Model Selection in Peptide-receptor Radionuclide Therapy for an Accurate Determination of Time Integrated Activity Coefficients

N Atikah¹, A Riana¹, A Dwi, Z Anwari¹, Misrawati¹ and D Hardiansyah¹
¹Department of Physics, Universitas Indonesia
Jl. Margonda Raya, Jawa Barat 16424, Indonesia
Email: atikahnur369@gmail.com

Abstract. Calculation of accurate time-integrated activity coefficients (TIACs) is desirable in nuclear medicine dosimetry. The accuracy of the calculated TIACs is highly dependent on the fit function. However, systematic studies of determining a good function for peptide-receptor radionuclide therapy (PRRT) in different patients have not been reported in the literature. The aim of this study was to individually determine the best function for the calculation of TIACs in tumor and kidneys using a model selection based on the goodness of fit criteria and Corrected Akaike Information Criterion (AICc). The data used in this study was pharmacokinetic data of ¹¹¹In-DOTATATE in tumor and kidneys obtained from 4 PRRT patients. Eleven functions with various parameterizations were formulated to describe the biokinetic data of ¹¹¹In-DOTATATE in tumor and kidneys. The model selection was performed by choosing the best function from the function with sufficient goodness of fit based on the smallest AICc. Based on the results of model selection, function $A_1 e^{-(\lambda_1+p_{ph2}) t}$ was selected as the best function for all tumor and kidneys in patients with meningioma tumors. By using this function, the calculated of TIACs could be more accurate for future patients with meningioma tumor.

1. Introduction
Molecular Radiotherapy (MRT) is defined as internal radiation therapy which delivers radiopharmaceuticals into the body. Most hospitals apply internal radiation therapy with fixed dose method, which delivers a predetermined fixed dose to certain patients [1]. This fixed dose method does not individualize the patient. Therefore it may cause overdose or underdose which lead to ineffective treatments [1]. Development of dosimetry in internal radiation therapy has enabled each patient to receive a specific dose which suitable with their respective physiological conditions. Individual dosimetry plays an important role in internal therapy because it aims to maximize radiation doses to the tumor site while minimizing radiation dose to organs at risk (OAR) [2]; [3]. Therefore, the real challenge of therapeutic planning in nuclear medicine is how to determine an accurate dosimetry.

In nuclear medicine, the general method which is used to calculate and optimize the injection dose is the method formulated by the Medical Internal Radiation Dose (MIRD) [4]. The internal dosimetry is calculated by the MIRD method, which consists of two parameters that can be optimized, namely the Time-Integrated Activity Coefficients (TIACs) which is related to the Area Under the Curve (AUC) of the activity curve against time and the S-value [5]. Recent studies have indicated parameters that have the highest influence on the inter-individual variability in calculating the absorbed dose in the target organ is the TIACs value [6]. For example, in the kidney, based on the main effect value derived from the global sensitivity analysis (GSA) method, the TIACs value of the kidney has a greater effect, about
90% of the output variance, while the S-value of the kidney only affects about 10% of the output variance [6]. Therefore, the dosimetry requires an accurate good prediction of TIACs value in order to produce an accurate calculation of absorbed dose.

The sum of Exponential (SOE) functions model is a widely used method to analyze TIACs [7]. SOE function method is a method which is used to analyze the distribution of radiopharmaceuticals and describe the curve of radiopharmaceutical activity in each tissue or organ of the body. SOE modeling was generated based on the assumption that radiopharmaceutical pharmacokinetics can be formulated by an exponential function equation with physical and biological decay rates [8]. The SOE method also requires model selection to determine the best model function because a data may be fitted with many function models. Model selection is needed to provide an assessment of the curve fitting quality or goodness of fit and determine the best model with AICc (Corrected Akaike Information Criterion) parameters to obtain the best final model [9]; [10].

However, systematic studies to individually determine the best function for peptide receptor radionuclide therapy (PRRT) in different patients have not been reported in the literature. Therefore, the purpose of this study was to individually determine the best function for calculating TIACs in tumors and kidneys using a model selection based on goodness of fit and Corrected Akaike Information Criterion (AICc) criteria.

2. Materials and Methods

2.1. Patients/Data

This study used biokinetic data on peptide-receptor radionuclide therapy (PRRT) as secondary data [11]. PRRT biokinetic data were obtained by digitizing the data with Web Plot Digitizer software version 4.4 (https://apps.automeris.io/wpd/). The processed data was biokinetic data which were obtained from 4 patients which were diagnosed with a meningioma tumor after pre-therapy injection of $^{111}$In-DOTATATE which was used for model fitting [11]. Pre-therapy dosimetry was performed for 3 and 2 PRRT cycles towards 1st and 2nd patient, respectively. In the pre-therapy measurement process, $^{111}$In-DOTATATE with an activity of 140±14 MBq (total peptide amount 75±10 nmol) was injected intravenously as an infusion. In full-body planar scintigraphy, measurements were taken at 2 hours, 4 hours, 1st, 2nd, and 3rd days after injection. The software ULMDOS [12] and NUKDOS [13] were used to determine the activity-time data [11]. There were totally 7 biokinetic data from tumor sites and kidneys which were used in this study.

2.2. Sum of exponentials (SOE) Method

SOE modeling is generated based on the assumption that radiopharmaceutical pharmacokinetics can be formulated as an exponential equation with physical and biological decay rates [8]. There are eleven functions with various parameterizations of mono- and bi-exponential functions (Eq. (1)-(11))

\[ f_4(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + A_2 e^{-(\lambda_2+\lambda_{phys})t} \]  \hspace{1cm} (1)

\[ f_{3a}(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + A_2 e^{-(\lambda_{phys})t} \] \hspace{1cm} (2)

\[ f_{3ap1}(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + A_1a e^{-(\lambda_{phys})t} \] \hspace{1cm} (3)

\[ f_{3ap2}(t) = A_1 b e^{-(\lambda_1+\lambda_{phys})t} + A_1 (1-b) e^{-(\lambda_{phys})t} \] \hspace{1cm} (4)

\[ f_{3b}(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} - A_1 e^{-(\lambda_2+\lambda_{phys})t} \] \hspace{1cm} (5)

\[ f_{3c}(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + (100 - A_1) e^{-(\lambda_2+\lambda_{phys})t} \] \hspace{1cm} (6)

\[ f_{2a}(t) = 100 e^{-(\lambda_1+\lambda_{phys})t} - 100 e^{-(\lambda_2+\lambda_{phys})t} \] \hspace{1cm} (7)

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\[ f_{2b}(t) = A_1 e^{-(\lambda_1 + \lambda_{phys})t} \]  
(8)

\[ f_{2c}(t) = A_1 e^{-(\lambda_1 + \lambda_{phys})t} - A_1 e^{-(\lambda_{phys})t} \]  
(9)

\[ f_{2d}(t) = -A_1 e^{-(\lambda_2 + \lambda_{phys})t} + A_1 e^{-(\lambda_{phys})t} \]  
(10)

\[ f_{2e}(t) = A_1 e^{-(\lambda_1 + \lambda_{phys})t} + (100 - A_1) e^{-(\lambda_{phys})t} \]  
(11)

Where \( \lambda_{phys} \) is the radioactive decay constant of the radionuclide, \( A_k \) and \( \lambda_k \) are the fractional absorption in % activity and the biological decay constant, respectively. These functions are designed to be attached to the data with fraction of the injected dose (%ID) units. For simulation purposes, the numerical software SAAM II version 2.3 (https://tegvirginia.com/software/saam-ii/) was used in the SOE modelling.

2.3. Model Selection

The model selection provides an assessment of the curve fitting results (Goodness of fit) and determines the best model with AICc (Corrected Akaike Information Criterion) parameters to get the best final model. Goodness of fit was determined by graphical visualization, Coefficient of Variation (CV) and Correlation Matrix (CM\text{ij}) [8]. Graphical visualization was conducted by direct observations of the fitted curve. The Coefficient of Variation (CV) describes the level of precision of the fitting parameters and was determined by dividing the standard deviation value with the average value [14]. The requirement for the maximum value of CV of an acceptable fit is 50% [8]. In addition, the off-diagonal values of the Correlation Matrix (CM\text{ij}) show linearity between the parameters that composed a function, acceptable fits are defined as the maximum value of off-diagonal elements equal to -0.8 ≤ CM\text{ij} ≤ 0.8 [8] [15].

Corrected Akaike Information Criterion (AICc) is modified from Akaike Information Criterion (AIC), where the AICc includes the parameter number of data points (N) [10]. AICc (Eq. (12)) is used to select the best equation in the model that has a small ratio between the number of data points (N) and the number of parameters (K) (N/K < 40) [9] [10]. The weighting of AICc (\( \omega_{AIC_i} \)) is the value of the weight of AICc which is shown in the following equation (Eq. (13)-(14)).

\[
AICc = OF + 2K + \frac{2K(K + 1)}{N - K - 1} 
\]  
(12)

AICc weighting:

\[
\Delta i = AICc_i - AICc_{min} 
\]  
(13)

\[
\omega_{AIC_i} = \frac{e^{-\Delta i/2}}{\sum_{i=1}^{F} e^{-\Delta i/2}} 
\]  
(14)

Where N and K are the number of data points and adjustable parameters, respectively. F is the size of the model set, AICc\text{min} is the lowest AICc of all fitted functions, \( \Delta i \) is the difference of the AICc values to AICc\text{min}, and \( \omega_{AIC_i} \) is the corresponding weight, and -2ln(P) the estimated value of the OF at the minimum. With absolute weighting, the condition of the fit parameter boundary (K) becomes less than and equal to the number of data points (N) minus 2 or K N-2 [8].
2.4. Determination of TIACs
The TIACs value was obtained by integrating the best model that had been gained in the previous process. The selection of integration limits with a range time from 0 to 10 times the half-life ($t_{1/2}$) of radionuclides which is in accordance with Anwari's research [16]. This means that the calculation of TIACs is carried out until the decay activity of radionuclides in the body is very low. The TIACs value is obtained from the following equation:

$$\text{TIACs} = \frac{1}{A_0} \int_0^{10t_{1/2}} A(t) dt$$  \hspace{1cm} (15)

Where $A(t)$ is the accumulated activity at time $t$ and $A_0$ is the initial activity.

3. Result and Discussion
It was highly recommended to conduct the selection model in order to obtain the best function on individual dosimetry for Peptide Receptor Radionuclide Therapy (PRRT) treatment. However, this method was not carried out in hospitals because it consumes high workload to perform model selection on each patient's biokinetic data. In this study, the SOE method was applied to tumor and kidney biokinetic data to obtain accurate TIAC values. Based on the results of model selection, function 2b ($A_1 e^{-\left(\lambda_1 + \lambda_{phys}\right)t}$) is the best function for all tumor organs and kidneys in patients who suffered meningioma tumor. This function was selected as the best function based on the goodness of fit test and has the smallest AICc value and the largest AICc weighting compared to other functions. Figure 1 shows the results of the curve fitting for the function f2b to the data.

![Figure 1](image)

**Figure 1.** Example of the fitted curves of kidneys and tumor (patient 1, N3)

Based on the graphical visualization, the curve fitting results have shown that the f2b function describes the data well. Physically, f2b has a greater compatibility to be the best function than other functions. The f2b function shows a decrease in the injection dose received by tumor and kidneys organ based on the decay of its physical and biological lambda. After observing the graphic visualization, the goodness of fit test was also checked for the CV and CM values. After that, the AICc value has been calculated to determine the best function. Table 1 shows the results of the model selection, namely the CV value, CM value, AICc, and the AICc weighting of the f2b function.
Table 1. Model Selection of Tumor Biokinetic Data

| Measurement | Maximum CV value (%) | Maximum CM value (Abs) | AICc | AICc weighting (%) |
|-------------|----------------------|------------------------|------|-------------------|
| N1          | 31.25                | 0.75                   | -39.52 | 75.58            |
| N2          | 26.7                 | 0.76                   | -38.3  | 97.86            |
| N3          | 30.84                | 0.76                   | -41.47 | 94.22            |
| N4          | 39.16                | 0.74                   | -43.72 | 87.94            |
| N5          | 40.07                | 0.74                   | -41.1  | 89.29            |
| N6          | 42.92                | 0.72                   | -38.42 | 88.73            |
| N7          | 36.57                | 0.73                   | -34    | 98.26            |

Table 2. Model Selection of Kidneys Biokinetic Data

| Measurement | Maximum CV value (%) | Maximum CM value (Abs) | AICc | AICc weighting (%) |
|-------------|----------------------|------------------------|------|-------------------|
| N1          | 22.22                | 0.76                   | -46.32 | 99.87            |
| N2          | 23.38                | 0.78                   | -44.3  | 99.22            |
| N3          | 23.13                | 0.77                   | -45.13 | 99.63            |
| N4          | 22.52                | 0.74                   | -34.42 | 99.93            |
| N5          | 22.5                 | 0.74                   | -32.08 | 99.93            |
| N6          | 22.3                 | 0.78                   | -76.72 | 73.87            |
| N7          | 14.77                | 0.78                   | -65.07 | 99.96            |

The table above is for the model selection results from the f2b function. When compared to other functions, the f2b function meets the criteria of goodness of fit as seen from the CV and CM values. So, based on the model selection table above, the CV value is below 50% and the CM value is between -0.8 and 0.8. The AICc value of the f2b function also has the smallest value from other functions which are the best candidate functions, while the AICc weighting also has the largest value. By using this function, TIACs calculation is more accurate for patients with meningioma tumors.

In this study, researcher determined the best function in the internal dosimetry of PRRT, especially for cases of meningiomas in tumors and kidneys. In the future, the f2b function can be used for meningioma patients, therefore it can assist clinical activities to determine accurate TIAC. However, reproducibility study to the best function derived using model selection in this study is needed.

4. Conclusion
In this study, we individually determine the best function in the internal dosimetry of PRRT, especially for meningioma cases in tumors and kidneys. Function f2b was found as the best function for most of the data. Therefore, this function might be used for the future meningioma patients.

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