistical criterion that characterizes a curve fitting between expected (provided by the model) and experimental data. It ultimately provides a level of significance for the model data in comparison to experimental data. PMOD program has implemented χ2 statistics in the following form (7):

$$\chi^2 = \sum_i w_i \left[y(t_i) - \hat{y}(t_i)\right]^2, \qquad (3)$$

Where $w_i = 1/\sigma_i^2$.

Equation 3 implies that the squared residuals are multiplied by the weights w_i and this weight function is calculated from the standard error σ_i.

A model-characterizing criterion indicates the suitability (validity) of a model to study a physiologic system with an experimental data set. To determine the correct underlying model for an experimental data set, the most common way is to choose such a model that best fits the experimental data. This idea, however, does not work because this process possibly favors complex model among all the available models (9). The reason is that, the complex model has more degrees of freedom and can therefore fit to the experimental data better than other models. Thus, to choose a correct model, it is suggested not only to minimize the sum-squared residue, but also to minimize the complexity of the model (9). A simplified model with fewer parameters provides more precise results (7).

A model-characterizing criterion accounts the number of parameters and the data points in such a way that higher order models are penalized. Different model characterizing criteria exist so far those are been used in different modeling and statistical study (9). The basic difference between all the existing criteria lies in the way by which they penalize the higher order models.

Model characterizing parameter AIC provides a quantitative evaluation of a proposed model for an experimental data set. AIC is based on the idea that it selects a model that minimizes the difference in the calculated-data (minimization of the difference of experimental and model data) by considering that the new calculated-data had same distribution as that of the original data (10, 11). AIC uses maximum likelihood estimation technique for computing the residuals and it has the following form:

$$AIC = n \ln\left(\sum_i w_i \left[y(t_i) - \hat{y}(t_i)\right]^2\right) + 2\rho \qquad (4)$$

Where n denotes the number of measurements in the experimental data set, ρ is the number of model parameter, is the experimental data and is the estimated value by the model.

Equation 4 depicts that the number of model parameter (ρ) is added with the AIC estimation, i.e. more the number of parameters are included in the model, AIC increases. But to validate a model in terms of AIC, a minimum value of AIC is expected. The calculation of an optimum AIC may be defined in the following steps.

Consider an experimental data set, $y_1, y_2, \ldots y_n$ that would be used to calculate model parameters for a physiologic system. Now, the first step is to define a model with compartments that perfectly match with that physiologic process. Next, the experimental data are fitted with the proposed model to estimate the model parameters and its corresponding model characterizing criteria, e.g., AIC is chosen. The next step comprises if the proposed model suits well with biologic system for which the model is developed. It is documented in the PMOD user manual that this optimization requires fitting the experimental data gradually with higher order and more complex model (7). PMOD program provides a library of different model from which the user can switch from one to another. During consecutive studies, care should be taken so that the selected model should match the biologic process. From each study, a quantitative measure of AIC (or other criteria, e.g. MSC) is obtained. If these values (AIC) are plotted with corresponding studies, the minima of the plot should indicate the best AIC value and the model that relates to that AIC value would be the best among all the tested models for that experimental data set.

MSC penalizes (number of model parameters) and n (number of data points) in a different scale than those of AIC. MSC also uses maximum likelihood estimation technique for computing the residuals. The expression for MSC is as follows:

$$MSC = \ln\left(\frac{\sum_i w_i \left[y(t_i) - \bar{y}(t_i)\right]^2}{\sum_i w_i \left[y(t_i) - \hat{y}(t_i)\right]^2}\right) - 2\rho / n \qquad (5)$$

Where n denotes the number of measurements, ρ is the number of model parameter and $\bar{y}(t_i)$ is the mean value of the experimental data.

Equation 5 shows that MSC depends on the average of the experimental data $\bar{y}(t_i)$, rather than individual data point. $y(t_i)$ Unlike to AIC, the maximum value of MSC corresponds to more appropriate model.

Maximum Likelihood Estimation for Multi-parameter Calculation

For a simplistic case, let $f(y \mid w)$ is the probability density function (PDF) for a data vector $y = y_1, y_2 \ldots y_n$ that yields a single parameter w. This expression can be illustrated in the following way:

$$f(y = (y_1, y_2, \ldots, y_n) \mid w) = f_1(y_1 \mid w) f_2(y_2 \mid w) \ldots f_n(y_n \mid w) \qquad (6)$$

Once the experimental data are collected and a model is defined, then one seeks such a PDF, among all the probability densities, that is supported by the model. To get the expected PDF, the likelihood function is required, that can be obtained by reversing the roles of the defined PDF $f(y \mid w)$ as follows:

$$L(w \mid y) = f(y \mid w) \qquad (7)$$

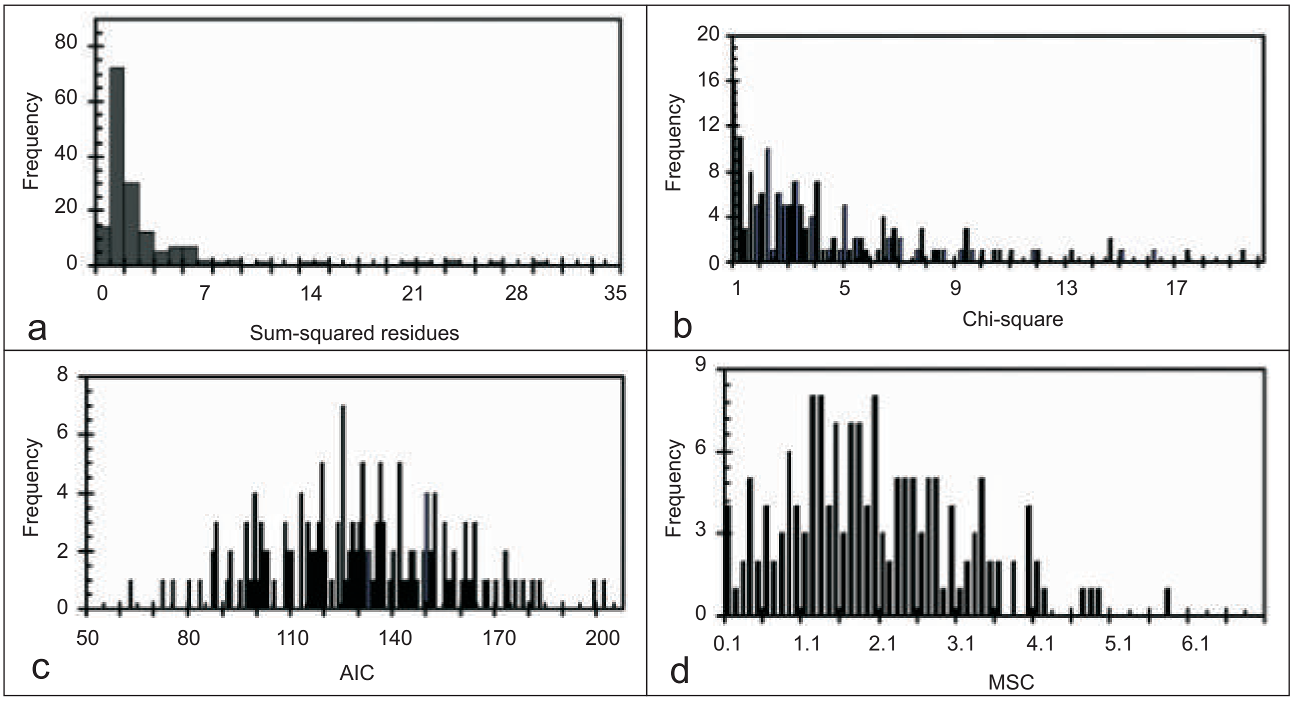

Figure 2. The histogram plots for: SSR (a), χ*2* (b), AIC (c), and MSC (d)

Thus $L(w|y)$ indicates the likelihood of the parameter w for the given data vector y and is called likelihood function. Now if the parameter w is replaced by a combination of number of parameters, then the PDF $f(y|w)$ becomes,

$$f(y=(y_1,y_2,...,y_n)\,|\,(w_1,w_2,...,w_\rho) \qquad (8)$$

The following relation gives the likelihood function:

$$L(w_1,w_2,...,w_\rho \,|\, y_1,y_2,...,y_n) = $$
$$L=\sum_{i=1}^{N}(w_1,w_2,...,w_\rho \,|\, y_i) \qquad (9)$$

Materials and Methods

PET Acquisition and Data Collection

Pharmacokinetic data of a total of *121* tumor lesions (volume<*35* mL) from *51* oncology-patients, irrespective of location and histology, were included in the present study. All tumors were confirmed by histology and/or by clinical follow up observation. Dynamic PET acquisition was performed after administration of *250-370* MBq FDG using a dynamic protocol of *10*×*30* s, *5*×*60* s, *5*×*120* s, and *8300* s time frames consecutively with a dedicated PET system (ECAT EXACT HR+, Siemens, Erlangen, Germany). A transmission scan was performed prior to the radionuclide administration for the attenuation correction of the acquired data. The volumes-of-interest (VOIs) for tumor-lesion and input-curve were generated from the attenuation corrected-images following usual clinical procedure discussed in previous studies (3,4,5,6, 12).
Dynamic PET data were analyzed with PMOD (7). The quantitative evaluation of tracer kinetics was performed using the *3*-compartment model (Figure 1). The model-parameters *k1* to *k4* and the fractional blood volume (v_B) were calculated for each VOI. For the non-linear parameter-estimation, one has to use iterative method, by starting with an initial guess of the parameters and then optimizing the parameters to yield a good fit (13).

Fitting Method

For the present study, a different approach for optimization of the model characterizing criteria has been used. Instead of changing the model feature (same compartment model was used for all the studies), different numbers of model parameters (*k1 to k4*) were included. Each experimental data set (total 121 studies) was fitted 2 times by including: (i) all the parameters (*k1* to *k4*) and (ii) *k1* to *k3*. The optimization of model characterizing criterion (both for AIC and MSC) were performed from these two studies.
Following the compartment fitting procedure, visual evaluation of each plot was performed to check the quality of each fit. Each model curve was compared with the corresponding time-activity curve. The Marquardt-Levenberg iterative algorithm was used for fitting purpose. The model-parameters were accepted when *k1* to *k4* was less than one and the fractional blood volume v_b values exceeded zero. The units of the parameters *k1* to *k4* are *1*/min, where v_b is unit less.

Data Analysis

The distribution patterns for the four goodness-of-fit parameters (SSR, χ^2, AIC, and MSC) were studied by generating histograms. The number of cases tallying within ±*10%* range of the mean value was compared among the parameters. The corresponding-relations among the model characterizing criteria were studied by drawing the scatter-plot and by calculating the correlation of coefficients. The analysis was performed with MS Excel 2000 and Sigma

Goodness-of-fit parameters	Quantities	Magnitude of the arithmetic quantities	Standard deviation (?SD)	No. of lesions [a] (within ?10% magnitude of arithmetic quantities)
AIC	Mean	129.58	26.60	65 (54%)
	Median	129.35		64 (52.5%)
	Peak value	124		64 (52.5%)
MSC	Mean	1.94	1.14	19 (16%)
	Median	1.78		24 (20%)
	Peak value	1.25		15 (12%)

[a] The lesion number is expressed as percent of total lesions

Table 1. The arithmetic quantities considered for goodness-of-fit parameters

plot. Finally, these results were investigated with respect to tumor and input-volume.

Results

The histograms for SSR, χ^2 criterion, AIC and MSC are presented in Figure 2 consecutively. The SSR shows a very sharp peak with a long tail of distribution. Maximum number of studies is accumulated within minimum range of the parameter-value what was expected. Although most of the studies exist with the peak area, but a long tail ultimately shifts its mean from the peak value. The distribution for the measured χ^2 values shows a logarithmic decreasing pattern. The minimum χ^2 corresponds to higher significance that indicates good agreement between experimental and model data. From χ^2 analyses (Figure 2b), very good agreement ($p<0.001$) was observed between the measured and estimated model data for *108* studies (*89%*). Ten studies (*8%*) showed considerable level of significance ($p<0.01$), and only *3* studies (*3%*) showed low significance ($0<0.1$).
A normal distribution was found for AIC criterion. Apparently the distribution for MSC is not showing any sharp peaks. The positively skewed normal distribution indicates that the mean value shifts from its peak value.
As it is described earlier that the model characterizing criteria AIC and MSC provide quantitative measurement to validate a proposed model to study a physical phenomenon based on experimental data. It is also mentioned that the estimation of model parameters follow the MLE principle what ensures that estimated parameters or criterion could reveal the most likely information of the physical phenomenon from the experimental data. In general, a probability distribution sufficiently defines a function or parameter or criterion if maximum number of studies exists within the peak-area of that distribution. For a quantitative comparison between AIC and MSC, the number of lesions within ±*10%* range of mean, median and peak values for each of these two criteria were tallied and are expressed as percent of total lesion numbers (Table 1). The standard deviations (±SD) for these two criteria were found varying over a wide range with respect to the magnitude of the measured quantity. According to the principle of maximum likelihood estimation, the peak value of a distribution generally corresponds to likelihood-estimated value. For normal distribution, it is more likely that mean, and likelihood estimated value provides the same measurement, as is found for AIC. But for MSC, the distribution is positively skewed and the mean value is shifted right to peak value.
To find the corresponding-relations among the four parameters and criteria (SSR, χ^2, AIC and MSC), the correlation coefficients were calculated as is summarized in Table 2. In general, a probability with $p<0.05$ is enough to make a statistical inference in favor of any measurements or experimental results (14). All the parameters those were used for assessment and validation of this model study showed considerable significances what was expected. Even though, some correlation coefficients were found

Pairs of goodness-of-fit parameters	Correlation Coefficient (DF=119)	Probability
SSR – χ2	0.20	p<0.05
SSR – AIC	0.234	p<0.01
SSR – MSC	-0.16	p<0.052
χ2–AIC	0.765 [b]	p<0.001
χ2 – MSC	-0.255	p<0.01
AIC- MSC	-0.72 [b]	p<0.001

[b] Very significant

Table 2. Correlation coefficients for SSR, χ2 – AIC and MSC with input-volume

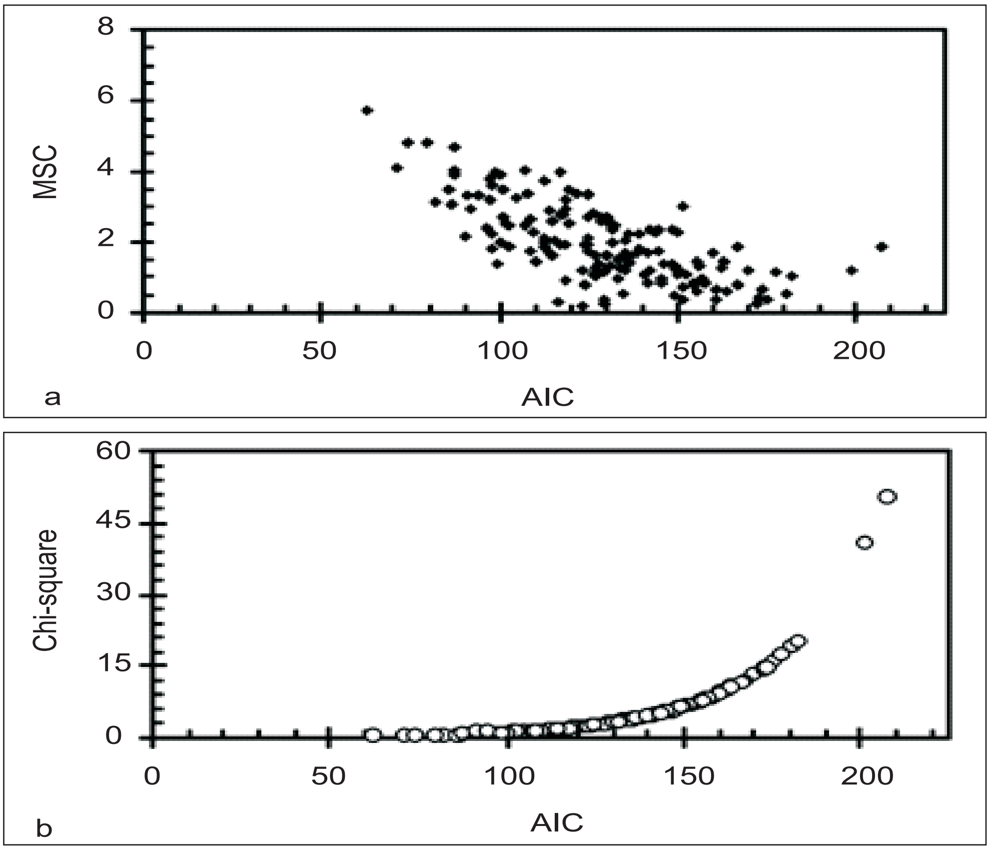

Figure 3. The scatter plots between AIC-MSC (a) shows a negative and Chi-square-AIC (b) shows positive correlation between them.

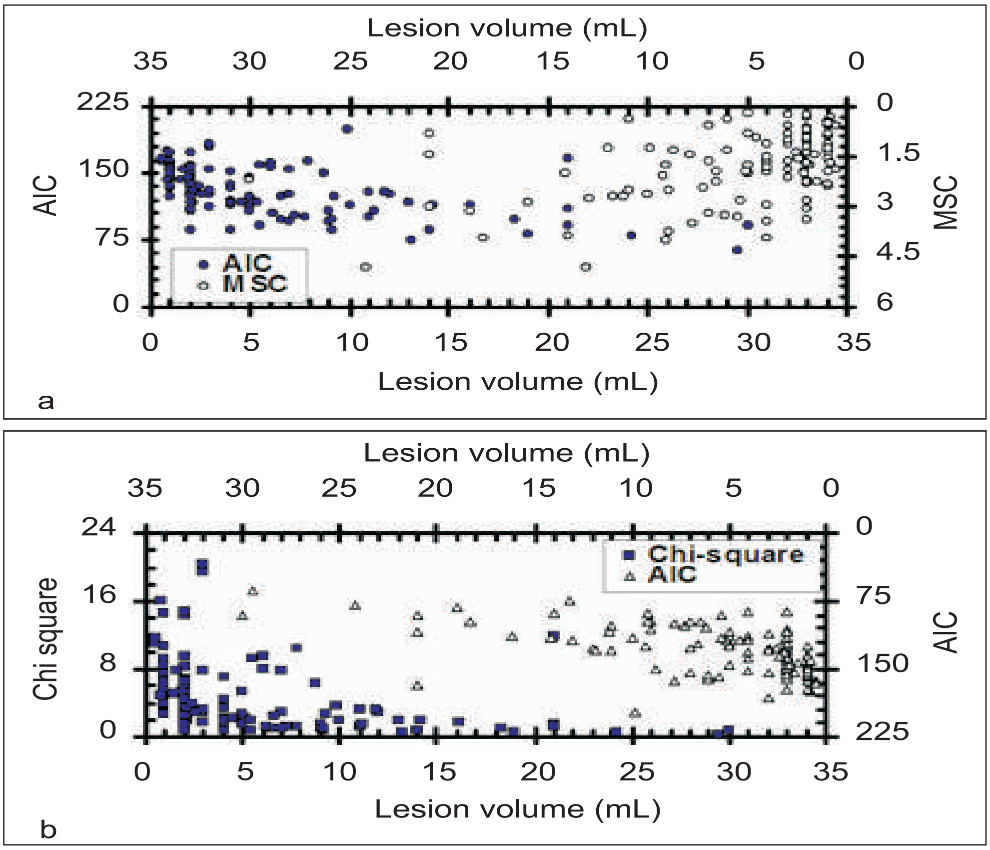

Figure 4. The scatter plots of AIC and MSC (a) and $\chi 2$ and AIC (b) with respect to lesion volume.

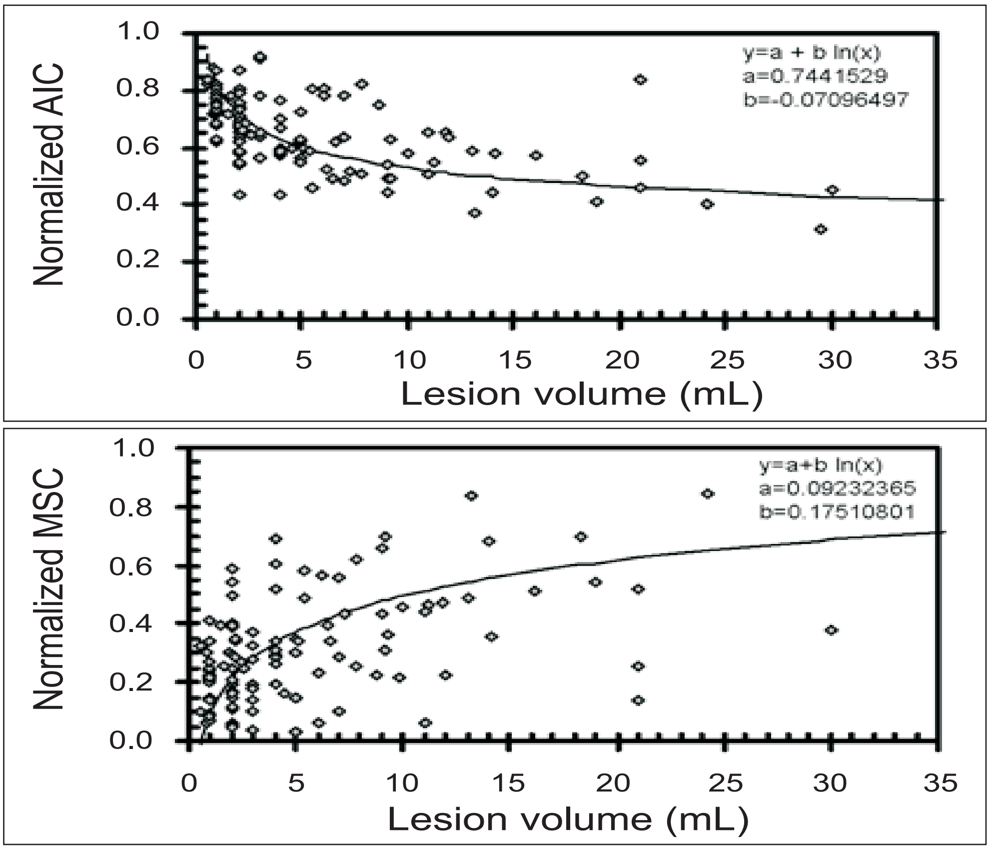

Figure 5. Curve-fitting equations for AIC (above) and MSC (below) with respect to lesion volume. Four parameters were included in the model.

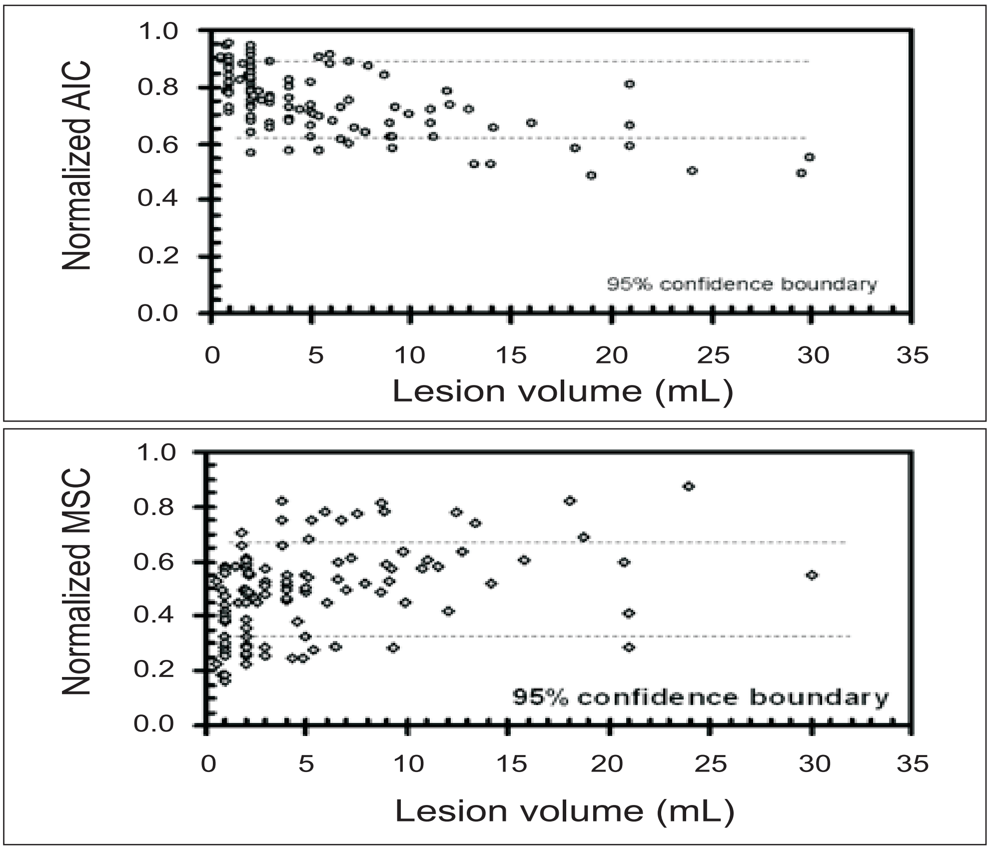

Figure 6. The boundaries those include the data points at 95% confidence level for the logarithmic curve fittings shown in figure 5. Three (instead of four) model-parameters were included in these studies.

with high order of significance. For example, a positive correlation between 2χ and AIC and negative correlation between AIC and MSC were observed with a probability of $p<0.001$ (Figure 3). The correlation between $\chi 2$ and MSC, AIC and SSR also showed very good correlation with a probability of $p<0.01$.

Figure 4 shows the scatter-plots for $\chi 2$, AIC and MSC against the lesion volumes (mL). The AIC values are less scattered and 105 cases (87% of total) exist within ±1 standard deviation (±1 SD). MSC values are more scattered than that of AIC and 78 cases (64% of total) existed within ±1 SD. The scatter plots with $\chi 2$ and AIC against lesion size are less scattered as is depicted in Figure 4b.

Optimization of Model Characterizing Criteria

The optimization of model characterizing criteria requires multiple studies with different model-features. The experimental data used for this study were collected from the patients who had confirmed tumor lesions and were diagnosed with FDG PET study. The 3-compartment model yielded 4 model parameters ($k1$ to $k4$) and those parameters indicate the transport rate among the compartments.

The PMOD program provides the users a set of model to use for an experimental data set. But before using a model for an experimental data set, it is essential to match a physical process to that of a proposed model. For the present study, the experimental data were collected from a particular group of patients those were diagnosed with tumor lesions and were studied with FDG in PET. For the optimization purpose, the two criteria AIC and MSC were estimated in two phases: by including all the parameters ($k1$ to $k4$) and by considering three parameters ($k1$ to $k3$). The changes in AIC and MSC with respect to the lesion volumes for the two phases were compared each other.

Figure 5 shows the fitting equations generated for criteria AIC and MSC against the lesion volumes where *4* model-parameters ($k1$ to $k4$) were included. The two data set for AIC and MSC were normalized with respect to their corresponding maximum value. This normalized scale aligned both the parameters in the same scale. The curve-fitting equations were generated for two criteria (AIC and MSC) using Table Curve program (15). The curve fitting equation associates a data boundary that includes the data-points those exist within *95%* confidence level for the fitting curve. It was found that 82 studies (68% of total) for AIC and 74 studies (61% of total) for MSC existed within that confidence level when four model parameters were considered. The fitting equations show that, both AIC and MSC are logarithmic (natural) functions with different coefficients. AIC has a decreasing and MSC has an increasing trend with respect to the tumor volume (Figure 5). The correlation coefficient between AIC and lesion volume was $r=-0.393$ ($p<0.001$). The correlation coefficient between MSC and lesion volume was $r=0.20$ ($p<0.01$).

The experimental data set was fitted with the same compartment model but with less parameters (3 instead of 4). The idea was to optimize the two model characterizing criteria (AIC and MSC) by comparing the plots obtained from two studies (considering 4 and 3 model parameters). The estimated AIC and MSC (with 3-compartment parameters) are plotted (Figure 6) against the lesion volume and they were fitted (the fitted line is not shown in Figure 6) with same logarithmic (natural) functions at the same confidence level as were done earlier in Fig. 5. The numbers of data points at *95%* confidence level were tallied both for AIC and MSC. It was found that 98 studies (81% of total) for AIC and 85 studies (75% of total) for MSC existed within that confidence level. These numbers are slightly higher than previous numbers those were calculated with 4 parameters.

The input-volume drawn for each study was compared with corresponding SSR, $\chi 2$, AIC and MSC values. The correlation coefficients were found less significant in comparison to those calculated for lesion volumes. Table 3 shows the correlation coefficients for these three parameters with respect to the input volume.

Discussion

PK modeling with PET data essentially requires validating a model based on goodness-of-fit parameters and model characterizing criteria in order to assess the accuracy of the measured physiologic parameters. $\chi 2$ statistics is used as a cost function that yields a level of significance of the model data with corresponding experimental data. But only good fit is not a guaranty to assess a perfect model. It is also essential to reduce the complexity of the model (less parameters) and to increase the general acceptability (better prediction of the model results) as well. Two model characterizing criteria AIC and MSC are more focused in this study to reveal their role in validating a 3-compartment model for FDG PET studies.

The proposed modeling study was performed on FDG PET studies among the patients who were clinically and histologically diagnosed with confirmed tumor lesion. The 3-compartments in the proposed model represent tracer concentrations in three forms: first compartment represents plasma or blood concentration; second represents free tracer concentration within the tumor lesion and the third one represents the specifically bound tracer within the tumor lesion. Once tracer is injected to the patients' blood stream, tracer accumulates within the tumor area and this rate of accumulation depends on different physiologic and clinical factors. Depending on the glucose metabolism within the tumor cells, this tracer might be fully trapped within the lesion or a part of this tracer might transfer back to plasma. FDG has a high tendency to metabolize within the tumor lesion, so there is a little chance for the tracer to be transferred back to the plasma (2). This physiologic phenomenon indicates that the transport rate $k4$ is preferentially negligible for most of the patients' cases. The

Name of fitting parameters and model criteria	Correlation Coefficients (r)	Probability (DF=119)
SSR	0.048[c]	p>0.05
χ*2*	0.034[c]	p>0.05
AIC	0.107[c]	p>0.05
NSC	-0.182	p>0.05

Table 3. Correlation Coefficient for SSR, χ*2* AIC AND MSC with input-volume

results presented in this study support this physiologic phenomenon. AIC and MSC calculated with 4 model parameters varied over a wider range than those were found with 3 model parameters, i.e., the model with 3 parameters yielded less scattered AIC and MSC than other study. 3 model-parameter study also exhibited better agreement between experimental and model data (more lesions existed within the 95% confidence boundary when data were fitted with natural logarithmic function) than the case when the model was defined with 4 parameters.

The calculation of AIC depends on the magnitude of individual data point calculated by the model and on the number of parameters used for a model as is shown in Eq. 4. To characterize a model in terms of AIC, less number of model-parameters is suggested for a model to be fitted well with a measured data set. On the other hand, MSC depends on the average of an experimental data rather than the magnitude of the individual data point (Eq. 5). So it can be predicted that, if a data set contains some data points with high noises or fluctuations (e.g. frequently happens for the PET data), then the average for the whole data set would change significantly, no matter how many data points exhibit the fluctuations.

A high fluctuation (higher standard deviation) in the experimental data set was observed during estimation of different arithmetic quantities (Table 1). These high fluctuations in the experimental data mainly arose from the signal noise and also from the varieties of patients. Each patient has individual tracer distribution even though they had common clinical feature of disease (tumor lesion). The tracer distributions within patients' body differ in a large extent depending on individual physiologic functions, location of the lesion, size, metabolic rate etc.

The lesions included in the present study varied within volume range $0.5 < VOI < 35$ mL. Significant number of small lesions (VO 1 mL) was included in the data. It was intended to investigate the effects of small tumor-volume on the overall model evaluation. From the analysis, AIC was found logarithmically decrease with an increase in lesion volume. It's obvious that size-measurement of smaller lesions associate more errors than those happen for higher lesions. Figures 4b and 5a indicate that χ*2* and AIC gradually converge to the fitting line (less scattered) as the lesion volumes increase. This phenomenon indicates that larger lesions yield precise quantitative measurements for the statistical parameters and criteria.

The accurate measurement of input function is crucial in this compartment analysis. For the input function, the mean value of the VOI data obtained from a large arterial vessel, such as the descending aorta, was used. A vessel VOI consisted of at least of 7 ROIs in sequential PET images. The descending aorta was preferentially used to generate the input functions because it extends from upper chest to lower abdomen of the body. The recovery coefficient was 0.85 for a lesion-diameter of 8 mm for the PET system used in this study (4,5). Partial volume correction was used for small vessels with diameter <8mm but not for the aorta. The input-VOI didn't show significant correlation with SSR, χ*2* and AIC ($p>0.05$), but it showed significant correlation with MSC. This non-significance correlation of input VOI with SSR, χ*2* and AIC was not investigated and is beyond this study. It is suggested that a comparison of individual input ROI, instead of VOI can provide better correlation with SSR, χ*2* and AIC.

Conclusion

The relationship among 4 statistical parameters and criteria were investigated for FDG dynamic PET studies with a PK 3-compartment model. The cost function χ^2 statistics showed very good agreement (p<0.001) between model and experimental data (89% cases). Two model characterizing parameters AIC and MSC were studied with respect to the lesion volume. In comparison to MSC, AIC showed better correlation with corresponding lesion volume. The number of lesions those existed within the confidence boundary (95% level) for both AIC and MSC criteria were found more when 3 model parameters (instead of 4 parameters) were considered for the 3 compartment model. Larger lesions yielded gradual consistent χ^2 and AIC, i.e. the data converged to fitting line.

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